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FORMULATION AND OPTIMIZATION OF SUSTAINED RELEASE TABLET OF PREGABALIN

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ABSTRCT

The aim of the current study was to formulate and optimize sustained release matrix tablet of pregabalin in order to achieve the prolonged therapeutic action by releasing the drug over an extended period of time after a single dose administration which would help to improve the patient compliance. The matrix tablets were prepared using direct compression technique. Optimization was done by using 3^2 Factorial design using design expert. Matrix polymers of Polyox family like PEO WSR 303, PEO WSR 301 were used to make the sustained release tablet. Matrix tablets were evaluated for various physical parameters like hardness, friability, weight variation, drug content and In vitro dissolution study. After the evaluation the results obtained were found satisfactory which clearly shows that the C8 matrix formulation containing polymers of the Polyox family (i.e PEO WSR 303 AND PEO WSR 301) has able to sustained the release of drug up to 24 hours. Thus it will ultimately help to increase the patient compliance as the dosing frequency of pregabalin is thrice a day which will reduce to once a day.

KEYWORDS: Pregabalin, PEO WSR 303, PEO WSR 301, sustained release.

INTRODUCTION[1-5]

Greater attention has been focused on development of sustained or controlled release drug delivery systems with concomitant recognition of the therapeutic advantages of controlled drug delivery. Controlled drug delivery systems have been introduced to overwhelm the drawback of fluctuating drug levels associated with conventional dosage forms. A sustained release system delivers the active agent at slower rate than the conventional dosage form but the release is substantially affected by external environment. Their are various ways to

sustained the release of drug out of which the most convenient way is sustained released matrix formulation.

Pregabalin is a structural analogue of gabapentin which is used in many treatments but especially it is used for neurologic pain. It is administered 150 mg in three divided dose per day. Thus it is a suitable candidate for making a sustained release tablet. Polyethylene oxide which are also known as Polyox are the hydrophilic polymer. These are available in various grades. Out of these PEO WSR 303, PEO WSR 301 are used for current work.

MATERIALS AND METHOD

Pregabalin was obtained as a gift sample from DANA Pharmaceuticals Pvt.Ltd, Ambarnath, India and all other excipients used were of analytical grade

METHODS

FORMULATION [6-12]

The matrix tablets of Pregabalin were prepared by using 3^2 factorial design. All the ingredients were accurately weighed and passed through mesh 60#.In order to mix the ingredients thoroughly drug & polymer were blended geometrically in a mortar and pestle for 15 minutes then magnesium Stearate, MCC, talc and PVP K30 were mixed one by one. After thoroughly mixing the ingredients, the powder blend was passed through 44# sieve and compressed on rotary tablet punching machine.

Table 1: Formulation table

Materials (mg)	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**
Pregabalin	150	150	150	150	150	150	150	150	150
Polyox WSR 303	60	60	60	80	80	80	100	100	100
Polyox WSR 301	60	80	100	60	80	100	60	80	100
MCC	98	78	58	78	58	38	58	38	18
PVP K30	20	20	20	20	20	20	20	20	20
Magnesium Stearate	8	8	8	8	8	8	8	8	8
Talc	4	4	4	4	4	4	4	4	4
Tablet Weight(mg)	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

EVALUATION PARAMETERS[13-18]

Pre compression parameters

All the formulations were evaluated for their pre compression parameters like bulk density, tapped density, compressibility index, hausner's ratio and angle of repose.

Post compression parameters

Hardness

The hardness of the tablets was determined using Monsanto hardness tester in terms of kg/cm^2. Average hardness of three tablets was taken to study the reproducibility.

Friability

Six tablets from each were exposed to Roche friability test apparatus for 100 rotations and percentage loss in weight was measured against initial weight

% Friability (F) = $\{1-(W/W_0)\}$ X 100

Where, W0= Initial weight of tablet

W = Weight of tablets after the test

Uniformity of weight

20 tablets were selected at random from each formulated batch to check the uniformity of weight using electronic balance. Average weight and maximum percent deviation (Positive and negative) were determined.

Drug Content

Ten Tablets were weighed and average weight was calculated. All the 10 tablets were crushed in a mortar. The powder equivalent to 10 mg was accurately weighed, dissolved in 0.1 N HCl & made up to 100ml of 0.1 N HCl. The volumetric flask was then shaken for approximately 20 minutes. The solution was filtered and 1 ml of filtrate was diluted to 10ml using 0.1 N HCl. Absorbance was measured at 210 nm using 0.1 N HCl as a blank. The amount of drug present in one tablet was calculated.

In-Vitro Drug Release Study

The test was performed on the prepared pregabalin tablets using the USP dissolution apparatus II. Six individual tablets from each formula were tested. Test was performed in 900 ml of 0.1 N HCl for two hours and then in phosphate buffer 6.8. In all studies, the temperature of the dissolution medium was maintained at 37 ± 0.5^0C.The Aliquots of 5 ml were withdrawn at regular intervals, filtered and analyzed spectrophotometrically at 210 nm.

RESULT AND DISCUSSION

Table 2: Precompression studies for C1 to C9

Formulation	Bulk density (gm/cm^3)	Tap density (g/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
C1	0.27±0.0021	0.33±0.0024	18.1±0.14	1.22±0.010	28.44±0.24
C2	0.29±0.0027	0.34±0.0017	14.7±0.12	1.17±0.011	29.39±0.19
C3	0.30±0.0023	0.36±0.0015	16.6±0.09	1.20±0.004	27.71±0.24
C4	0.32±0.0028	0.37±0.0090	13.5±0.05	1.15±0.010	30.61±0.27
C5	0.31±0.0011	0.36±0.0012	13.8±0.12	1.16±0.011	28.59±0.18
C6	0.32±0.0012	0.38±0.0027	15.7±0.13	1.18±0.009	31.28±0.15
C7	0.29±0.0016	0.35±0.0016	17.1±0.16	1.20±0.005	33.14±0.26
C8	0.30±0.0070	0.34±0.0070	11.7±0.09	1.13±0.010	30.55±0.21
C9	0.31±0.0013	0.36±0.0080	13.8±0.11	1.16±0.007	32.56±0.31

The angle of repose for all the 9 batches from C1 to C9 is in the range of 27.71±0.24 to 33.14±0.26 and the Carr's index was found within the range of 11.7±0.09% to 18.1±0.14%, while all the batches he Hausner's ratio in the range of 1.13±0.010 to 1.22±0.010.

Thus as per the readings obtained it shows that the powder mixture of all the batches shows a moderate to good flow property.

Post Compression Parameters

Table 3: Post compression Parameters of C1 to C9

Form.	Hardness (kg/cm^2) Mean (n=3)	Weight variation (mg) (n=20)	% Friability (n=6)	Drug Content (%) (n = 10)
C1	5.6±0.011	396.85±1.1	0.41	99.33±0.47
C2	5.8±0.024	401.22±1.4	0.37	97.47±0.57
C3	6.0±0.018	397.79±2.0	0.24	98.85±0.64
C4	5.7±0.015	399.82±2.2	0.28	98.46±0.29
C5	6.1±0.008	401.36±1.7	0.48	97.47±0.50
C6	5.6±0.042	397.98±3.1	0.50	97.43±0.58
C7	5.9±0.025	402.18±2.6	0.49	100.86±0.44
C8	6.5±0.053	400.27±1.3	0.47	99.11±0.54
C9	6.3±0.034	398.64±2.4	0.43	97.51±0.54

After compression of the batches with combination of polymers all the 9 batches shows an acceptable range of hardness, friability that is 5.6 to 6.5 kg/cm^2 hardness and for friability is 0.24 to 0.50 %.

The Uniformity of weight of tablet ranges from 396.85±1.1 to 402.18±2.6 with an acceptable standard deviation.

The % drug content ranges from 97.43±0.58 to 100.86±0.44

In Vitro Dissolution Studies

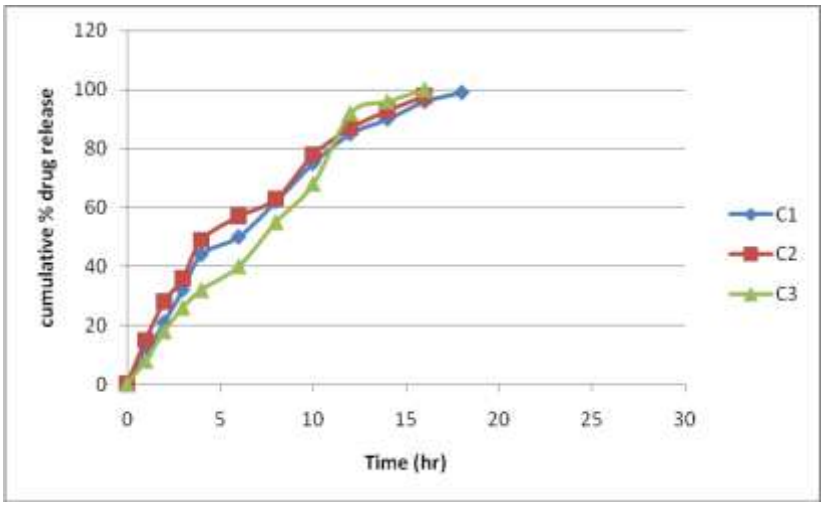

Fig. 1: A Plot of % CDR Vs time of batch for C1 to C3

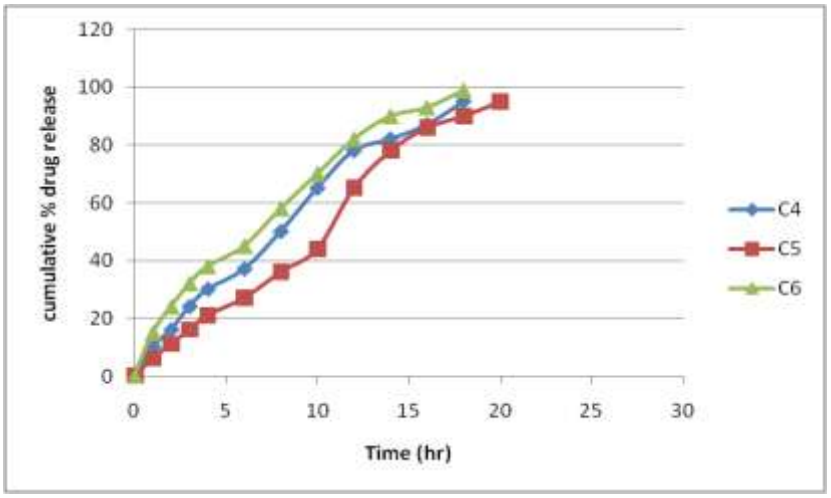

Fig. 2: A Plot of % CDR Vs time of batch for C4 to C6

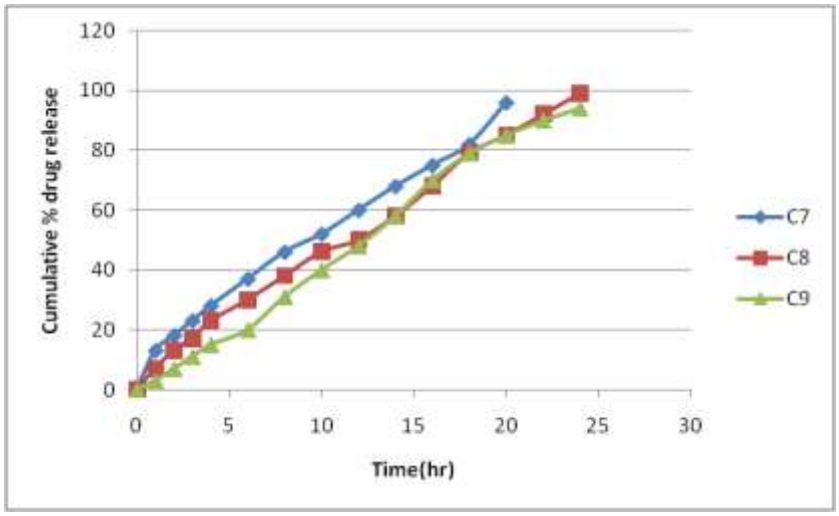

Fig. 3: A Plot of % CDR Vs time of batch for optimization C7 to C9

After the formulation of the batches with combination of polymers they are incorporated to the in vitro dissolution studies and are tested upto 24 hours. All the batches are able to sustained the release of drug for minimum upto 16 hours and maximum upto 24 hours. The batch C1, C2 and C3 was able to release the drug upto 18, 16, 16 hours and the percent of drug release was 99%, 97%, 98%. In these batches the concentration of PEO303 was kept fixed 50 mg and the concentration of the PEO301 was kept in increasing order 50, 60 and 70 mg. Thus it shows that with increase in concentration of PEO301 which is less viscous polymer the time of drug release decreases. The other formulations that is C4 to C6 PEO303 was taken 60mg and for batches C7 to C9 was taken 70mg and again the concentration of PEO301 was taken in increasing order that is 50, 60 and 70mg. From all the above batches C7 was able to release 100% drug but the time of sustaining the drug was upto 20 hours. While the formulation C8 and C9 was able to release drug upto 24 hours but C8 gives 99% drug release and C9 gives 97% drug release. Thus C8 was chosen as an optimized batch and further studies were carried out on it.

Surface Response Data

A. Response 1 : % CDR at 12th hr (Hours)

Analysis of Variance Table(Partial Sum of Squares III)

Table 4 : ANOVA For Response surface Quadretic Full Model

Source	Sum of Squares	Df	Mean square	F value	p-value prob>F	
Model	1879.56	5	375.91	957.08	< 0.0001	Significant
A -polyox WSR 303(%)	1702.86	1	1702.86	4335.52	*< 0.0001*	Significant
B - polyox WSR 301(%)	33.28	1	33.28	84.72	*0.0027*	Significant
AB	3.78	1	3.78	9.63	*0.0532*	
A^2	127.68	1	127.68	325.08	*0.0004*	Significant
B^2	11.96	1	11.96	30.44	*0.0117*	Significant
Residual	1.18	3	0.39			
Core total	1880.73	8				

The Model F-value of 957.08 implies the model is significant. There is only a 0.01% chance that a model F-value this large could occur due to noise. Values of "Probe > F" less than 0.0500 indicate model terms are significant. In this case A, B, AB, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

Final Equation in terms of coded Factors.

R1 (%CDR at 12 hrs) = +78.06 -16.85* A +2.35* B -0.97* AB -7.99* A^2 +2.44* B^2

Final Equation in Terms of Actual Factors:

12 hrs) = +78.06 -16.85* Polyox WSR 303+2.35* Polyox WSR 301-0.97* Polyox WSR 303* Polyox WSR 301-7.99* Polyox WSR 303$_2$+2.44* Polyox WSR 301$_2$

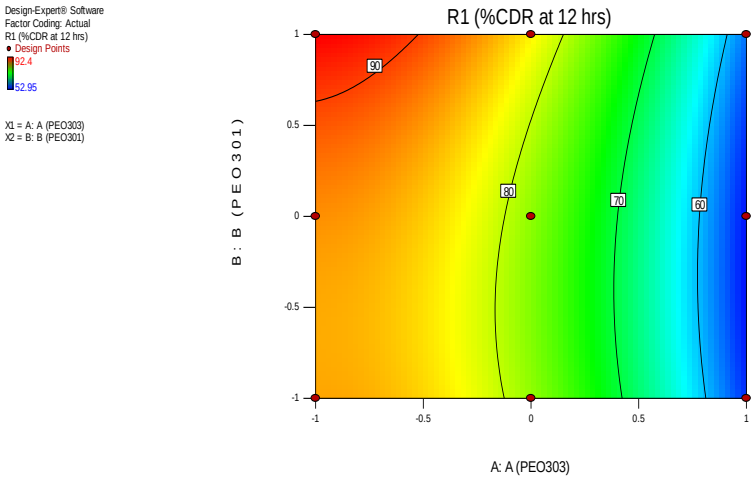

Fig. 4: Contour plot showing the effect of Polyox WSR 303 & Polyox WSR 301 on % CDR at 12th hr (Hours)

As seen from the, contour plot of the % CDR at 12th hour revealed that there was corresponding decrease in % CDR with increase in the concentration of Polyox WSR 303(A). Moreover it was revealed that increase in concentration of Polyox WSR 301(B) also led to decrease in %CDR. Thus combination of both in suitable concentration might decrease the rate of release of drug of the Sustained release tablets.

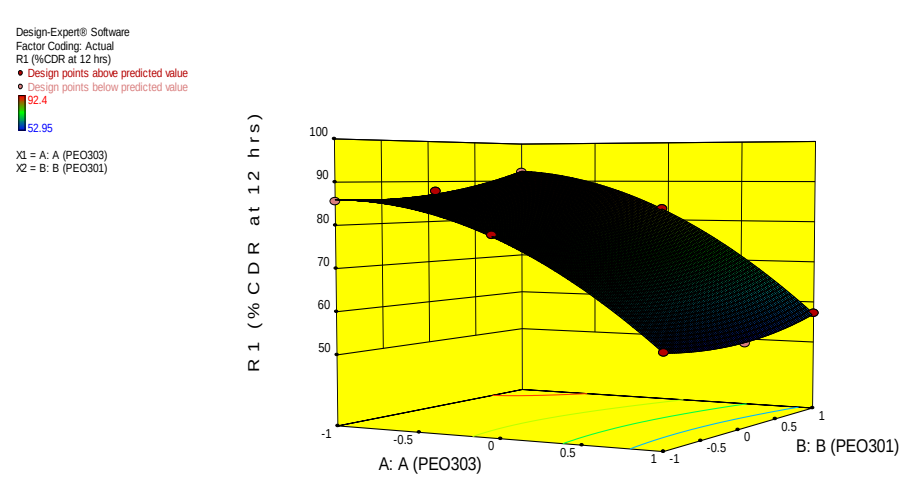

Fig. 5: Response surface plot (3D) showing the effect of Polyox WSR 303 & Polyox WSR 301 on %CDR at 12th hour

B. Response 2 : % CDR at 16th hour

Analysis of Variance Table(Partial Sum of Squares III)

Table 5 : ANOVA For Response surface Quadretic Full Model (% CDR at 16th hour)

Source	Sum of Squares	Df	Mean square	F value	p-value prob>F	
Model	1380.00	5	276.00	58.04	0.0035	Significant
A -polyox WSR 303(%)	1289.79	1	1289.79	271.24	0.0005	Significant
B -polyox WSR 301(%)	16.43	1	16.43	3.46	0.1600	
AB	2.82	1	2.82	0.59	0.4972	
A^2	56.36	1	56.36	11.85	0.0412	Significant
B^2	14.60	1	14.60	3.07	0.1780	
Residual	14.27	3	4.76			
Core total	1394.26	8				

The Model F-value of 58.04 implies the model is significant. There is only a 0.35 % chance that a model F-value this large could occur due to noise. Values of "Probe > F" less than 0.0500 indicate model terms are significant. In this case A, B, AB, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

Final Equation in terms of coded Factors:

% CDR at 16th hour = +87.10-14.66*A+1.66* B-0.84* A*B-5.31*A^2+2.70* B^2

Final Equation in Terms of Actual Factors:

% CDR at 16th hour = +87.10-14.66*Polyox WSR 303+1.66* Polyox WSR 301-0.84* Polyox WSR 303* Polyox WSR 301-5.31* Polyox WSR 303^2+2.70* Polyox WSR 301^2

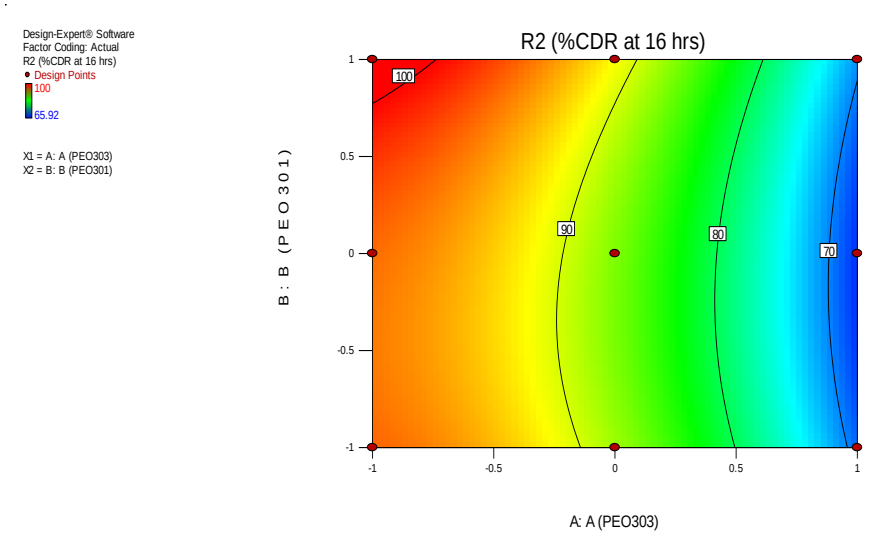

Fig. 6: Contour plot showing effect of Polyox WSR 303 & Polyox WSR 301 on % CDR at 16th hour

As seen from the figure contour plot of % CDR at 12th hour revealed that there was corresponding decrease in % CDR at 16th hour with increase in the concentration of Polyox WSR303 & Polyox WSR301. Thus combination of both in suitable Concentration might sustain the % CDR of the sustained release tablet for 24 hours.

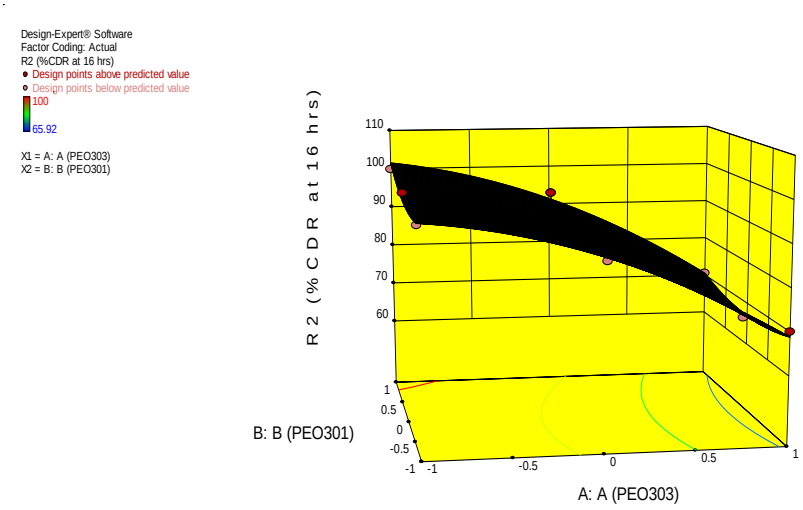

Fig. 7: Response surface plot (3D) showing the effect of Polyox WSR 303 & Polyox WSR 303 on % CDR at 16th hour

CONCLUSION

In the present study the attempt was made to formulate the sustained release matrix tablet of pregabalin using polymer of Polyox family i.e. PEO WSR 303 and PEO WSR 301. The tablets were formulated using the direct compression technique and the compressed tablets were evaluated for hardness, friability, drug content and in-vitro drug release study. All the tablets formed give the satisfactory results for hardness, friability, weight variation test and drug content. But only C8 batch give the satisfactory results for the drug release upto 24 hrs. Therefore it is proved that the Polyox polymer is capable of sustaining the release of the drug for 24 hrs and due to which the tablet dosing can be reduce.

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