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Development and evaluation of sustained release matrix tablets of pregabalin: A case study based on quality by design to analyze the impact of variables

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Abstract: The current research work describes systematic development of sustained release matrix tablets of a hydrophilic drug, pregabalin, using employing rational blend of hydrophilic polymers such as polyoxyethylene and carbomer as the release controlling polymers. As per the QbD-based approach, the patient-centric quality target product profile was defined and critical quality attributes were earmarked. Preliminary studies were conducted for screening the formulation and process variables. Systematic optimization of the highly critical and influential formulation variables were optimized with the help of an orthogonal experimental design. The impact of independent factors such as the amount of polyvinyl pyrrolidone, polyethylene oxide and carbomer 971P was optimized on *in vitro* drug release parameters at different time points as the dependent factors. The optimized tablet formulation was subjected to film coating with opadry color concentrate with the help of standard pan coating process. Further, the process optimization was performed for evaluating the impact of key process parameters on the quality attributes of the drug product. Overall, the study indicated successful development of the sustained release tablet formulation of pregabalin using hydrophilic polymers, where experimental design use provides significantly benefit in the product and process understanding.

Keywords: Drug delivery, sustained release tablets, solubility, drug release, pharmacokinetics.

INTRODUCTION

Pregabalin is a gabapentinoid and acts by inhibiting certain calcium channels. It was approved for medical use in the United States in 2004for the treatment of epilepsy, anxiety, diabetes and shingles. Pregabalin, sold under the brand name LYRICA® CR (Pfizer Inc., USA) and each sustained-release tablet contains 330mg of the drug.

As a BCS class drug with good water solubility and permeability characteristics, pregabalin is rapidly absorbed following oral administration, with peak plasma concentrations occurring between 0.7 and 1.3 hours (Cook *et al*., 2008). Oral bioavailability is approximately 90% and is independent of dose and frequency of administration. The elimination half-life is approximately 6 hours and steady state is achieved within 1 to 2 days of repeated administration.

At present, there are literature reports on the process of pregabalin sustained release tablets: Hydroxylpropyl methylcellulose (HPMC K-100), Polyvinylpyrrolidone (PVP K-30) and microcrystalline cellulose (MCC 101 and MCC 102) were obtained by direct compression. However, floatability, an important index for evaluation of sustained-release preparations, was not studied in this literature and its sustained-release duration was 12 hours. The study in this paper, a controlled release matrix tablet was developed to control drug release according to the characteristics of drug therapy. The sustained release time reached 24 hours, which is expected to achieve once-a-day drug administration control. The need for a controlled-release drug system for effective treatment of pregabalin has also been discussed in the literature (Asghar *et al*., 2018; Lee *et al*., 2020; Morano *et al*., 2019). Meanwhile, the floating time of pregabalin sustained release matrix tablets in this study reached 15.5h, which was close to the reference preparation 16h. The research in this paper is based on the QbD concept of formulation technology research and development, its ultimate goal is to achieve the production of high-quality products, we have carried out sufficient research, obtained a large number of data, the results are consistent with the reference preparation. However, the content reported in the literature does not cover these important points. In view of the available literature reports (Varsha *et al*., 2013), the developed formulation was rationally designed and optimized for controlling the effect of influential variables on the patient-centric critical quality attributes.

The formulation development was work was divided in two stages. In the first stage, the influence of ethyl cellulose, crospovidone, polyoxyethylene and carbomer 971P on CQAs was studied through the preliminary studies and the proportion of the above excipients on the product quality attributes was determined. The second stage involved systematic optimization of the influential variables (i.e., crospovidone, polyoxyethylene 300 and carbomer 971P) with the help of orthogonal array experimental design to obtain a design space (Jain *et al*., 2019). The design space developed at lab scale was

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verified for its reproducibility to provide the robust formulation with desired quality attributes during the scale-up phase (Prasad *et al*., 2020; Nair *et al*., 2017; Hosny *et al*., 2018).

MATERIALS AND METHODS

Pregabalin (Batch No. PRE-A-9-190509) was purchased from the vendor Zhejiang Menovo pharmaceutical, Co., Ltd. Various excipients used in Reference Listed Drug (RLD) were procured for the preparation of controlled release tablet formulation. Ethyl cellulose (Viscocity 10 Cp) was purchased from Nutrition & Biosciences USA 1, LLC, Crospovidone was purchased from Star-Tech& JRS Specialty Products Co. Ltd., USA, polyoxyethylene was purchased from Specialty Products US, LLC, while Carbomer 971P and magnesium stearate was purchased from Lubrizol Advanced Materials Inc. USA and Huzhou Zhan wang Pharmaceutical Co. Ltd., China, respectively. Gastric solution Type film-coated premix (Opadry 85F140030-CN) was purchased from Shanghai Kalekang Coating Technology Co. Ltd., China. All other chemicals and reagents used in the work were of analytical grade.

Quality target product profile (QTPP)

Based on the clinical and pharmacokinetic characteristics of LYRICA® CR, the product label as well as the *in vitro* dissolution and physicochemical characteristics of the drug, to guide the development of the test product that are therapeutically and pharmaceutically equivalent to the RLD (Beg *et al*., 2020).

Critical quality attributes (CQAs)

Critical quality attribute is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality" (Beg *et al*., 2020). The identification of a CQA from the QTPP is based on the severity of harm to a patient should the product fall outside the acceptable range for that attribute (Panigrahi *et al*., 2018; Dev *et al*., 2019; Castillo *et al*., 2019; Thombre *et al*., 2021).

Stage-I: Research and development process

Dissolution method development

The development of dissolution methods is to determine a dissolution method that plays the best role in predicting and referencing pharmacokinetics of preparations so as to allow the evaluation of the production of Pregabalin Sustained-release tablets during development. (Kim *et al*., 2020) It is mainly developed by the pH solubility test, the development of dissolution conditions and the content determination method of dissolution.

PH solubility curve of drug substance

Pregabalin (pKa1=4.2, pKa2=10.6), the solubility analysis of the drug was performed in 0.06N HCl (pH1.2), acetate buffer (pH4.5) and phosphate buffer (pH6.8) to identify the maximal soluble fractions.

Development of dissolution conditions

According to the dissolution determination method of pregabalin sustained-release tablets contained in FDA dissolution database, 900ml of 0.06 N hydrochloric acid solution was used as the dissolution medium, the paddle was used as the device and the rotation speed was 50rpm. The initial development prescription was studied. The results showed good partition. In addition, dissolution of different samples at different conditions and dissolution media were also studied.

Determination of drug content

According to the method of dissolution determination contained in the import registration standard JX2014026, the content determination method was high performance liquid chromatography. According to high performance liquid chromatography (General Principle 0512) (National Pharmacopoeia Committee., 2020); using octadecylsilane bonded silica gel as filler (Kromasil 100 C18 column, 150×4.6 mm, 5μm particle size). The mobile phase mixture contained phosphate buffer (pH 6.5) and acetonitrile (95:5) which was operated at flow rate of 1.2mL/min, column temperature of 40^{o}C and detection wavelength of 210nm. Accurately measured 100μl each of the reference solution and the test solution and inject it into the liquid chromatography instrument. The reference solution is continuously injected 5 times. The relative standard deviation of the peak area is not more than 2.0% and the chromatogram was recorded.

Stage-II: Research and development process

Excipient Compatibility Studies (Tian et al., 2019)

As per the technical guideline for prescription study of chemical drug, compatibility studies were performed. API and excipients were mixed at the ratio such as 1:5 and 20:1 and placed at different temperature (60^{o}C, 40^{o}C), Humidity (90%±5%RH, 25^{o}C) and light conditions (total illumination not less than 1.2×106Lux·hrand near-ultraviolet energy not less than200w·hr/m2).The physical mixture of API and different excipients were weighed in the glass vials and sealed with rubber stoppers. The vials were then exposed to different stress conditions, followed by evaluation of the appearance, assay, related substances and other quality indicators on the initial day 0, followed by day 10 and day 30.

Selection of excipients for formulation development

Based on the results of the drug excipients compatibility studies, the excipients which showed no physiochemical instability with the drug were selected for the formulation development. The excipients having good compatibility with pregabalin were selected within the range of use as per the compendial requirements. The initial prototype formulations were prepared based on the target attributes like appearance, dissolution, content uniformity and other items.

Selection of drug substance particle size for product development

The drug substance with physical shape in flake or powder shape in micrometer range has better fluidity and can improve compressibility. As pregabalin is easy to dissolve (Yu *et al*. 2017), the effect of particle size may not significantly influence the dissolution profile and affect the drug absorption *in vivo*. In order to determine the appropriate range of particle size distribution, the study was performed to evaluate the particle size suitable for formulation development (Yasin *et al*., 2021).

Preparation of sustained release matrix tablets of pregabalin (Asghar et al., 2018)

The sustained release matrix tablets of pregabalin were prepared by direct-compression method. The required quantity of drug substance and excipients such as polyvinyl acetate, povidone, sodium lauryl sulfate and silicon dioxide weighed individually. Further, ethyl cellulose and polyethylene oxide were weighed and together passed through 24 mesh, while carbomer and crospovidone together through 40 mesh and pregabalin through 40 mesh (particle size: d90: 425µm; d10: 160µm). The mixture of ethyl cellulose and polyethylene oxide were placed in the mixer and pregabalin, carbomer and crospovidone mixture was added and mixed at 15rpm for 30 min. The blend was subjected to lubrication with magnesium stearate. The tablets were compressed using 22×10.8 mm oval punch and weight was adjusted to achieve the target weight and the difference in tablet weight was controlled in the limit of ± 3% with hardness in 290N~320N.

Systematic optimization of the sustained release matrix tablets

According to previous research experience, it was assumed that the dissolution of pregabalin sustained-release tablets can be controlled by adjusting the weight release controlling excipients such as crospovidone, polyoxyethylene and carbomer 971P.Orthogonal factorial design was selected for optimization of three factors at their three levels (-1, 0, 1) was applied for systematic optimization (Madgulkar *et al*., 2008), which provided a total of nine experimental batches of trial formulations to study the impact of formula factors on three key quality attributes such as drug release at 1h, 4h and 24h. Table 1 enlists the list of factors studied and their ranges evaluated for the sustained release tablet formulation, while table 2 provides details on the experimental trials suggested by the orthogonal design for optimization of the pregabalin sustained release tablet form (Asghar 2019).

Film coating of the sustained release tablets

According to the ratio of film coating premix: purified water = 2: 8 (W: W) recommended by the supplier of Opadry, the coating solution (20% w/v) was prepared and film coating was applied.The tablets with required occupancy were added into the high-efficiency pan coating machine and the preheating was doneat 38^{o}C to 41^{o}C for 20 min before the tablets subjected to pan coating process. The film coating was performed by compressed air with atomizing pressure 0.1MPa, while other parameters were kept at standard setting for film coating process pan speed 15rpm, fan frequency 1600rpm, material temperature 38^{o}C to 41^{o}C, liquid supply speed coating at 1-2rpm. After the coating is completed, tablets were dried for and discharged for 5 minutes. The tablets were coated for attaining film coating weight gain of 3% from the initial weight of the tablets.

Characterization of the film coated sustained release tablets

The prepared tablets were evaluated for technological characterizations such as weight variation, hardness and thickness, friability were determined as per the standard procedures described in USP XXXI. Water content in the formulation was evaluated by Karl-Fisher titration method.

Formulation process optimization using experimental design

The impact of process was optimized with the help of a suitable experimental design, (Gupta *et al*., 2017) while final composition of the optimized tablet formulation was selected for this study. The critical process steps involved in the product development were identified by risk assessment approach, such was materials sieving, blend mixing, lubrication, compression and coating were studied and suitable justifications were provided for high risk process steps.

Mixing speed and time optimization

The powder blend mixing speed was optimized by varying the mixing speed of the blender at 15, 20, 30, 40 and 60rpm, respectively. The mixing time was optimized at fixed speed of 15rpm. The blend uniformity was measured by selecting samples from six different locations of the blender.

Total mixing time optimization

To investigate the effect of different total mixing time, varying time points (1 minute, 3 minutes and 5 minutes) were selected for evaluating their impact on content, mixing uniformity and dissolution.

Rotational speed and pressure of press plate

The impact of rotational speed of tablet punching machine was evaluated at low, medium and high speeds, where the prepared tablets were evaluated for hardness and thickness, punch sticking and assay.

STATISTICAL ANALYSIS

For all the three CQAs, linear fitting with interaction terms was found to be the best suited model. Table 5 enlists the ANOVA parameters for each of the CQAs values as per the selected first-order polynomial model

given in Eq. (1-3). All the polynomial equations distinctly revealed the prevalence of interactions among the studied independent-factors on the CQAs. In addition, statistical parameters are used to evaluate the selected model and the data fit well.

Y1 (Drug release in 1h)=18 + 1.25 * A - 1.25 * AB + 1.25 * AC - 1.25 * ABC ….Eq. (1)

Y2 (Drug release in 4h) = 42.87 - 0.87 * A - 0.62 * C + 0.62 * AC - 0.87 * BC …..Eq. (2)

Y3 (Drug release in 24h) = 98.87 - 0.87 * A + 0.12 * B + 0.37 * AC + 0.37 * BC…Eq. (3)

RESULTS

Use the Qbd method to rapidly develop pregabalin sustained release tablets. Table 1 lists the research factors for the formulation of the sustained release tablets. Table 2 provides the details of the experimental test suggested by the orthogonal design for optimizing the formulation of pregabalin sustained release tablets. Table 3 shows the data that the maximum dissolution fraction of pregabalin was observed in 0.06N HCl and simulated gastric juice (pH 1.2). Table 4 lists the characteristic data of pregabalin sustained-release tablets. Table 5 is a summary of the ANOVA parameters using 1h/4h/24h as CQA, and it is believed that the selected horizontal model is in line with drug release. Table 6 provides the optimal values of indicator factors, predicted values of responses, and detailed values of statistical parameters. Table 7 shows the optimization results of mixing speed and time, determined as 15 revolutions per minute and 30 minutes. Table 8 shows that the optimal total mixing time is 3 minutes. Table 9 shows the results of pressure and speed optimization, with values fixed within a certain range and relatively stable. Table 10 shows the effect of coating weight on the dissolution curve. Figure 1 shows the drug release data obtained under different media, instruments, and speed conditions. The response surface analysis in Figure 2 shows the interaction between three types of CQA: PVPP, polyoxyethylene 303, and carbomer 971, further indicating their impact on sustained-release tablets. The yellow design space in Figure 3 is used as the optimal area, and the marked points are used as the optimization formula.

DISCUSSION

Quality target product profile (QTPP)

According to the target formulation objectives, the QTPP (Namjoshi *et al*., 2020) framework elements of pregabalin sustained-release tablets usually include a summary of the quality attributes of the target product. The defined QTPP elements are designed as target products with RLD compliant dosage form, dose intensity, route of administration, dosage strength, pharmacokinetics, stability, drug product quality attributes, container closure system, administration and concurrence with labeling.

Critical quality attributes (CQAs)

Among the quality attributes of pregabalin sustained release tablets, tablet size, fragility, drug content, related substances, dissolution and microbial limit are considered as key parameters. These parameters were selected as CQA (Vlieger *et al*., 2019). To monitor the quality of drug products throughout the development life cycle.

Dissolution method development

Table 3 enlists the solubility profile of the pregabalin in different dissolution media, where maximal soluble fraction of the drug was observed in 0.06N HCl and simulated gastric fluid (pH 1.2). However, a slightly less soluble fraction of the drug was observed in other media like acetate buffer (pH 4.5) and phosphate buffer (pH 6.8). In a nutshell, the solubility of pregabalin does not change significantly with the pH value of the medium.

Fig. 1 provides data pertaining to %drug released in different media and dissolution apparatusat varying speed. Among all the studied conditions, the drug showed predictive release profile in 900mL of 0.06N hydrochloric acid solution. The dissolution profile of pregabalin sustained-release tablets in 0.06N HCL medium in paddle apparatus at 50rpm indicated gradual increases with time and the dissolution curve data is basically consistent with the FDA dissolution data. In pH1.2 medium, pH4.5 acetate buffer and pH6.8 phosphate buffer, the paddle method is 50rpm and the cumulative dissolution gradually increases with time. Therefore, 0.06N HCL, volume 900ml, paddle method 50 revolutions and sampling time 1h, 2h, 4h, 6h, 8h, 10h, 12h, 16h and 24h were used as dissolution curve method.

Drug-excipient compatibility study

The drug-excipient compatibility study was performed by mixing at 1:5 and 20:1 ratio and placed at temperature (60^{o}C, 40^{o}C), Humidity (90%±5%RH, 25^{o}C) and light (the total illumination not less than 1.2×106Lux·hr and near-ultraviolet energy not less than 200w·hr/m2) and for appearance, assay, related substances and the other quality indicators on 0^{th} day, 10^{th} day and 30^{th} day. Upon exposure of drug-excipient physical mixtures to the light conditions, there was no significant difference in the appearance, assay and related substances of the drug from the samples on day 10 and day 30 as compared to the samples on day 0.

Under the exposed humidity conditions, all the drug-excipient mixtures showed agglomeration after 30 days. There was no significant difference observed, however, in the drug content and related substances from the samples on day 10 and day 30as compared to day 0. On the contrary, upon exposure to high temperature condition, pregabalin with PVPP showed formation of agglomerates after 30 days, but no such phenomenon was observed for pregabalin with all other excipients and also in case of blank excipients without drug.

Table 1: Orthogonal factor design for system optimization

Independent factors		Levels		Dependent factors
		Coded value	Actual (mg)	
X1	Crospovidone	-1	302.7	Y1: Drug release at 1h Y2: Drug release at 4h Y3: Drug release at 24h
		0	280.0	
		+1	257.3	
X2	Polyoxyethylene	-1	179.7	
		0	157.0	
		+1	134.3	
X3	Carbomer	-1	166.3	
		0	155.0	
		+1	143.7	

Table 2: Trial formulations of pregabalin sustained release tablets suggested by the 2-Level factorial experimental design

Name	DOE1	DOE2	DOE3	DOE4	DOE5	DOE6	DOE7	DOE8	DOE9
Pregabalin	330	330	330	330	330	330	330	330	330
EthylCellulose	143	177	211	177	211	211.1	211	211.1	245.1
Crospovidone	302.7	302.7	302.7	280	280	280	257.3	257.3	257.3
Polyethylene oxide	179.7	157	134.3	179.7	157	134.3	179.7	157	134.3
Carbomer	166.3	155	143.7	155	143.7	166.3	143.7	166.3	155
Magnesium stearate	11.3	11.3	11.3	11.3	11.3	11.3	11.3	11.3	11.3
Total	1133.0	1133.0	1133.0	1133.0	1133.0	1133.0	1133.0	1133.0	1133.0

Table 3: Solubility of pregabalin in different pH medium

Solvent	Saturation concentration	API dissolved in 900 ml medium (mg)	Equivalent to 330 mg/tablet
0.06N HCL	46.56	41904	127
pH 1.2	47.49	42741	129
pH 4.5 acetate buffer	36.67	33003	100
pH 6.8 phosphate buffer	34.96	31464	95

Table 4: Characterization data of the pregabalin sustained-release tablets of DOE Trials

Item	RLD	DOE1	DOE2	DOE3	DOE4	DOE5	DOE6	DOE7	DOE8	DOE9
Batch	AW6452	PST/2006001	PST/2006002	PST/2006003	PST/2006004	PST/2006005	PST/2006006	PST/2006007	PST/2006008	PST/2006009
Description		Pink film-coated tablets, white after uncoating								
Weight of 10 tablets	1.167	1.16	1.165	1.159	1.162	1.165	1.164	1.161	1.164	1.166
Hardness (N)	311	350	378	358	377	357	367	376	374	380
Thickness (mm)	6.98	7.08	7.00	7.00	6.94	6.98	7.00	6.88	6.92	6.96
Friability (%)	2.92	0	0	0	0	0	0	0	0	0
Water content	/	3.2	3.1	2.8	2.6	3.1	3.0	3.7	3.3	3.6
Floating time (h)	16	15.5	11	11	15	12	11	14.5	13	10
Time (h)	Cumulative %drug release from sustained release tablet formulations									
	RLD: AW6452	PST/2006001	PST/2006002	PST/2006003	PST/2006004	PST/2006005	PST/2006006	PST/2006007	PST/2006008	PST/2006009
0	0	0	0	0	0	0	0	0	0	0
1	17	16	17	17	17	17	17	17	17	18
2	28	26	28	28	27	28	29	27	28	29
4	42	41	43	46	41	43	44	42	41	44
6	54	52	55	58	52	55	56	54	53	56
8	63	60	64	67	61	64	66	63	62	65
10	70	68	72	75	68	72	74	71	70	73
12	76	74	78	81	75	78	81	77	76	82
16	86	85	90	92	85	89	93	88	87	93
24	96	99	98	100	97	99	100	100	98	99

Table 5: Summary of ANOVA parameters indicating model fitting for drug release in 1h/4h/24h as the CQA

ANOVA for selected factorial model						
Analysis of variance table [Partial sum of squares - Type III]-1h						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Model	50.00	4	12.50	1.56	0.3719	Not significant
A-Crospovidone	12.50	1	12.50	1.56	0.2999	Not significant
AB	12.50	1	12.50	1.56	0.2999	Not significant
AC	12.50	1	12.50	1.56	0.2999	Not significant
ABC	12.50	1	12.50	1.56	0.2999	Not significant
Residual	24.00	3	8.00			
Cor Total	74.00	7				
Analysis of variance table [Partial sum of squares - Type III]-4h						
Model	18.50	4	4.63	37.00	0.0069	Significant
A-Crospovidone	6.13	1	6.13	49.00	0.0060	Significant
C-Carbomer 971	3.13	1	3.13	25.00	0.0154	Significant
AC	3.13	1	3.13	25.00	0.0154	Significant
BC	6.12	1	6.12	49.00	0.0060	Significant
Residual	0.37	3	0.12			
Cor Total	18.88	7				
Analysis of variance table [Partial sum of squares - Type III]-24h						
Model	8.50	4	2.13	17.00	0.0212	Significant
A-Crospovidone	6.13	1	6.13	49.00	0.0060	Significant
B-Polyoxyethylene 303	0.12	1	0.12	1.00	0.3910	Not significant
AC	1.13	1	1.13	9.00	0.0577	Not significant
BC	1.13	1	1.13	9.00	0.0577	Not significant
Residual	0.37	3	0.12			
Cor Total	8.88	7				

Table 6: Point prediction tool indicating the optimum values of the factors and predicted values of the responses along with detailed values of the statistical parameters

Factor	Name	Level	Low Level	High Level	Coding
A	Crospovidone	267.30	257.30	302.70	Actual
B	Polyoxyethylene 303	179.70	134.30	179.70	Actual
C	Carbomer 971	143.70	143.70	166.30	Actual

Predicted optimized formulation and statistical parameters							
Response	Mean	Std Dev	SE Mean	90% CI low	90% CI high	90% TI low	90% TI high
Drug release in 1h	18	2.82	1.50	14.46	21.53	5.00	30.99
Drug release in 4h	45.21	0.35	0.23	44.65	45.77	43.50	46.92
Drug release in 24h	99.32	0.35	0.23	98.7642	99.88	97.61	101.03

Table 7: Mixed speed and time optimized results for the blending step

Item	15rpm		
	20min	30min	40 min
Lot No.	PST/2007001-A	PST/2007001-A	PST/2007001-A
1	288.67	291.59	287.66
2	284.34	288.65	297.37
3	289.42	292.08	288.05
4	291.55	285.16	289.13
5	285.32	289.48	292.76
6	287.50	291.52	293.83
Average	287.8	289.7	291.5
RSD%	1.0	1.0	1.4

Table 8: Total mixing time optimization for the final lubrication step

Item		Time		
		1 min	3 min	5 min
Bulk Density (gm/cc)		0.39	0.38	0.39
Tap Density (gm/cc)		0.52	0.52	0.53
Carr index		25.5	27.5	26.5
Mixing uniformity	1	285.33	291.14	290.75
	2	284.97	285.71	291.90
	3	289.46	284.40	284.21
	4	291.86	285.09	291.73
	5	291.03	287.88	288.52
	6	289.64	289.15	289.65
	Average	288.7	287.2	289.5
	RSD%	1.0	1.0	1.0
Punch Sticking		NO	NO	NO
Weight of 10 tablets		1.165	1.164	1.164
Hardness (N)		394	399	394
Thickness (mm)		6.97	6.96	6.91
Dissolution Method (37℃, Paddle, 50 rpm, 1000 ml 0.06M Hydrochloric acid solution); n=6				
Time	RLD：AW6452	RLD:DN5396	PST/2007001-1	PST/2007003-3	PST/2007001-2
1h	17	26	18	17	17
2h	28	38	27	27	26
4h	42	53	42	42	41
6h	54	65	53	53	52
8h	63	74	61	62	61
10h	70	81	69	70	68
12h	76	86	75	76	74
16h	86	94	86	86	84
24h	96	98	98	99	97

Table 9: Results of pressure and speed optimization study

Item			Hardness (N)	
			290~320N	320~350N
Punch Sticking			No	No
Actual hardness（N）			297	342
Thickness（mm）			6.86	6.75
Dissolution Method (37℃, Paddle, 50 rpm, 1000 ml 0.06M Hydrochloric acid solution); n=6				
Time	RLD：AW6452	RLD:DN5396	PST/2007003-1	PST/2007003-3
1h	17	26	16	17
2h	28	38	26	27
4h	42	53	40	42
6h	54	65	51	53
8h	63	74	59	62
10h	70	81	66	70
12h	76	86	73	76
16h	86	94	83	86
24h	96	98	98	99

Item	RLD：AW6452	Speed		
Average（g）	1.167	Low 1.164	Medium 1.166	High 1.163
RSD（%）	0.7	0.5	0.4	0.3
Average Hardness (N)	311	394	388	401
Thick（mm）	6.98	6.91	6.95	6.91
Punch Sticking		No	No	No
Assay (%)	98.1	96.9	96.7	97.4

Time	RLD：AW6452	RLD:DN5396	PST/2007003-3	PST/2007003-5	PST/2007003-6
1h	17	26	17	17	16
2h	28	38	27	27	27
4h	42	53	42	41	41
6h	54	65	53	51	52
8h	63	74	62	60	61
10h	70	81	70	67	68
12h	76	86	76	73	74
16h	86	94	86	82	84
24h	96	98	99	95	97

Table 10: Results of the coating optimization results

Batch No.			PST/2007003-2	PST/2007003-3	PST/2007003-4
Tablet Coating weight gain			2%	3%	4%
Actual weight gain			1.9%	2.9%	4.1%
Hardness (N)			377	394	417
Dissolution Method (37°C, Paddle, 50 rpm, 1000 ml 0.06M Hydrochloric acid solution); n=6					
Time	RLD: AW6452	RLD:DN5396	PST/2007003-2	PST/2007003-3	PST/2007003-4
1h	17	26	18	17	17
2h	28	38	28	27	27
4h	42	53	43	42	43
6h	54	65	54	53	54
8h	63	74	63	62	63
10h	70	81	71	70	71
12h	76	86	77	76	77
16h	86	94	89	86	87
24h	96	98	99	99	100

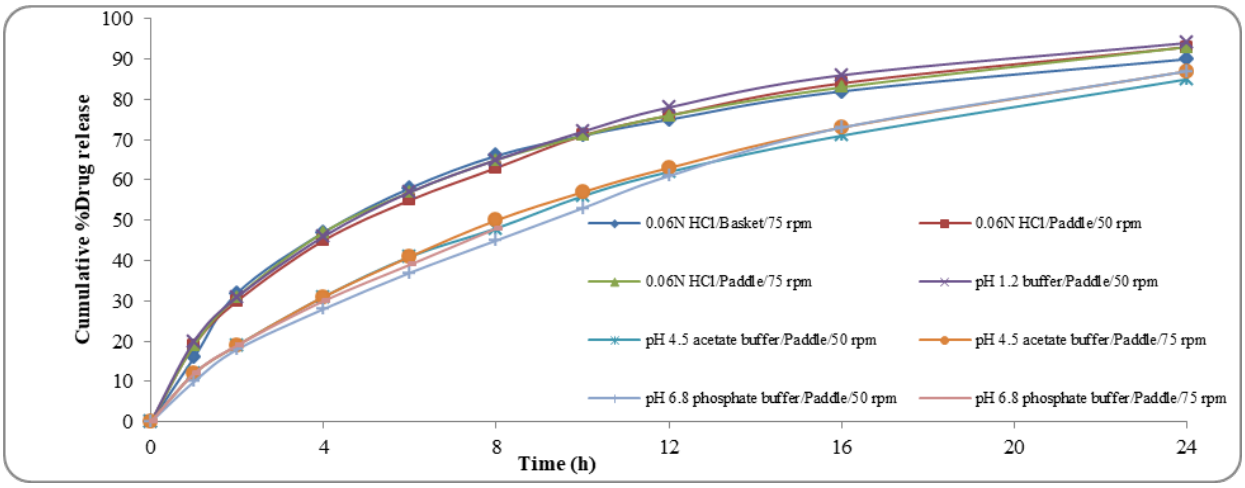

Fig. 1: Drug release data obtained during dissolution method development with different media, apparatus and speed conditions.

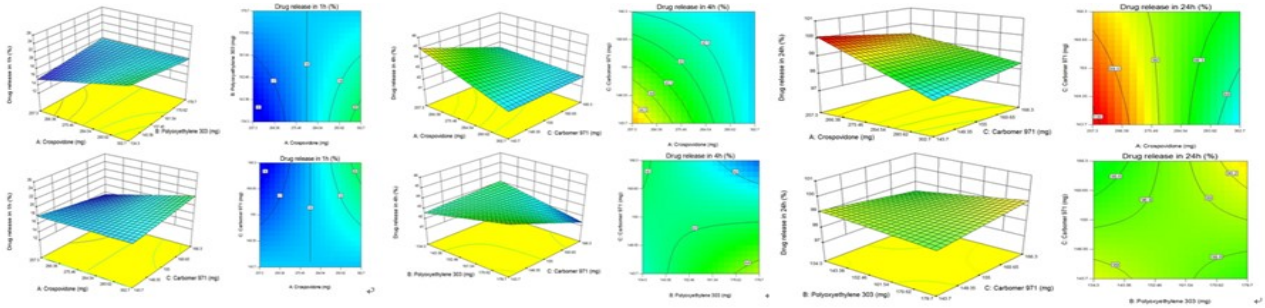

Fig. 2: 3D-response surface plots and 2D-contour graphs indicating the effect of CMAs such as A: Crospovidone, (B) Polyoxyethylene 303 and (C) Carbomer 971 on cumulative %drug release in 1h/4h/24h as the CAA.

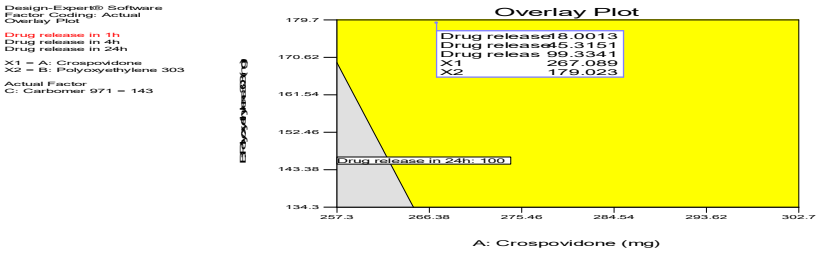

Fig. 3: Overlay plot indicating yellow color design space as the optimum region and flagged point as the optimized formulation.

This could be attributed to the hygroscopic nature of the PVPP and further exposure to high temperature which caused material agglomeration. When pregabalin and polyoxyethylene samples were placed at a high temperature of 60°C for 30 days, the content of the sample was significantly reduced and the related substances levels were significantly increased. However, at high temperature (40°C), the drug content and related substances showed no significant changes as compared to the initial sample. Further, pregabalin with film coating premix exposure to high temperature condition for 30 days showed increase in the level of unknown impurities and total impurities, which could be attributed to the chemical reaction of drug with iron oxide present in the color coating premix.

Selection of excipients and their quantities for the product development

According to the results of drug excipient compatibility study, after understanding the excipients used in RLD, the excipients selected for pregabalin sustained-release tablets are: EC, PVPP, PEO, Carbomer, MS and Film-coated premix (gastric soluble type). In addition, excipients and RLD used in the formulation are similar in quality and quantity.

Selection of drug substance particle size for product development

After selection of the excipients, the sustained release tablet formulations were prepared using drug substance of different particle size. The drug substance with particle morphology in flake or powder shape in the micrometer range showed better fluidity and good compressibility. As pregabalin is free water soluble drug (Aydogan *et al*., 2015), thus impact of particle size was very negligible. However, the drug substance with larger particle size slowed down the release rate of the drug.On the basis of prior experience, the particle size selection was carried out in order to achieve dissolution performance without affecting the flow properties of the drug.

Optimization data analysis and response surface mapping

The 2-Level factorial (Ramarao and Madhuri, 2022) design was selected for the optimization of sustained release matrix tablet formulations of pregabalin. Table 4 provides technological characterization data of the prepared tablet formulations, along with the *in vitro* drug release data. Further, the obtained data was subjected to mathematical model fitting to various polynomial equations.

Fig. 2 shows that the response surface analysis furnished vital interaction (s) among the CMAs and their impact on CQAs of the sustained release tablets of pregabalin. For all three CQAs (drug release in 1h, 4h and 24h), the studied independent factors revealed the two-factor interactions between factors A and B and between factors A and C. The impact of these two types of interactions on CQA is very common. This could be attributed to the sustained drug release mechanism of the selected release controlling polymers. The impact of Carbopol 971P on drug release rate was highly pronounced as compared to that of Polyoxyethylene 303.

Search for optimum formulation of sustained release tablets

Fig. 3 portrays the overlay plot depicting the design space region and flagged point as the optimized formulation, while table 6 point-prediction tool indicating the optimum values of the factors and predicted values of the responses along with detailed values of the statistical parameters for the optimized formulation. The final composition of optimized sustained release tablet formulation of pregabalin is: 330mg; Ethyl Cellulose-10cp: 211mg; Crospovidone-XL: 267.3mg; Polyethylene oxide WSR303: 179.7mg; Carbomer-971P: 143.7mg; Magnesium Stearate: 11.3mg.

Process optimization for the sustained release tablets

According to the DoE results obtained after product optimization, the critical process parameters like Mixed Speed and Time, total mixing time, rotational speed and pressure of the rotary tablet punching machine were optimized.

Mixed speed and time optimization

The mixing time was varied at fixed mixing speed of the blender (data provided in table 7). When the product was mixed for 20min, 30min and 40min (all at fixed 15rpm), the RSD was observe to be less than 5.0%. The mixing uniformity was good and the mixing time was finally determined to be 30min.

Total mixing time optimization

Total mixing time indicated the time involved in final mixing step which involved lubrication of the blend after mixing pregabalin with all other excipients (data provided in table 8). When lubrication was performed for 1min, 3min and 5min, the mixing uniformity was found to be good. The lubrication time has no influence on the dissolution profile. Hence, the final value for total mixing time was set at 3min.

Pressure of tablet press and rotational speed optimization

The hardness of tablet changes during coating, thus hardness of a plain tablet can only be controlled within the required range during tablet pressing. By varying the pressure and rotational speed of the tablet pressure, the impact on dissolution profile was monitored (data provided in table 9). Hence, pressure (at 290-320 N) and speed of press (20rpm) were fixed at a particular value for attaining consistent results

Coating weight optimization results

Table 10 show insignificant impact of the coating weight was observed on the dissolution profile of the tablet.

CONCLUSION

The present research work indicated successful development of sustained release tablet formulation of pregabalin. DoE helped in understanding the impact of input product related variables on the CQAs of the drug product and optimized formulation was selected. Further, process optimization helped in getting the best values for the process parameters. Overall, the obtained optimized formulation showed holistically identical in the product performance and process capability in matching the dissolution profile with that of the marketed RLD product. The research of this paper focuses on the process and at present there is a lack of *in vivo* bioequivalence studies with reference preparations. In the next plan, clinical studies and safety evaluation will be carried out. At the same time, we will also conduct a scale-up study of the process.

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