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FORMULATION AND EVALUATION OF PREGABALIN PULSATILE DRUG DELIVERY SYSTEM

Dr. Rama Bobba, Narala Varsha *, l. Jyothi rani, k. Sudhamani, H. Ramana

[1] Department Of Pharmaceutics, Malla Reddy Institute Of Pharmaceutical Sciences, Malla Reddy Vishwavidyapeeth, Maisammaguda, Dhulapally, Post Kompally, Medchal Mandal, Secunderabad-500 100

Abstract:

The present research was undertaken to formulate and evaluate a pulsatile drug delivery system of Pregabalin with the objective of providing time-controlled drug release in synchronization with the circadian rhythm of neuropathic pain. Pregabalin, an antiepileptic and analgesic agent, requires controlled release to improve therapeutic efficacy, reduce side effects, and enhance patient compliance. In this study, various polymers were employed to develop core and coating layers that could modulate the lag time followed by a rapid release of the drug.

The prepared formulations were evaluated for pre-compression and post-compression parameters, which were found to be within pharmacopeial limits. In vitro drug release studies revealed that the optimized formulation provided a desirable lag phase, followed by a rapid and complete release of Pregabalin, thereby meeting the criteria for pulsatile delivery.

The results suggest that a pulsatile drug delivery system of Pregabalin offers a promising approach for chronotherapeutic management of neuropathic pain and related disorders, ensuring improved drug release behaviour, better patient compliance, and therapeutic effectiveness compared to conventional dosage forms.

***Keywords**: Pregabalin, Pulsatile Drug Delivery System*

Corresponding author:

Narala Varsha*

Department of Pharmaceutics,
Malla Reddy institute of pharmaceutical sciences,
Secunderabad, Telangana.
Email Id- varshapatel1829@gmail.com

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INTRODUCTION:

Pulsatile drug delivery system (PDDS) can be defined as a system where drug is released suddenly after a well-defined lag time according to the circadian rhythm of the disease. PDDS can be classified according to the pulse regulation of drug release into three main classes; time-controlled pulsatile release (single or multiple unit system), internal stimuli induced release and external stimuli-induced pulsatile release systems. PDDS can also be classified according to the dosage form into three main types; capsules, pellets and tablets among which the 'core-in-cup' tablet system. The core-in-cup tablet system consists of three different parts: a core tablet, containing the active ingredient, an impermeable outer shell and a top cover plug layer of a soluble polymer.[8]

In the field of oral delivery, besides a widespread use of pro-longed-release dosage forms increasing interest has been focused on the development of formulations able to release active pharmaceutical ingredients after programmed lag times or to specific regions of the gastrointestinal (GI) tract. The time dependent approach, in particular, is based on the relatively constant small intestinal transit time (SITT; 3 ± 1 h standard error) of dosage forms.[9]

On the contrary, the duration of gastric residence of solid dosage forms, which depends on their size and density as well as fasted or fed conditions of subjects, is unpredictable; hence, by the application of an outer gastro resistant layer, which dissolves only after the dosage form is emptied from the stomach, the influence of variable gastric emptying can be overcome. Subsequently, a lag phase imparted to the drug containing core allows the system to reach delay duration comparable to SITT. The goal of chronotherapeutic is to synchronize the timing of treatment with the intrinsic timing of illness. Theoretically, optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ at the most appropriate time. In contrast, many side effects can be minimized if a drug is not given when it is not needed. Unlike homeostatic formulations, which provide relatively constant plasma drug levels over 24 hours, chronotherapeutic formulations may use various release mechanisms. e.g., time-delay coatings (Covera-HSTM), osmotic pump mechanisms (COER-24TM), and matrix systems (GeminexTM), that provide for varying levels throughout the major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome. The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets and capsules. In most cases, however, special drug delivery technology must be relied upon to synchronize drug concentrations to rhythms in disease activity.[16,17]

Advantages of pulsatile delivery

- ✓ Extended daytime or night time activity.
- ✓ Reduced side effects
- ✓ Dosage frequency.
- ✓ Reduction in dose size.
- ✓ Improved patient compliance.
- ✓ Lower daily cost to patient due to fever dosage units are required
- ✓ Drug adapts to suit circadian rhythms of body functions or diseases.
- ✓ Drug targeting to specific sites like colon.
- ✓ Protection of mucosa from irritating drugs.
- ✓ Drug loss is prevented by extensive first pass metabolism.

Drawbacks of pulsatile delivery

- ✓ Lack of manufacturing reproducibility and efficacy
- ✓ Large number of process variables.
- ✓ Multiple formulation steps.
- ✓ Higher cost of production.
- ✓ Need of advanced technology.
- ✓ Trained/skilled personal needed for manufacturing.[18]

MATERIALS

Pregabalin Procured from Dana pharmaceuticals Pvt.Ltd, Ambarnath, Provided by SURA LABS, Dilsukhnagar
Sodium Starch Glycolate S.D. Fine chemicals limited (Hyderabad)
Mannitol S.D. Fine chemicals limited (Hyderabad)
PVP K 30 S.D. Fine chemicals limited (Hyderabad)
Sodium Stearyl Fumerate S.D. Fine chemicals limited (Hyderabad)
Aerosil S.D. Fine chemicals limited (Hyderabad)
Weighing Balance Sartourious
Tablet Compression Machine (Multistation) Lab press
Limited, India.
Hardness tester Monsanto, Mumbai, India.
Vernier callipers Mitutoyo, Japan.
Roche Friabilator Lab India, Mumbai, India
Dissolution Apparatus Lab India, Mumbai, India
UV-Visible Spectrophotometer Lab India, Mumbai, India
pH meter Lab India, Mumbai, India
FT-IR Spectrophotometer Bruker, Germany

METHODOLOGY

Analytical method development:

a) Preparation of calibration curve in 0.1N HCL:

10mg of Pregabalin pure drug was dissolved in 10 ml of methanol (stock solution 1). 1ml of solution

was taken and makes up with10 ml of 0.1N HCL (100µg/ml) stock-2. From this 1ml was taken and make up with 10 ml of 0.1N HCL (10µg/ml) stock-3. The above stock-II solution was subsequently diluted with 0.1N HCL to obtain series of dilutions containing and 2,4,6,8 and 10µg/ml of solution. The absorbance of the above dilutions was measured at 276 nm for 0.1 N HCL by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The Same procedure repeated in pH 6.8 phosphate buffer.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The solid powder sample directly place on yellow crystal which was made up of ZnS. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-1}.

Formulation development of Tablets:

Formulation of core tablets by direct compression: The inner core tablets were prepared by using direct compression method as shown in the Table. Powder mixtures of Pregabalin, microcrystalline cellulose, Sodium Starch Glycolate, Aerosil ingredients were dry blended for 20 min. followed by addition of Sodium Stearyl Fumerate. The mixtures were then further blended for 10 min., 300 mg of resultant powder blend was manually compressed using , Lab press Limited, India with a 9 mm punch and die to obtain the core tablet.

Formulation of mixed blend for barrier layer: The various formulation compositions containing Ethyl cellulose and HPMC K100M, Sodium Stearyl Fumerate, Aerosil and Microcrystalline Cellulose. Different compositions were weighed dry blended at about 10 min. and used as press coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Preparation of press-coated tablets: The core tablets were press-coated with 450 mg of mixed blend as given in Table. No. 7.2 450 mg of barrier layer material was weighed and transferred into a 10 mm die then the core tablet was placed manually at the center. The remaining of the barrier layer materiel was added into the die and compressed by using Lab press Limited, India

Table 7.1: Formulation development of core tablets

Ingredients	C1	C2	C3
Pregabalin	150	150	150
Sodium Starch Glycolate	25	50	75
Mannitol	101	76	51
PVP K 30	15	15	15
Sodium Stearyl Fumerate	6	6	6
Aerosil	3	3	3
Total weight	300	300	300

Table 7.2: Formulations for press coated tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core Tablet	300	300	300	300	300	300	300	300	300
Dammar gum	50	75	100	-	-	-	-	-	-
Guar Gum	-	-	-	50	75	100	-	-	-
Xanthan Gum	-	-	-	-	-	-	50	75	100
Sodium Stearyl Fumerate	3	3	3	3	3	3	3	3	3
Mannitol	95	70	45	95	70	45	95	70	45
Aerosil	2	2	2	2	2	2	2	2	2
Total weight	450	450	450	450	450	450	450	450	450

***In* vitro drug release study of pulsatile Pregabalin tablets**

***In vitro* drug release of Pregabalin core tablets**

In vitro dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus. pH 6.8 phosphate buffer was used as dissolution medium. Release pattern was studied visually by taking sample of 5 mL at the specific time intervals. Also, the sample was analyzed at 276 nm for 6.8 phosphate buffer using a UV spectrophotometer.

***In vitro* drug release study of coated tablets**

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCL was removed and pH 6.8 phosphate buffer was added process was continued from up to 8 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 276 nm using UV-spectrophotometer.

RESULTS AND DISCUSSION:

Table 8.1: Calibration data of Pregabalin in **0.1N HCL**

Concentration [µg/ml]	Absorbance
0	0
2	0.162
4	0.349
6	0.527
8	0.703
10	0.881

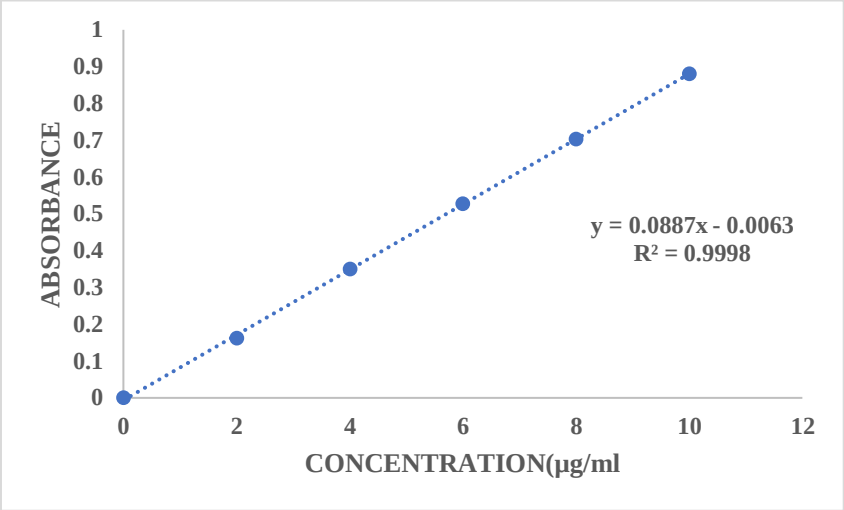

Fig:8.1: Standard Graph of Pregabalin in **0.1N HCL**

Standard graph of Pregabalin in **phosphate buffer (pH 6.8)**

Pregabalin showed maximum absorbance in phosphate buffer (pH 6.8) at 276 nm. The solution obeyed Beer-Lambert's law for concentration range of 2 to 10 µg / mL with regression coefficient of 0.999. Standard curve of prepared Pregabalin in phosphate buffer pH 6.8 is shown below.

Table 8.2: Calibration data of Pregabalin in **pH 6.8 phosphate buffer**

Concentration [µg/ml]	Absorbance
0	0
2	0.166
4	0.324
6	0.507
8	0.674
10	0.848

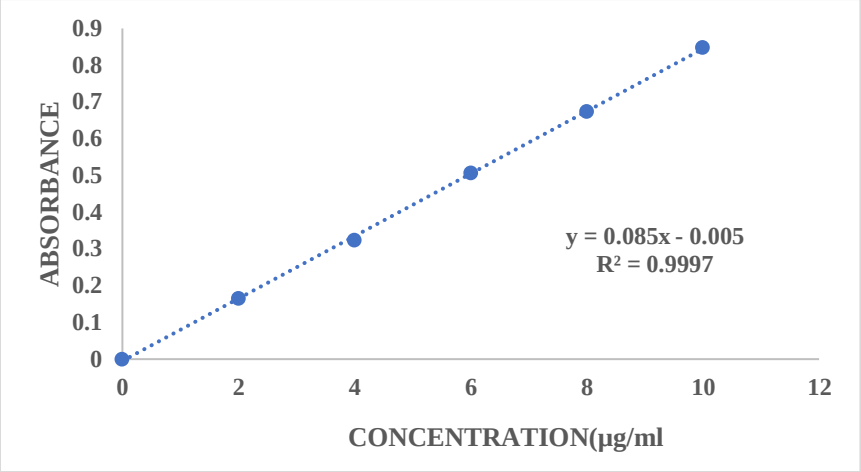

Fig: 8.2: Standard Graph of Pregabalin in **pH 6.8 phosphate buffer**

8.3: FT-IR (Fourier Transform Infrared Spectrophotometry)

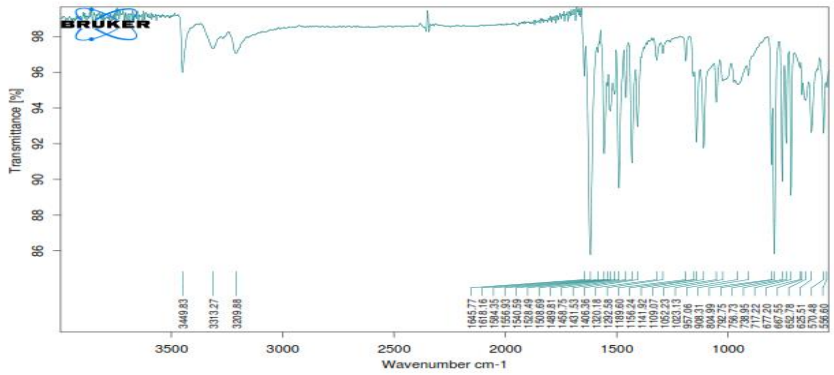

Fig.:8.3. FTIR spectra of Pregabalin pure **drug**

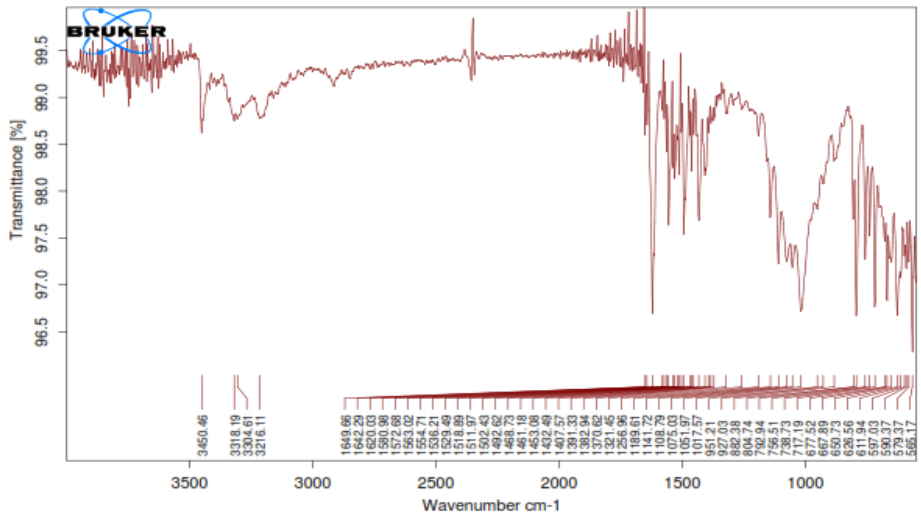

Fig: 8. 4. FTIR spectra of Optimized Formula

The spectra for pure Pregabalin and for the physical mixture of Pregabalin and all the polymers were determined to check the intactness of the drug in the polymer mixture using FTIR Spectrophotometer.

The comparative FTIR studies of Drug and excipients combination had shown negligible variation in the values as compared with that of only pure form of Drug. Therefore, it implies good compatibility of drug and excipients.

From the above table, the wave number of mixture of drug with excipients is within the range of wave number of pure drug. This implies that the excipients are compatible with the drug since their combination did not alter the functional groups of pure drug

Table 8.3: Pre compression parameters of Cap core tablets

Formulation Code	Angle of repose (o) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
C1	27.49	0.35	0.39	11.25	1.12
C2	28.22	0.34	0.39	14.51	1.16
C3	29.33	0.35	0.39	14.41	1.15

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.34 to 0.35 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.38 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 11.25 to 14.51which were showed that the powder has good flow properties. All the formulations have shown the Hausner ratio ranging from 0 to 1.15 indicating the powder has good flow properties.

Table 8.4: Post compression parameters of Core tablet:

Formulation code	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In vitro* disintegration time (min)
C1	298.21	2.31	0.42	2.24	99.18	10
C2	300.82	2.52	0.19	2.53	98.27	15
C3	300.76	2.43	0.22	2.39	99.33	18

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits

Weight variation and thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 8.4. The average tablet weight of all the formulations was found to be between 298.21to 300.82. The maximum allowed percentage weight variation for tablets weighing <300 mg is 10% and no formulations are not exceeding this limit. Thus, all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 2.24 to 2.53.

Hardness and friability: All the formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table 8.4. The average hardness for all the formulations was found to be between (2.31– 2.52) Kg/cm^2 which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator and the results were shown in table 8.4. The average percentage friability for all the formulations was between 0.18-0.24 which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 8.4. The drug content values for all the formulations were found to be in the range of 98.27 **to** 99.33. According to IP standards the tablets

must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the formulations comply with the standards given in IP.

***In vitro* disintegrating time:** All the formulations were evaluated for *in vitro* disintegration time according to the procedure described in methodology section and the results were shown in table 8.4. The *in vitro* disintegration time values for all the formulations were found to be in the range of 10 to 18.

Table 8.5: Pre compression Parameters of Pregabalin coated Tablets

Formulation code	Angle of repose (o) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	17.10	0.318	0.38	16.31	1.19
F2	28.97	0.342	0.4	15.0	1.176
F3	18.19	0.34	0.43	20.93	1.26
F4	22.61	0.36	0.42	14.28	1.16
F5	26.56	0.33	0.41	19.06	1.24
F6	23.10	0.33	0.42	22.35	1.28
F7	19.85	0.33	0.41	19.51	1.24
F8	21.80	0.32	0.42	24.70	1.32
F9	17.74	0.33	0.4	17.5	1.21

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.32 – 0.342 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.4- 0.43 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 14 to 24 which show that the powder has good flow properties. All the formulations have shown the Hausner ratio ranging between 0.16 to 0.176 indicating the powder has good flow properties.

Table 8.6: Post compression parameters of Coated tablet:

Formulation code	Average Weight (mg)	Hardness (kg/cm2)	Thickness	Friability (%loss)	Drug content (%)
F1	451.82±0.13	4.83±0.22	3.13±0.79	0.55±0.29	99.29
F2	449.63±0.96	4.67±0.52	3.68±0.65	0.24±0.35	98.21
F3	448.89±0.75	4.11±0.96	3.86±0.49	0.48±0.95	99.37
F4	450.75±0.65	4.17±0.47	3.46±0.33	0.62±0.48	100.01
F5	447.84±0.38	4.78±0.38	3.99±0.18	0.45±0.86	97.24
F6	449.16±0.66	4.63±0.56	3.13±0. 96	0.51±0.25	99.53
F7	448.83±0.34	4.95±0.49	3.45±0. 82	0.39±0.96	98.76
F8	450.37±0.77	4.82±0.73	3.88±0.98	0.32±0.82	99.14
F9	448.86±0.85	4.18±0.22	3.19±0.76	0.46±0.77	99.72

8.5 Post compression parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Weight variation and thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 8.6. The average tablet weight of all the formulations was found to be between 447.84±0.38 to 451.82±0.13. The maximum allowed percentage weight variation for tablets weighing >450 mg is 5% and no formulations are not exceeding this limit. Thus, all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 3.13±0.79 to 3.99±0.18.

Hardness and friability: All the formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table. The average hardness for all the formulations was found to be from 4.11±0.96 to 4.11±0.96 Kg/cm^2 which were found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator and the results were shown in table. The average percentage friability for all the formulations was between 0.24±0.35 - 0.55±0.29 which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 8.6. The drug content values for all the formulations were found to be in the range of **(**97.24to 100.01**).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the formulations comply with the standards given in IP.

***In Vitro* Drug Release Studies of Pregabalin core tablet:**

In vitro dissolution studies of Pregabalin core tablets were performed using USP XXIII Type II rotating paddle dissolution apparatus by using phosphate buffer (pH 6.8) as a dissolution medium. From formulation C1-C3 Pregabalin core tablets, C2 showed faster drug release than the other formulations. Faster drug release can be correlated with the high disintegration time. So, C2 formulation was selected as best formulation for further press coating and enteric coating formulations. *In vitro* drug release profiles of all Pregabalin core tablets were shown in Table 8.7 and Figure.8.5.

Table 8.7. Drug release of Pregabalin core **tablets**

Time (min)	C1	C2	C3
0	0	0	0
5	13.28	18.89	11.89
10	22.08	36.84	26.41
15	38.14	56.59	38.89
20	68.76	83.13	59.92
30	92.22	97.88	93.35
45	95.65	98.68	97.67
60	97.29	99.77	98.29

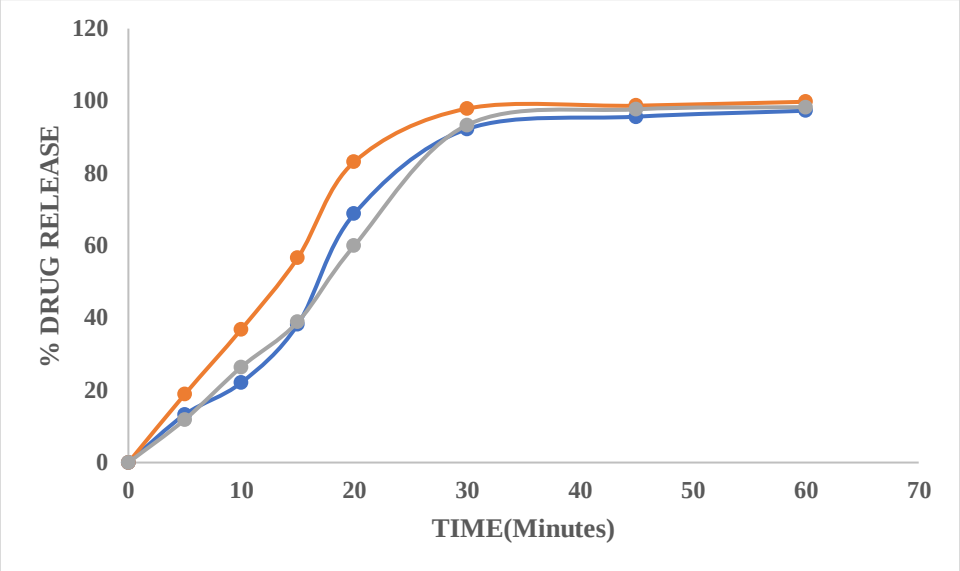

Fig 8.5 Cumulative % drug released of Pregabalin core **tablets**

***In vitro* drug release study of Pregabalin** pulsatile **tablets**

Based on the above characters formulation C2 was selected as best formulation and that C2 formulation were used for the further study i.e., delayed release using press coated method. The time dependent pulsatile tablets were prepared by using different concentrations of Dammar gum. The formulations C1, C2, and C3 showed maximum drug release at immediately.

Table 8.8: Cumulative % drug Release of Coated Pregabalin Tablets **containing Dammar gum**

Time(hr)	F1	F2	F3
0	0	0	0
0.5	10.14	08.31	5.12
1	20.81	18.29	15.22
2	25.52	22.12	24.34
3	38.45	35.92	38.86
4	45.33	42.81	40.23
5	58.74	51.27	44.63
6	64.38	61.13	48.75
7	69.22	70.43	52.82
8	72.08	78.84	61.08
9	77.12	88.86	66.52
10	83.31	90.46	74.13
11	93.65	95.33	85.29
12	97.37		96.54

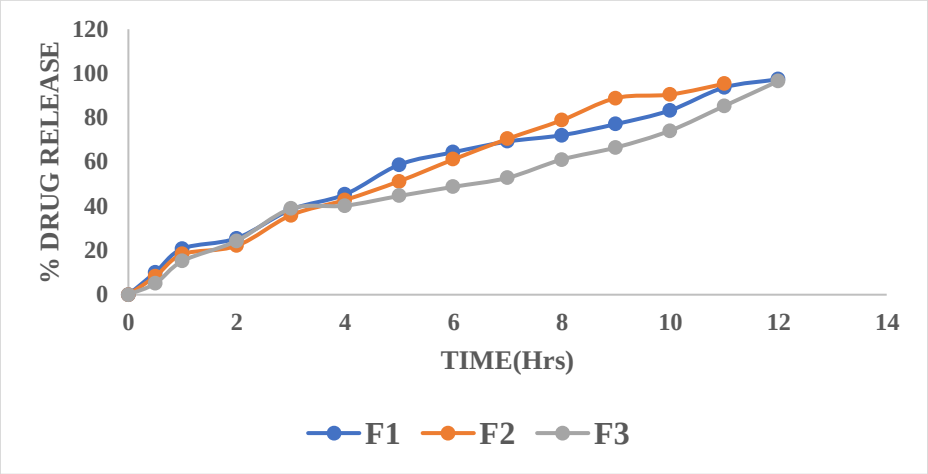

Fig: 8.6: Cumulative % drug release study of Pregabalin pulsatile **tablets (F1, F2 & F3)**

The formulations F1 to F3 were containing Dammar gum. At low concentration such as 50, 75, 100 mg of Dammar gum was unable to delay the drug release hence that formulations were not considered. Then the coating polymer concentration was increased to 60%, it was showed maximum % drug release 97.37% at 12 hours and lag phase was 6 hours. Among 3 formulations F1 was showed good result and consider as optimized.

Table 8.9: Cumulative % drug Release of Coated Pregabalin Tablets containing Guar Gum

Time (Hr)	F4	F5	F6
0	0	0	0
0.5	10.82	0.21	0.11
1	22.65	5.91	0.71
2	38.81	10.59	3.53
3	41.43	17.21	15.83
4	86.71	25.32	30.38
5	91.16	33.22	47.93
6	99.67	48.51	55.77
7		53.25	62.38
8		69.08	65.12
9		76.97	75.21
10		88.34	84.68
11		95.25	91.76
12			96.62

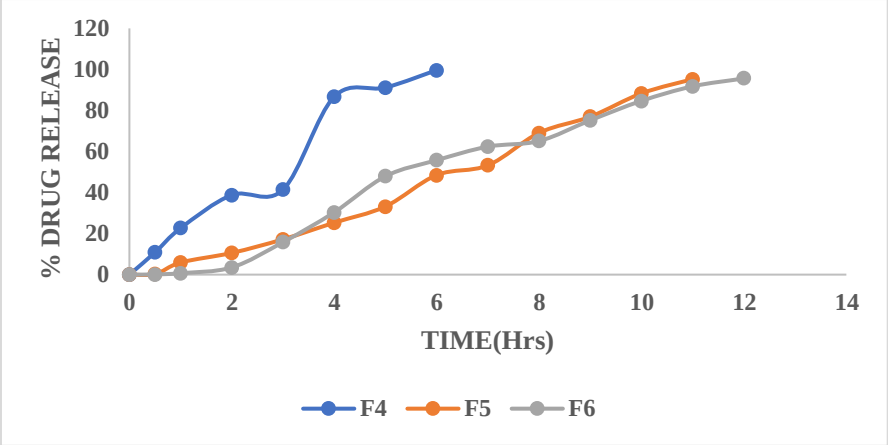

Fig: 7.6: Cumulative % drug release study of Pregabalin pulsatile tablets (F4, F5 & F6)

The formulations F4 to F6 containing different concentrations of Guar Gum, at low concentration of coating material it was not delayed up to desired time the core tablet immediately releases at 2 hr. whenever the coating material concentration was increased to 75 mg the maximum % drug release of core tablet from coated tablet at 11 hrs. So F6 formulation also was not good formulation. Then the coating material concentration was increased to 100 mg it was delayed up to 12 hours then core tablet released up to desired time period i.e., 96.62% at 12 hours.

Table 8.9: Cumulative % drug Release of Coated Pregabalin Tablets containing Xanthan Gum

Time (hr)	F7	F8	F9
0	0	0	0
0.5	0.91	0.61	0.21
1	0.56	8.45	11.45
2	5.96	15.88	18.95
3	17.38	21.47	25.47
4	28.74	36.83	39.83
5	33.39	48.49	45.84
6	39.44	52.39	55.44
7	44.38	61.92	66.92
8	51.92	71.72	76.29
9	64.83	78.83	79.83
10	71.36	84.93	85.93
11	79.22	97.82	95.27
12	92.61		99.85

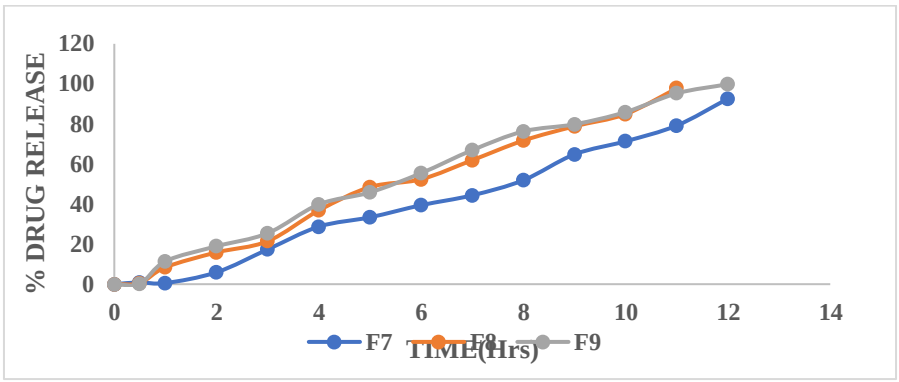

Fig 7.7: Cumulative % drug release study of Pregabalin pulsatile tablets (F7, F8, F9)

The formulations F7 to F9 were containing Xanthan Gum. At low concentration such as 50, 75 mg of Xanthan Gum was unable to delay the drug release up to desired time hence that formulations were not considered. Then the coating polymer concentration was increased to 100 mg F9 was showed maximum % drug release 99.85% at 12 hours and lag phase was 2 hours. Hence F9 Formulation was considered as optimized Formulation.

CONCLUSION:

The present study focused on the formulation and evaluation of a pulsatile drug delivery system of Pregabalin with the aim of achieving time-controlled release to provide therapeutic efficacy in alignment with circadian rhythm of neuropathic pain. Various polymers and excipients were utilized to optimize the lag time and drug release profile. Pre-compression and post-compression parameters of the formulations were found to be within pharmacopeial limits, ensuring good flow properties, uniformity, hardness, and friability. Among the prepared formulations, the optimized batch exhibited the desired lag time followed by a rapid and complete drug release, meeting the criteria for pulsatile delivery.

This system successfully demonstrated the potential to deliver Pregabalin in a controlled and predictable

manner after a programmed lag phase, thereby improving patient compliance and therapeutic outcomes. The study concludes that pulsatile drug delivery of Pregabalin can be a promising approach for chronotherapeutic management of neuropathic pain and related conditions, minimizing dosing frequency and reducing side effects associated with conventional immediate or sustained-release dosage forms.

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