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Formulation and Evaluation of a Cost-effective Pregabalin Powder for Oral Solution in Sachet: Physicochemical Characteristics and Stability Compared To LYRICA®

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Abstract

Aim of this research is to design Pregabalin Powder for Oral solution in a Sachet pack. The manufacturing process involved in formulating the product is by a simple direct blending and filling process. Apart from Pregabalin API, the excipients used in the final product includes Sorbitol as bulking agent, Sucralose as sweetener, Strawberry as flavor, Sodium Citrate as buffering agent and Sodium Benzoate as preservative. The finalized composition and process was completely optimized with respect to Critical Material Attribute (CMA) and Critical Process Parameter (CPP). The Physico-chemical characteristics, organoleptics and stability of the formulated product was found comparable to LYRICA® Oral Solution. Based on the accelerated stability results, the shelf life of the designed product was set to be stable for 24 months at controlled room temperature storage condition. The manufactured Pregabalin Powder for Oral solution in Sachet was found to be cost-effective compared to LYRICA® Oral Solution and expected to be appealing for patients both nationally and internationally. The designed product could become a potential alternative to already available capsule and oral solution in the market.

Keywords: Pregabalin; Direct Blending; Powder; Sachet

Abbreviations

CMA: Critical Material Attribute; CPP: Critical Process Parameter; FDA: Food and Drug Administration; EULAR: European League against Rheumatism; USP: United States Pharmacopoeia; PSD: Particle Size Distribution; BD: Bulk Density; TD: Tapped Density; CI: Carr's Index; HR: Hausner Ratio; LOD: Loss on Drying; HDPE: High Density Polyethylene; CDER's: Centre for drug evaluation and Research's; IID: Inactive Ingredient Database; MDE: Maximum Daily Exposure; SUPAC: Scale Up And Post Approval Changes; OFAT: One Factor at a Time; AV: Acceptance Value; PFOS:

Powder for Oral Solution; QTPP: Quality Target Product Profile; DMF: Drug Master File.

Introduction

Pregabalin is a drug indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy; postherpetic neuralgia; treatment of partial onset seizures in patients 1 month of age and older; fibromyalgia and management of neuropathic pain associated with spinal cord injury. In the market under the brand name LYRICA®, Pregabalin is available as capsule, extended release tablet and oral solution [1]. Pregabalin was approved by the United States Food and Drug Administration (FDA) in 2004. Pregabalin is utilized for neuropathic pain and seizures. FDA-Approved Indications include Neuropathic pain associated with spinal cord injury [2], Neuropathic pain associated with diabetic peripheral neuropathy [3], Neuropathic pain originating from postherpetic neuralgia [4], Adjunctive treatment for partial-onset seizures in adults with epilepsy [5], Treatment of fibromyalgia [6], European League Against Rheumatism (EULAR) guidelines note that pharmacological therapies should be considered for individuals experiencing severe pain or sleep disturbance. Pregabalin could be most appropriate when addressing both severe pain and sleep disturbance concurrently [7]. Off-Label Uses include Generalized anxiety disorder [8], Social anxiety disorder [9], Insomnia [10], Chronic pain conditions [11], Uremic pruritus [12,13], Chronic cough [14], Restless leg syndrome [15,16], Complex regional pain syndrome [17], Prophylaxis of migraine [18], Trigeminal neuralgia 19]. There is significant controversy regarding the efficacy of Pregabalin for the off-label indications [20]. Therefore, clinicians should carefully monitor patients for therapeutic success while monitoring adverse drug reactions [21].

Problem Statement, Objective & Scope for Research

Though LYRICA® (Pregabalin) Oral solution is available in the market; the shelf life of the product is only 18 months and is marketed in bottles with 473 mL of drug product at 20 mg per mL dosing. The demerits of the Pregabalin oral solution are bulky to carry, limited shelf life period and cost wise expensive since each bottle on an average cost about 1300 US dollars. Hence the objective of the present research is in the development and evaluation of Pregabalin powder for oral solution which will be evaluated for comparable physico-chemical characteristics to LYRICA® Pregabalin oral solution as well as to evaluate the stability of the designed product in Sachet pack. By this approach, we can reduce the bulkiness of the product pack which makes it easy to carry anywhere; since the product is in powder form it will be stable as compared to liquid form and also the powder will be reconstituted with water as and when needed by the patients / care giver. With all these necessary changes in the product as well as in pack design we can definitely expect a stable and cost-effective alternative of Pregabalin drug product for the patients.

Materials & Methods

Materials

Pregabalin from Divis; Sorbitol from Zigamed; Sucralose from JK Sucralose; Strawberry flavor from Givaudan; Sodium Citrate & Sodium Benzoate from Avantor Performance Materials. All other reagents, salts, solvents used are of analytical grade.

Methods

Pregabalin is official in United States Pharmacopoeia (USP). The Assay and Related Substance methods mentioned in the compendial monograph is suitably modified and adopted for the analysis. All other general testing methods viz. Particle Size Distribution by Laser Diffraction, Particle Size Distribution by Sieve Analysis, Bulk density, Tapped density, Compressibility Index, Hausner Ratio, Angle of Repose, % LOD, Specific Gravity, Viscosity, pH, Microbial Enumeration Testing was done as per USP general chapter.

Experimentation, Results & Discussion

Pregabalin API Characterization

Pregabalin (Active Pharmaceutical Ingredient) was characterized with respect to

Alpine air jet sieve analysis for determining particle size distribution (PSD): These testing measures the particle size profiles in powdered ingredients and products. The Alpine uses an air jet to lift particles from the surface in conjunction with a vacuum to draw them back down and through the sieve. This action prevents sieve binding. In this method the results are reported in terms of % retained on each sieve. See Table 1 for PSD results.

Bulk density (BD) / tapped density (TD) and inference of Carr's index (CI) and Hausner ratio (HR) from the density data there of: Determination of bulk and tapped densities is a method to determine the bulk densities of powdered drugs under loose and tapped packing conditions respectively. Loose packing is defined as the state obtained by pouring a powder sample into a vessel without any consolidation, and tapped packing is defined as the state obtained when the vessel containing the powder sample is to be repeatedly dropped a specified distance at a constant drop rate until the apparent volume of sample in the vessel becomes almost constant. See Table 2 for density measurements.

Aqueous solubility as a function of pH: Aqueous solubility of Pregabalin was determined in aqueous solution of

different pH viz. 1.2, 4.5, 6.8 & 7.5 and based on the solubility study results, gravimetric grading is done and solubility class is ascertained. See Table 3 for pH Solubility data profile.

Loss on drying: Loss on drying (% LOD) was determined using Infrared moisture balance set at 105 degree Celsius / Auto mode and report the moisture content. See Table 4 for % LOD value.

Particulars	Retained on 600µm sieve	Retained on 250 µm sieve	Retained on 150µm sieve	Retained on 106µm sieve
Pregabalin API from Divis	16%	72%	87%	96%

Table1: Particle size distribution by alpine air jet sieve analysis.

From the particle size distribution data it's evident that Pregabalin API supplied by Divis is of coarser grade having an average particle size of about 100 microns. Since particle size is coarser we can expect good flow due to less interparticulate friction and efficient packing.

Particulars	Bulk Density g / mL	Tapped Density g / mL	Carr's Index %	Hausner Ratio
Pregabalin API from Divis	0.59	0.77	23	1.31

Table 2: Bulk Density, Tapped Density, Carr's Index, Hausner Ratio.

The density data and associated measurements in the form of Carr's Index and Hausner Ratio show the excellent flowability and good packing ability of Pregabalin API. Hence the formulation composition and the process don't need any flow aid to improve the blend flow nor any binder requirement to densify the particles.

pH	API Solubility
1.2 Acid Buffer	1 g in 30 mL
4.5 Acetate Buffer	1 g in 50 mL
6.8 Phosphate Buffer	1 g in 40 mL
7.5 Phosphate Buffer	1 g in 40 mg

Table 3: Aqueous Solubility as a Function of pH.

Pregabalin API is 'soluble' in pH 1.2 Acid buffers with a solubility rate of 33 mg per mL. In others viz. pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer and pH 7.5 Phosphate buffer the Pregabalin API is 'sparingly soluble' with a solubility rate of 20 to 25 mg per mL. Hence there is no need of any solubility enhancement technique to be done in the formulation process since the API exhibits appreciable intrinsic solubility profile.

Particulars	% Loss On Drying (105°C / Auto Mode)
Pregabalin API	0.31

Table 4: Loss on Drying (% LOD).

Pregabalin API was evaluated for % Loss on Drying to get insights related to external moisture or extragranular moisture and is found to be less than 0.5%, which in-turn shows less water activity and less hygroscopic nature of the API.

Brand Product Characterization

The brand product LYRICA® Oral Solution 20 mg/ mL. The brand product was characterized with respect to Appearance, Organoleptics, Excipients, Packing Configuration, Storage, Label Claim, Specific Gravity, Particle Size Distribution (By Malvern Zeta Sizer), Assay (Pregabalin, Methyl Paraben & Propyl Paraben), Related Substances, Viscosity, pH and Microbial Enumeration Testing. The details are presented in the Table 5 below,

Appearance	Clear Colorless Liquid
Organoleptics	Solution is Strawberry flavored and tastes sweet
Excipients	Artificial strawberry #11545, dibasic sodium phosphate anhydrous, methylparaben, monobasic sodium phosphate anhydrous, propylparaben, purified water, and sucralose
Packing Configuration	16 fluid ounce white High Density Polyethylene (HDPE) bottle with a polyethylene-lined closure; Total Volume is 473 mL
Storage	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature)

Label Claim	Each mL contains 20 mg of Pregabalin
Specific Gravity	1.02
Particle Size Distribution	No visible particles
Assay (Pregabalin)	99.80%
Assay (Methyl Paraben)	97.7
Assay (Propyl Paraben)	91.7
Related Substances	Highest Unknown Impurity (Relative Retention Time: 6.33): 0.07%, Total Impurities: 0.37%
Viscosity	1.1
pH	6.1 (Buffered)
Microbial Enumeration Testing	Result comply with USP <61> & <62> requirements for Total Aerobic Microbial Count, Total Combined Molds and Yeast Count & *Escherichia Coli*

Table 5: Brand Product Characterization.

The appearance of the product was tested visually against a bright background and the solution is clear and colorless liquid (micromeritically a true solution). Organoleptic property was inferred by giving small aliquots of solution to the willing volunteers and asked them to infer on the taste (during & after), flavor, mouth feel etc. Most of them observed pleasant mouth feel, acceptably flavored with sweet taste. Based on the list of excipients used by the brand product it can be inferred as Artificial strawberry is used as flavor; dibasic sodium phosphate anhydrous and monobasic sodium phosphate anhydrous are used as buffering agents to stabilize and enables the drug to be maintained within solution through favorable pH microenvironment; methylparaben and propylparaben are used as preservatives; purified water as solvent or vehicle; sucralose as sweetener. On the packing aspect, high density polyethylene bottles are used to hold the solution product throughout the shelf life. Based on the labeling storage recommendation, the solution bottles can be safely stored with temperature excursion of minimum 15°C to maximum 30°C. Specific gravity and Viscosity number reveals the product fluidity and nature is equivalent to Water. The brand product solution was subjected to particle size distribution using Malvern Zetasizer which revealed no particles showing the clear appearance of the product. Assay of Pregabalin, Methyl Paraben and Propyl Paraben content in the product complies with the statutory requirements. Impurity (degradation) level of the product was tested by Related Substance method which revealed very limited change and good stability of drug in solution. Solution pH of 6.1 revealed that both dibasic sodium phosphate anhydrous and monobasic sodium phosphate anhydrous are in-sync to create a equilibrium buffering condition for the drug to stay within solution also this pH microenvironment prevents the degradation and salting out (precipitation) of drug from the solution. Since the end product is solution form with sweet taste there is a possibility of microbial growth and to test this ability, Microbial Enumeration Test was performed and it was observed that the brand product solution is unfavorable for microbial growth due to the effective presence of preservatives viz. Methyl Paraben and Propyl Paraben.

Formulation Development of Pregabalin Powder for Oral Solution

Based on the marketed brand product (LYRICA® Oral Solution 20 mg/mL) composition and performance, the target was set for the developed product and initiated preliminary formulation activity using different permutation and combination of excipients to arrive for the final composition listed in Table 6 below, The final composition has Sorbitol as bulking agent, Sucralose as sweetener, Strawberry as flavor, Sodium Citrate as buffering agent and Sodium Benzoate as preservative. The finale blend was characterized with respect to bulk density, tapped density, carr's index, hausner ratio, water by kf and particle size distribution (by sieve analysis). Since Pregabalin constitutes major portion in the final product (about 75%), the density, compressibility and particle size distribution is comparable and not significantly different with respect to pure Pregabalin API no's. The final blend exhibits good flow, good densification characteristics as well as shows a balanced granular to fines ratio as evident from the following particle size distribution numbers mentioned in Table 7.

Ingredients	mg per Sachet
Pregabalin	300
Sorbitol	77
Strawberry Flavor	5
Sucralose	10
Sodium Citrate	5
Sodium Benzoate	3

Table 6: Composition of Pregabalin Powder for Oral Solution.

Bulk density g / mL	Tapped density g / mL		Carr's Index %			Hausner Ratio		Water by Kf
0.55	0.73		25			1.33		3.5
Particle Size Distribution (By Sieve Analysis)								
Sieve ASTM #	20	40	60	80	100	140	200	Pan
% Retained	0	2.4	9.38	17.83	17.49	19.82	26.33	6.75

Table 7: Final Blend Characterization Details.

The finalized composition was optimized by checking the compliance with Center for drug evaluation and research's (CDER's) inactive ingredient database22 (IID) and the details presented in the Table 8 below, The maximum daily dose as per the label information of the marketed brand product LYRICA® Oral Solution 20 mg/mL is 600 mg/day. Based on this information, the developed product can be consumed upto 2 sachets to reach the 600 mg/day dose accordingly the level of every excipient is checked against the IID levels for patient safety and product compliance to regulatory standards.

Ingredients	mg per Sachet	Maximum daily dose (mg)	IID database Maximum Daily Exposure (MDE)	Compliance of the developed product
Pregabalin	300	600	Not Applicable	Not Applicable
Sorbitol	77	154	53460 mg	Yes
Strawberry Flavor	5	10	261 mg	Yes
Sucralose	10	20	1080 mg	Yes
Sodium Citrate	5	10	1900 mg	Yes
Sodium Benzoate	3	6	660 mg	Yes

Table 8: Inactive Ingredient Compliance of the Final Composition.

Based on the above tabulated information it is clearly evident that the excipients used in the final composition are well within the maximum daily exposure limit prescribed in IID at the maximum daily dose amount of the drug product. Further the level of every excipient in the final formulation was optimized and finalized using OFAT (One Factor at a Time) method within the scope of SUPAC (Scale Up and Post Approval Changes) levels prescribed by CDER's USFDA guidance document23. The details as follows in Table 9.

Ingredients	mg per Sachet '-1' Level	mg per Sachet '0' Level	mg per Sachet '+1' Level	Remarks
Pregabalin	300	300	300	Not Applicable
Sorbitol	69.3	77	84.7	± 10% Variation
Strawberry Flavor	4.5	5	5.5	
Sucralose	9	10	11	
Sodium Citrate	4.5	5	5.5	
Sodium Benzoate	2.7	3	3.3	

Table 9: OFAT based optimization of final composition within SUPAC ambit.

Since 5 excipients in the composition was varied at 2 different levels, totally 10 experiments was performed as part of this exercise. The result of the experiment is tabulated below in Table 10.

Ingredients	mg per Sachet '-1' Level	Inference	mg per Sachet '+1' Level	Inference
Pregabalin	300	-	300	-
Sorbitol	69.3	Flow of the final product is poor.	84.7	Flow of the final product is comparable to centre point (77 mg / Sachet).
		Inherent Reconstitution time (without stirring) is slow.		Inherent Reconstitution time (without stirring) is is comparable to centre point (77 mg / Sachet).
Strawberry Flavor	4.5	No appreciable difference observed in the product flavoring as compared to centre point (5 mg / Sachet).	5.5	Intense flavoring effect observed as compared to centre point (5 mg / Sachet) but the flavoring effect is not nauseating but acceptable
Sucralose	9	No appreciable difference observed in the product sweetness as compared to centre point (10 mg / Sachet).	11	Intense sweetening effect observed as compared to centre point (10 mg / Sachet)
Sodium Citrate	4.5	Buffering capacity of the product is compromised as compared to centre point (5 mg / Sachet).	5.5	The pH balance shifts near 7 as compared to 6.1 observed for the centre point (5 mg / Sachet).
Sodium Benzoate	2.7	Preservative efficacy is intact and is comparable to centre point (3 mg / Sachet)	3.3	Preservative efficacy is intact and is comparable to centre point (3 mg / Sachet)

Table 10: OFAT based optimization of final composition within SUPAC ambit.

Manufacturing, Marketing Pack Presentation & Dosing Particulars of Pregabalin Powder for Oral Solution

Manufacturing of Pregabalin powder for oral solution is by direct blending process. Pregabalin, Sorbitol, Strawberry flavor, Sucralose, Sodium Citrate and Sodium Benzoate were sifted through #20 ASTM mesh fitted in Gansons Vibro Sifter and then blended in a Sams Technomek Double Cone Blender at 15 RPM for 10 minutes. After 10 minutes, the entire contents of the blender were sifted through #30 ASTM mesh fitted in Gansons Vibro Sifter and blended again in Sams Technomek Double Cone Blender at 15 RPM for 10 minutes. The final blend was then filled into 3 ply laminated aluminium pouches and finally sealed using Pakona powder filling and sealing machine. The whole manufacturing operation viz. dispensing of raw materials, sifting, blending, filling and sealing was done in the presence of de-humidifier to keep the relative humidity less than 50%. The temperature in the manufacturing area was maintained at 25 degree Celsius using air handling units and heating ventilation air conditioning systems. The market presentation or trade dress of the drug product is by enclosing 10 product filled sachets into a carton along with 15 mL graduated Dispo Van Syringe. During product usage, the patient or care giver will empty the contents of a sachet into a suitable container and reconstitute the contents of the container with 15 mL Water measured using the Syringe provided. One sachet of powder fill upon reconstitution with water gives a total dose of 300 mg Pregabalin per 15 mL or 20 mg Pregabalin per 1 mL. Depending on the Physicians prescription, the right amount can be administered to Pediatric or Geriatric patient group using the Syringe provided along with the marketed pack.

Optimization of Manufacturing Process

The manufacturing process mentioned in the before section was optimized based on the significance and rationality of every unit operation involved in the manufactured process as tabulated below in Table 11.

Unit Operation	Optimization Requirement	Optimization Parameter	Inference & Discussion
Sifting	No	Not Applicable	It's a mechanical process for de-lumping the materials
Blending	Yes	Blending Time: 5 min, 10 min & 15 min @ 15 RPM	Blending time optimization is done by evaluating 'Blend Uniformity' evaluation at different time intervals
Filling & Sachet Sealing	Yes	Pakona's Sachet Out-Put: 30, 45 & 60	Pakona Machine Out-Put optimization (for filling & sachet sealing) is done by evaluating the 'Uniformity of Dosage Units' at different Out-put speed.

Table 11: Optimization of Manufacturing Process.

Blending Time Optimization (Post Intermittent Sifting Process)

The blending time was optimized using blend uniformity evaluation. The sampling points in the Double Cone Blender have been mentioned pictographically below Figure 1 [24].

At each blending time point from within the blender the samples are withdrawn using sample thief with appropriate cc dies in-line with bulk density of the product. The blending time and blend uniformity results has been tabulated below in Table 12.

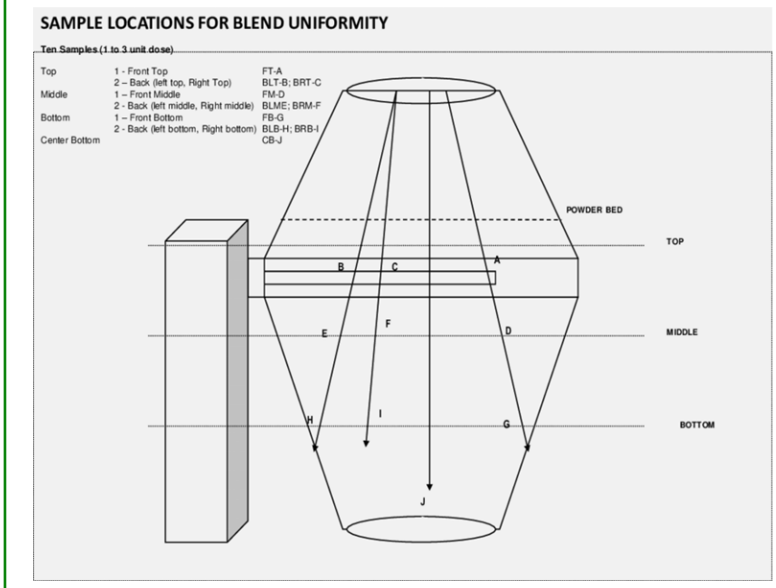

Figure 1: Sample locations for blend uniformity.

Assay value in %	Blending Time		
Sampling Location in Blender	5 min	10 min	15 min
A	98.62	101.52	100.11
B	99.35	101.43	100.23
C	99.82	101.14	98.97
D	98.28	101.27	99.04
E	98.43	100.89	99.84
F	99.08	99.94	100.13

G	99.54	99.87	99.71
H	100	102.19	100.15
I	100.5	99.86	100.16
J	99.06	100.3	99.43
Mean	99.27	100.84	99.777
Minimum	98.28	99.86	98.97
Maximum	100.5	102.19	100.23
Standard Deviation	0.71	0.81	0.48
%RSD	0.72	0.8	0.48

Table 12: Optimization of Blending Time Using Blend Uniformity Evaluation.

From the above tabulated blend uniformity data it is evident that the drug content in blend during blending operation (post intermittent sifting) done at 15 RPM remains same across the time points. There is no significant difference in the blend uniformity data and 10 min blending time was finalized based on the study outcome.

Sachet 'Filling Speed' Optimization

Pakona equipment was used for sachet filling & sealing process. The equipment was set to run at 3 different output speeds viz. 30, 45 & 60 sachets output per minute. To decide the optimal speed range, Uniformity of Dosage Units (Content Uniformity) testing of 10 no's was done at different output speed and the results are tabulated below in Table 13.

Assay value in %	**Filling Speed (Output)**		
Sampling in Output location @ different speed	**30**	**45**	**60**
1	99.84	103.92	101.26
2	99.4	100.71	100.42
3	99.99	103.8	101.11
4	100.47	100.43	101.07
5	101.44	100.98	101.44
6	99.93	100.6	101.37
7	100.47	100.38	100.11
8	100.82	101.43	100.81
9	99.87	100.32	101
10	100.47	100.22	100.47
Mean	100.27	101.279	100.906
Minimum	99.4	100.22	100.11
Maximum	101.44	103.92	101.44
Standard Deviation	0.59	1.41	0.44
%RSD	0.58	1.39	0.44
Acceptance Value (AV)	1.4	3.4	1.1
USP L1 Criteria (< 15)	Complies	Complies	Complies

Table 13: Optimization of Powder Filling Speed Using Content Uniformity Evaluation.

From the above tabulated details of Uniformity of Dosage Units (Content Uniformity) for different speed output of Pakona equipment its evident that the drug content in every sachet manufactured is uniform without much variation/ segregation and the Pakona equipment can be comfortably operated for Pregabalin powder filling into sachet at the speed range of 30-60 sachets output per minute.

Stability Evaluation

Pregabalin powder for Oral solution filled in sachet was evaluated for stability as per ICH at accelerated storage condition (40°C/75%RH for 6 months). Description, Assay (Pregabalin, Sodium Benzoate), Related Substances, Water by Kf & Microbial Enumeration Testing was done and tabulated below in Table 14; Also the sachet containing the powder was reconstituted in water and the compounded solution was stability evaluated (on-standing) at room temperature for 12, 24 & 36 hrs and evaluated for Appearance, Organoleptics, Viscosity, pH, Buffering capacity, Assay (Pregabalin, Sodium Benzoate), Related Substances, & Microbial Enumeration Testing. Based on the presented stability results, it's clear that Pregabalin is stable in both solid state form - powder blend in sachet as well as in the reconstituted solution form for about 36 hours.

Test Particulars	Initial	40°C / 75%RH 1st Month	40°C / 75%RH 3rd Month	40°C / 75%RH 6th Month
Stability of Powder for oral solution (PFOS) in sachet				
Description	White to off-white powder	White to off-white powder	White to off-white powder	White to off-white powder
Assay (Pregabalin) 90.00 – 110.00%	100.8	100.3	99.8	100.1
Assay (Sodium Benzoate) NLT 80.00%	99.3	98.9	96.4	93.9
Related Substances				
Highest Unknown Impurity {NMT 0.2%}	0.02	0.03	0.07	0.13
Total Impurity {NMT 1%}	0.21	0.23	0.26	0.31
Water by Kf (% Moisture Content)	3.6	3.4	3.4	3.6
Microbial Enumeration Testing	Result comply with USP <61> & <62> requirements	Result comply with USP <61> & <62> Requirements	Result comply with USP <61> & <62> Requirements	Result comply with USP <61> & <62> requirements
Stability of reconstituted powder for oral solution				
Test Particulars	**Initial**	**12 hrs @ Room Temperature**	**24 hrs @ Room Temperature**	**36 hrs @ Room Temperature**
Appearance	Clear colorless liquid	Clear colorless liquid	Clear colorless liquid	Clear colorless liquid
Organoleptics	Strawberry flavored Sweet tasting liquid	Strawberry flavored Sweet tasting liquid	Strawberry flavored Sweet tasting liquid	Strawberry flavored Sweet tasting liquid
Viscosity	1	1	1	1
pH	6	5.9	6.1	6
Buffering Capacity	Intact	Intact	Intact	Intact
Assay (Pregabalin) 90.00 – 110.00%	100.1	99.8	99.9	99.7

Assay (Sodium Benzoate) NLT 80.00%	99.5	99.7	99.8	99.8
Related Substances				
Highest Unknown Impurity {NMT 0.2%}	0.02	0.01	0.03	0.02
Total Impurity {NMT 1%}	0.22	0.21	0.21	0.21
Microbial Enumeration Testing	Result comply with USP <61> & <62> requirements	Result comply with USP <61> & <62> Requirements	Result comply with USP <61> & <62> Requirements	Result comply with USP <61> & <62> requirements

Table 14: Stability Evaluation.

Hence the care giver or pharmacist or paramedic can very well hold the reconstituted solution and can be best used for drug administration to patients for upto 36 hours from the time of reconstitution. Based on the stability results, the shelf life of the developed Pregabalin powder for oral solution in sachet is 24 months at USP controlled room temperature: The temperature maintained thermostatically that encompasses at the usual and customary working environment of 20°-25° (68°-77 °F). Excursions between 15° and 30° (59° and 86 °F) that are experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed.

Pharmacoeconomics

LYRICA® Pregabalin oral solution, 20 mg/mL packed in 473 mL bottle costs about 1300 US dollars and the cost of the final developed product - Pregabalin powder for oral solution, 300 mg per sachet (this powder upon reconstitution yields 20 mg/mL) costs 2.1 US dollars. At the metric level to the cost of the developed product is way less compared to brand – 300 mg dose of Pregabalin is present in 15 mL hence the cost equivalent of brand product for this 15 mL is 41.2 US dollars whereas for the developed product it remains as 2.1 US dollars. From the end user view point the developed product is attractive from the perspective of economy, logistic (no issue of bulkiness), dosing convenience and acceptably flavored and tasty.

Conclusion

In this research work, an honest attempt was made to develop and commercialize the Pregabalin powder for oral solution in sachet form. The motivation of this research work is in bringing a competitive differentiated generic product that will be convenient for the patients from financial, user-friendly and ease of mobility perspective. Before starting the research work, the quality target product profile (QTPP) was well defined by doing thorough study of the brand product, LYRICA® Pregabalin oral solution. Then the Pregabalin API was sourced after thorough review of drug master file (DMF) details and the sourced API was well characterized to decide the composition and process design. To keep things simple, the non-drug ingredients (excipient) addition in the composition was chosen that are pharmaceutically essential (Qualitative scope) and were kept minimal (Quantitative scope) without compromising on achieving comparable QTPP against the brand product. The composition and process was well optimized from IIG, SUPAC & QbD ambit. The final composition was stability evaluated in both solid-state and reconstituted-form and found to be stable and effective. Pharmacoeconomically the developed product is cost-effective and expected to give tough fight against the market erosion / new generic entries and would remain competitive and relevant to its objective and utility.

Conflict of Interest: None

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