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Development and Evaluation of Pregabalin Capsules Using QbD Approach

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ABSTRACT

Quality by Design (QbD) approach was employed to formulate Pregabalin Capsules, with the objective of making thee formulation cost effective. The formulated capsules consist of Lactose monohydrate as Diluent, Maize starch as Disintegrant and Talc as Glidant. Capsules were prepared by manual filling. Design of Experimentation (DoE) was employed to evaluate the effect of excipient concentrations in the blend on the various parameters like tapped density, Carr's index and Disintegration time. Results obtained from DoE suggested that increase in the concentrations of the blend, there is an increase in the responses which are in prescribed limit. In-vitro dissolution study of the optimized formulation had shown 100% release at 45th min whereas marketed formulation had shown 80% release. From this result it can be concluded that formulation of Pregabalin capsules using QbD approach has leaded to a cost effective and stable formulation.

Keywords: QbD approach; Pregabalin; Capsules; Design of experimentation; *In-vitro* release

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INTRODUCTION

The pharmaceutical Quality by Design (QbD) is a systematic approach of development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management [1]. Quality by Design (QbD) is an emerging approach to enhance the safety and efficacy of the drug supplied to the consumer, and also improves manufacturing quality performance.

QbD development process begins with a target product profile that describes the use, safety and efficacy of the product. It includes defining a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development, gathering relevant prior knowledge about the drug substance, potential excipients and process operation and use risk assessment to prioritize knowledge gaps for further investigation [2,3].

Then a formulation is designed and critical material (quality) attributes of the final product that must be controlled to meet the target product quality profile are identified. A manufacturing process to produce a final product having these critical material attributes are thus designed. Then the critical process parameters and input (raw) material attributes must be controlled to achieve these critical material attributes of the final product are identified and the risk assessment are used to prioritize process parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a design space or other representation of process understanding. A control strategy for the entire process is established that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment [4,5]. Then finally the process is continuously monitored to assure consistent quality.

The Pregabalin is a highly soluble and bioavailable drug and as per BCS classification this has been categorized as BCS class 1. Its solubility is pH independent and is freely soluble in all pH solutions ranging from pH 1.2 to 6.8. Tmax for Pregabalin is around 1.5-3 hours. It has more than 90% bioavailability and the absorption window is mainly stomach. The absorption is found to be independent of dose. It is primarily excreted in urine. It does not bind directly to GABAa or GABAb receptors but in turn enhances the density of GABA transporter proteins.
Pregabalin is an anticonvulsant and analgesic medication that was recently approved for adjunctive treatment of partial seizures in adults in both the United States and Europe and for the treatment of neuropathic pain from postherpetic neuralgia and diabetic neuropathy. It is both structurally and pharmacologically related to the anticonvulsant and analgesic medication gabapentin [6].
QbD approach will help in developing a robust, reproducible product with a manufacturing friendly process and desirable quality attributes built into it.

MATERIALS AND METHODS

Materials

Pregabalin was obtained from Biocon, Bangalore, India. The other chemicals and excipients used in the study were of analytical grade.

Methods

Defining the quality target product profile (QTPP) for Pregabalin capsules:

Following is a prospective summary of the quality characteristics of Pregabalin capsules that are desired to be achieved, taking into account the safety and efficacy of Pregabalin capsules which is shown in Table 1.

Table 1: Quality target product profile (QTPP) for Pregabalin capsules

Components		Desired Characteristics	Justification
Static Component	Dosage form	Immediate release capsule	To be same as the reference listed drug
	Route of administration	Oral	To be same as the reference listed drug
	Drug substance	Pregabalin	Pregabalin
	Dosage form strength	Pregabalin Capsules 300, 225, 200, 150, 100, 75, 50 and 25 mg	To be same as the reference listed drug
	Intended use	For management of neuropathic pain associated with diabetic peripheral neuropathy	For management of neuropathic pain associated with diabetic peripheral neuropathy
		Post herpetic neuralgia, adjunctive	Post herpetic neuralgia, adjunctive
		Therapy for adult patients with partial onset seizures	Therapy for adult patients with partial onset seizures
	Dosage design	Oral immediate release capsules intended to release the drug substance	Oral Immediate release capsules has been designed to be in line with the reference product
Dynamic Component	Container closure system	Bottle pack and Blister pack	Bottle pack
	Excipients	Lactose monohydrate, maize starch and talc.	Based on the compatibility Studies results, proposed excipients will be selected for the development.
	Quality Attributes	Assay, Content uniformity, Dissolution and Impurity profile	Assay, content uniformity, dissolution and impurity profile
Therapeutic moiety release and attributes affecting the Pharmacokinetic characteristics	Pharmacokinetic Profile and Dissolution	Pregabalin is rapidly absorbed with peak plasma concentrations occur within 1.5 hours.	Oral bioavailability of Pregabalin is ≥ 90% indicating it is highly permeable and it is highly
		Pregabalin oral Bioavailability is ≥ 90% and is independent of dose.	Soluble across the pH 1.2 to 7.5. Maximum plasma concentration (Cmax), the area under the curve (AUC) and Tmax ensures rapid onset of action.
Patient compliance to the product	Organoleptic	Shape, size and colour	Shape, size and Colour similar to the reference
	Scoring	NA	To match the reference listed Drug

Identification of Critical Quality Attributes (CQA's) for Pregabalin capsules:
Based on the above mentioned QTPP the following CQA's were established for the development of Pregabalin Capsules. CQA include the product attributes that have the potential to be altered by changes to process parameters or formulation variables during pharmaceutical development. These are directly related to the safety and efficacy of Pregabalin Capsules which are shown in Table 2.

Table 2: Critical Quality Attributes (CQA's) for Pregabalin capsules

Critical Quality Attribute	Range or Value	Reference / Discussion or development activities conducted to achieve the CQA
Assay	90-110%	As recommended By USP
Content uniformity	L1=15.0 or L2=25.0	As recommended By USP
Dissolution	5, 10, 15, 20, 30 and 45 Minutes	In-house
Impurity profile	a) PRB II : NMT 0.2% b) PRB III : NMT 0.2% c) Unidentified impurity: NMT 0.20% each d) Total Impurities: NMT 1.0%	As per ICH guidelines Impurities in New Drug Products Q3BR2

Identification of the Critical Material Attributes (CMA) for the drug substance and excipients that have an impact on the CQA of the drug product:
The critical material attributes of the excipients are discussed below in Table 3. The CMA's of excipient that have an impact on the CQA of the drug product were also summarized below.

Table 3: Critical material attributes (CMA) for the drug substance

Material Attribute	Reference/Discussion or development activities conducted to confirm the		
	Lactose monohydrate	Maize starch	Talc
Functional use	Diluent	Disintegrant	Glidant
Compendial Requirements	Complies		
Interaction with drug substance	Compatibility studies were performed and the above excipients were found to be compatible with drug substance. There was no significant degradation		
Impact of excipient concentration and characteristics on drug product performance or manufacturability	Impact of the excipient concentration was evaluated by Design of experiments		

Manufacturing process of Pregabalin capsules:
Pregabalin capsules were prepared by employing various excipients as shown in the formulation chart i.e. Table 4. Weighed quantity of Pregabalin, Lactose mono and Maize starch were shifted through sieve no.40 and blended for 10 minutes in a blender. After blending the blend was discharged from the blender, again passed through sieve no.40 and blended for 10 minutes. Talc shifted through sieve no.40 along with the other shifted materials and blended for 5 minutes. Encapsulation was done using a MF30 (Manual filling) machine with a target fill weight of 510 mg in size 0 empty capsules.

Table 4: Composition for an individual capsule

Sl.No	Excipent	Qty mg/capsule
1	Pregabalin	300*
2	Lactose monohydrate	120*
3	Maize starch	45
4	Talc	45
5	**Target Fill weight**	**510**

Characterization of blend:
The obtained blend was evaluated for their characteristics parameters like Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose.

Bulk density: Bulk density is determined by pouring the blend into a graduated cylinder via a large funnel and measuring the weight and volume obtained by the blend without tapping and calculated [7].

Tapped density: Tapped density is determined by placing a graduated cylinder containing known mass of blends on a mechanical tapped apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and minimum volume [8].

Carr's index: Carr's index was measured using the values of the bulk density and tapped density [8].

Angle of repose: Weighed quantity of granules was passed through a funnel kept at a height of 2 cm from the base. The powder is passed till it forms heap and touches the tip of funnel. The radius was measured and angle of repose was calculated [9].

Hausner's ratio: Hausner's ratio was determined by the ratio between the tapped density to that of the bulk density [9].

Evaluation of capsules:

Lock length: Ten individual capsules were taken from formulation trial batch and lock length was measured manually by using vernier callipers and average of ten capsules was noted [10].

Disintegration time: The capsules were placed in the basket rack assembly, which is 15 repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37ºC. To fully satisfy the test, the capsules should disintegrate completely into a soft mass having no palpably firm core without any fragments of the gelatin shell. If one or two capsules fail, the test should be repeated on additional of 12 capsules. Then, not fewer than 16 of the total 18 capsules tested should disintegrate completely [11].

Dissolution studies: The release of Pregabalin was determined using a dissolution apparatus of USP Type II (paddle) at 50 rpm. 900 ml of 0.06 N hydrochloric solution acid was used as the dissolution medium and were maintained at the temperature of 37.5 ± 0.5°C. A sinker was used to avoid capsule flotation. The samples were drawn at 5, 10, 15 30 and 45 min and equal amount of fresh medium were replaced to maintain the sink conditions. Samples withdrawn were analyzed to determine the percentage of drug released [12].

Optimization of formulation using DoE:

A Design of Experiment (DoE) with Simplex centroid design having three replicates at the center was used for the optimization study. The effect of formulation variables on response variables was evaluated by one way ANOVA [13].

RESULTS AND DISCUSSION

Characterization of Blend

From the results obtained it was evident that all the parameters were found to be in acceptable range including the flow which was confirmed by the Hausner ratio which is shown in Table 5.

Table 5: Characterization of blend

Sl. No	Parameter	Observed Value
1	Bulk density ,gm/cc	0.587
2	Tap density, gm/cc	0.786
3	Compressibility Index, %	25.31
4	Hausner ratio	1.34
5	Flow	Good

Evaluation of Capsules

From the results obtained it was evident that all the evaluation parameters are in prescribed range and are shown in Table 6.

Table 6: Evaluation of Pregabalin capsules

Sl. No	Parameter	Observed Value
1	Filled Capsule weight (mg)	591-603
2	Fill weight (mg)	492-512
3	Disintegration Time (Minutes and Seconds)	2' 02" -2'19"
4	Locking Length (mm)	23.01-22.97

Dissolution Studies

Dissolution studies of the formulated Pregabalin capsules were compared with two market products i.e. Lyrica capsules 300 mg both USA and Canada. From the results obtained it was evident that formulated Pregabalin capsules showed 106% drug release at 45 min, while the marketed capsules had shown a release of 97% at 45 min. These results suggests that formulated Pregabalin capsules had shown better dissolution profile than of the marketed formulations and the results are shown in the form of a graph in Figures 1 and 2.

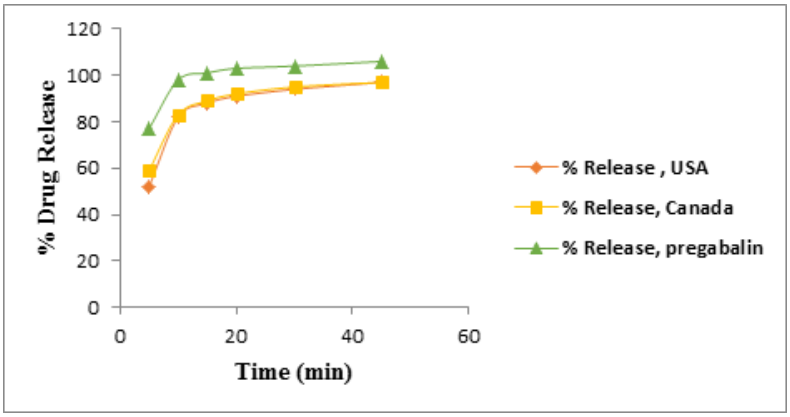

Figure 1: Comparison of the dissolution profile with marketed formulations

Optimization of Formulation using DoE

In the preliminary trails it was observed that density of the blend has significant influence on the fill weight of capsule and on en-capsulation process. Hence further trials were planned by design of experiments to evaluate the effect of density on the encapsulation process and to determine the fill weight for the each strength. A Design of Experiment (DOE) with Simplex centroid design having three replicates at the center was used for the optimization study. The following ranges around the target formulation were investigated using design of experiments (Tables 7-11).

Table 7: Ranges of various excipients

Factor	Minimum		Maximum	
	mg/Capsule	%	mg/Capsule	%
Lactose Monohydrate	133.50 mg	26.20%	210.00 mg	41.20%
Maize Starch	0 mg	0%	76.5 mg	15%
Talc	0 mg	0%	76.5 mg	15%

Table 8: Quantitative composition of Pregabalin capsules, 300 mg

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Pregabalin	300	300	300	300	300	300	300	300	300	300	300	300
Lactose	133.5	146.2	133.5	171.7	171.7	210	184.5	159	133.5	159	159	146.2
Maize starch	38.2	51	76.5	38.2	0	0	12.7	26.5	0	25.5	25.5	12.7
Talc	38.2	12.7	0	0	38.2	0	12.7	25.5	76.5	25.5	25.5	51
Capsule fill weight	**510**	**510**	**510**	**510**	**510**	**510**	**510**	**510**	**510**	**510**	**510**	**510**

Table 9: Lubricated blend characterization

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Bulk Density	0.56	0.56	0.56	0.55	0.53	0.5	0.52	0.56	0.55	0.56	0.55	0.55
Tapped Density	0.78	0.78	0.8	0.74	0.74	0.71	0.73	0.76	0.78	0.78	0.76	0.77
Compressibility Index, %	28.5	28.4	30.1	26.2	28.3	29.9	28.3	26.9	30.2	27.8	27.8	28.8
Hausner ratio	1.4	1.3	1.4	1.3	1.4	1.4	1.4	1.3	1.4	1.4	1.4	1.4

Table 10: Capsule physical parameters

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Description	Hard gelatin capsules size 0 with opaque white cap and Opaque white body. Filled with white powder.											
Individual Capsule Weight (mg)	603 - 611	596 - 623	600 - 621	590 - 624	583 - 621	551- 576	562- 584	584 - 621	608- 620	595 - 618	598 - 622	598 - 619
Fill weight (mg)	508	516	511	507	507.7	472.5	479.1	510	512	509	508	512.3

Locking Length (mm)	21.09 - 21.68	21.20 -21.30	21.12 - 21.42	21.40 - 21.6	21.30 - 21.45	21.49 - 21.62	21.30 - 21.51	21.29 - 21.46	21.40 - 21.61	21.39 - 21.65	21.41 - 21.7	21.31 - 21.51
Disintegration Time (min and sec)	01'50"- 02'25"	01'50" -01'5"	01'52"- 02'05"	01'41"- 02'03"	02'15" - 02'30"	01'48" -02'03"	01'56" -02'09"	02'06" -02'42"	02'02" -02'30"	01'50" -02'30"	02'04" -02'31"	02'05"- 02'30"

Table 11: Dissolution profile

Time (min)	5	10	15	20	30	45
F1	85	99	99	99	100	100
F2	91	100	101	102	102	103
F3	85	92	95	96	98	99
F4	91	98	100	101	101	102
F5	95	100	100	100	100	101
F6	85	90	92	93	92	93
F7	86	93	95	96	96	96
F8	90	96	97	99	100	100
F9	54	81	92	97	101	102
F10	98	103	103	103	103	103
F11	98	103	104	105	105	105
F12	62	90	98	102	103	103

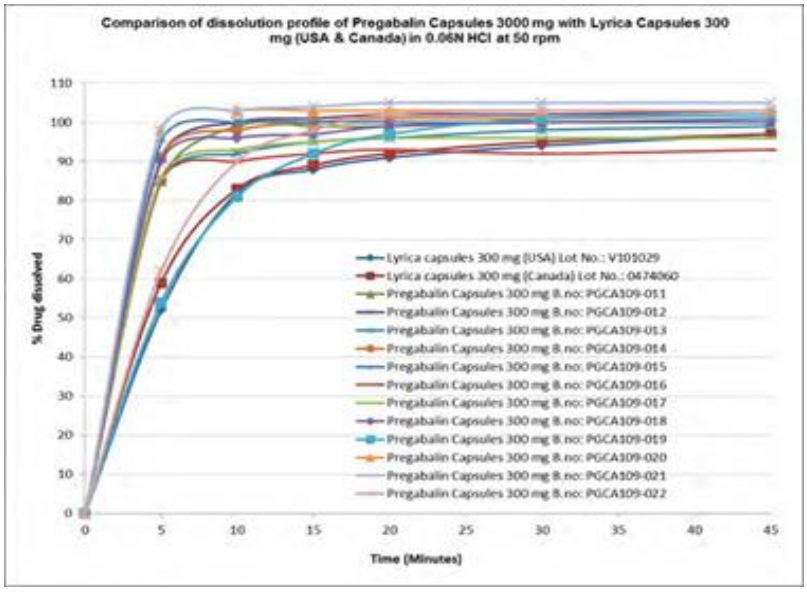

Figure 2: Comparison of dissolution profile of Pregabalin capsules with marketed formulations

The data was analysed and the relationship between the formulation factors and the resultant responses were constructed.

Effect of formulation variables on responses:

Tapped density: Change in the concentration of Lactose monohydrate, Maize starch and talc has a significant influence on the Tapped density of the Blend. Increase in the Lactose monohydrate concentration is decreasing the Tapped density of the blend. Increase in the Maize starch concentration is increasing the Tapped density of the Blend. Increase in the Talc concentration doesn't increase the Tapped density of the Blend significantly (Figure 3).
The relationship between the factors and the Tapped density is as follows:

Tapped density = +9.24401E-003 * Lactose-+0.010407 * Maize Starch-+0.010237 *Talc

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Carr's index: Change in the concentration of Lactose monohydrate, Maize starch and Talc has no significant influence on the Carr's index of the Blend. Whereas the Lactose monohydrate and Maize starch mixture (AB) has a significant influence on the Carr's index of the Blend. Increase in the Lactose monohydrate and Maize starch mixture (AB) concentration is increasing the Carr's index of the Blend. The effect is not significant in the case of Lactose monohydrate and Talc mixture (AC) and Maize starch and talc mixture (BC) (Figure 4).
The relationship between the factors and the Carr's index is as follows:

Carr's index = +0.39134 * Lactose+0.39360 * Maize Starch+0.39425 * Talc-2.26838E-003 * Lactose * Maize Starch (AB)-8.84301E-004 * Lactose * Talc (AC)-8.11602E-004 * Maize Starch * Talc (BC)

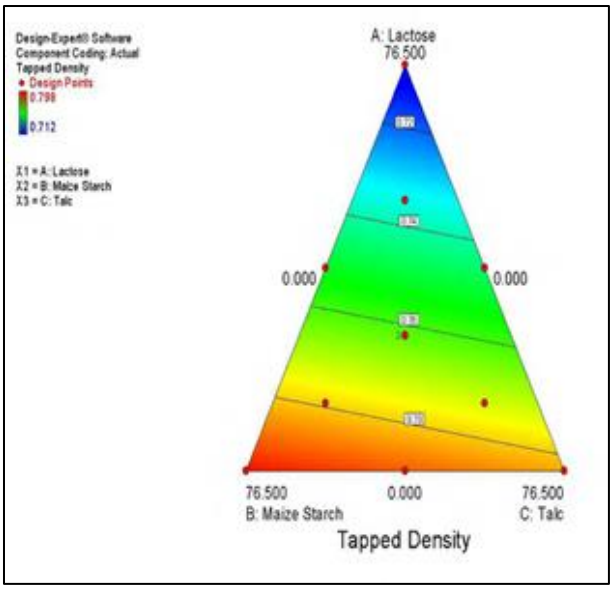

Figure 3: Response graph for tapped density

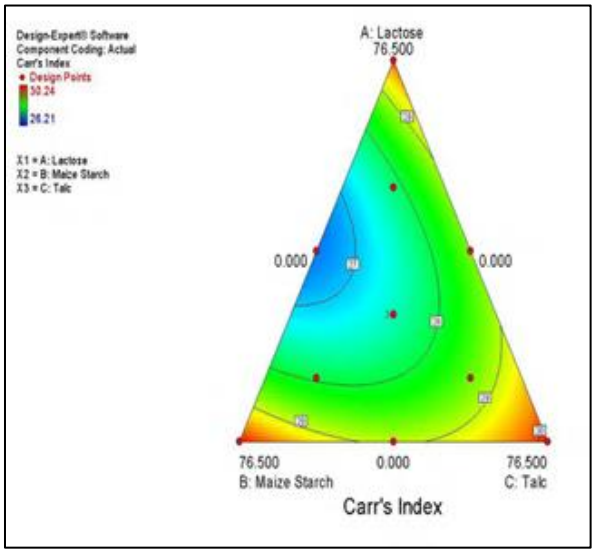

Figure 4: Response graph for Carr's index

Disintegration time: Change in the concentration of talc has a significant influence on the Disintegration time of the capsules. Increase in Talc concentration is increasing the Disintegration time of the capsules. Lactose monohydrate and Maize starch has no significant effect on the disintegration time of the capsules (Figure 5).
The relationship between the factors and the disintegration time is as follows:

Disintegration time =+1.70225 * Lactose+1.64996 * Maize Starch+2.12491 *Talc

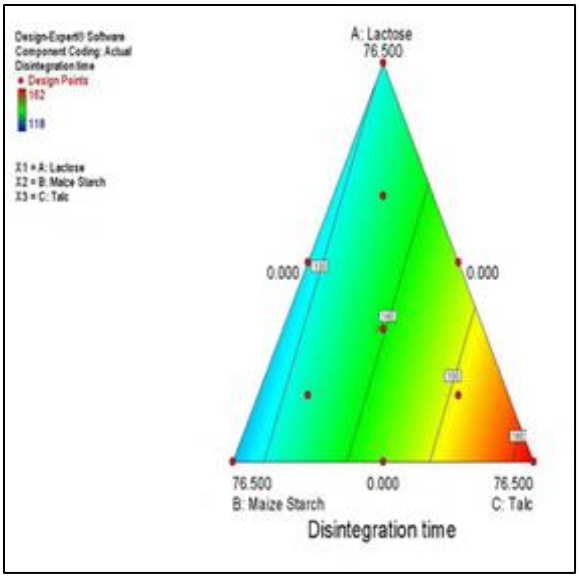

Figure 5: Response graph for disintegration time

CONCLUSION

Pregabalin capsules were formulated using manual filling machine. It was observed that no significant difference in the dissolution profile of Pregabalin capsules with RLD, hence direct filling approach was proposed for further trials. In addition the further trials were planned by DoE to evaluate the effect of density on encapsulation and fill weight for each strength. Results obtained from DoE suggest that the excipients have a phenomenal effect on capsules, as the concentration of the excipient increases there is an increase in the blend characteristics. Hence it can be concluded that employing QbD approach in the formulation of Pregabalin capsules has leaded to a pharmaceutically equivalent, low cost, quality improved and stable formulation.

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Conflict of Interest

The author confirms that this article content has no conflict of interest.

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