Research Article

STABLE COMPOSITION AND SIMPLE MANUFACTURING PROCESS OF PREGABALIN CAPSULES

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ABSTRACT

Pregabalin is indicated for epilepsy. Pregabalin drug product is available in market as Solution, Capsules and Extended Release tablets. This research aims to formulate a stable composition and process for Pregabalin Capsules that exhibits comparable physico-chemical characteristics to brand product capsules. Before initiating the formulation work, API and Brand product was completely characterized. Excipients were selected based on the brand product characterization and Drug-Excipient compatibility study. Based on the API characterization, brand product characterization and Drug-Excipient compatibility study, preliminary formulation work was initiated. A direct blending process was followed for final blend preparation. The final blend was filled into capsule shells using ACG-Pam MF-30 capsule filling machine. During stability evaluation of different prototypes at accelerated storage condition of 40°C / 75% RH, the formulation containing Colloidal Silicon Dioxide showed higher level of impurity, Pregabalin Related Compound-C (4-Isobutylpyrrolidin-2-one) or Pregabalin Lactam Impurity. The observation of incompatibility of Pregabalin with Colloidal Silicon Dioxide was doubly confirmed by Drug-Excipient compatibility studies. When the incompatibility reaction was investigated at molecular level, it was observed that one mole of water gets released when Pregabalin reacts with Colloidal Silicon Dioxide. This was further confirmed by mass balancing the molecular weights of reactants, Pregabalin and Colloidal Silicon Dioxide with the product, Pregabalin Related Compound-C. Thus the final formulation was made without Colloidal Silicon Dioxide and has Lactose Anhydrous as diluent; Pregelatinized Starch as Binder and Disintegrant; and Talc as glidant and lubricant. The drug product showed comparable physico-chemical characteristics with brand and also found to be stable.

Key Words: Direct Blending, Incompatibility with Colloidal Silicon Dioxide.

INTRODUCTION

Pregabalin is a 3-isobutyl chemical derivative of inhibitory neurotransmitter γ -amino butyric acid (GABA).¹ An anti-epileptic drug, Pregabalin acts by blocking Ca^{+2} ion entry into neuron by binding to voltage gated Ca^{+2} channels at the synapse region in turn modulating the release of excitatory neurotransmitters such as Glutamic acid, Noradrenalin, etc. According to WHO latest records, around 50 million people are suffering with epilepsy worldwide and around 2.4 million people are being diagnosed every year. Recent estimates show that 70% of people suffering with epilepsy can live seizure free if they are diagnosed and treated properly. Besides treating epilepsy Pregabalin is also used for management of fibromyalgia, post therapeutic neuralgia, neuropathic pain etc. Because of economic reasons, generic prescriptions are increasing now-a-days when compared to brand prescriptions. Therefore the current research targets the need to develop a cost effective, robust and quality generic for the Pregabalin innovator product.^{2, 5-10}

MATERIALS & METHODS

Pregabalin from Divi's, India; Anhydrous Lactose from DFE, Germany; Pregelatinized Starch from Colorcon, USA; Talc from Imerys, USA; Colloidal Silicon Dioxide from Evonik, USA; Empty Hard Gelatin Capsule Shells from Acg, India; All the reagents, salts, solvents used were of USP grade from Avantor & Merck, India. Columns and Impurities used were of USP

monograph specified. Brand product Capsules, 1 bottle of each strength was sourced with licence in-compliance with local and international regulatory norms.

Equipments & Instruments

#20 and #40 ASTM Sieves of Dharma Scientifics; Double Cone Blender of Gansons; Manual Capsule Filling Machine (MF-30) of Acg-Pam; Stop Watch of Casio; De-humidifier of Origin; Digital Hygrometer of HTC; Electronic Weighing Balance of Shimadzu; Vernier Caliper of Mitutoyo; Disintegration Tester With Disks of Electrolab; Bulk Density / Tap Density Tester of Electrolab; Particle Size Distribution Tester of Electrolab; Dissolution Tester of Electrolab; HPLC of Waters; Milliq Water of Merck Millipore; Infra Red Moisture Balance of Ohaus.

Methods

Pregabalin and Pregabalin Capsules were official in USP. USP method was followed in the determination of Assay, Related Substances and Dissolution. USP general chapter guidance was followed for the determination of Bulk Density / Tapped Density, Loss On Drying, Particle Size Distribution, Blend flow, Weight Variation of Capsules, Weight Variation of Capsule fill content, Lock Length Variation, Disintegration Time and Uniformity of dosage units.

API Characterization

API was characterized with respect to Bulk density, Tapped density, Angle of repose and Particle size distribution.

Brand Product Characterization

All strengths of the brand product was characterized with respect to description of capsule, size of the capsule shell, weight of capsule and content, capsule fill weight, lock length, disintegration time, dissolution, composition and packaging configuration.

Drug-Excipient Compatibility Study

Binary mixtures of drug and excipient in the ratio of 1:1 was prepared and placed in a Petridish and exposed to 40°C / 75% RH for 14 days in both open and closed condition. The samples were analyzed for assay and related substances.³⁻⁴

Formulation

Based on API characterization, Brand product evaluation and Drug-excipient compatibility study results, excipients were selected for prototype formulation. Since 25 mg is the lowest strength, trials were taken to optimize the composition based on stability outcome. A direct blending process with a dose proportional approach was followed. Except Colloidal Silicon Dioxide and Talc, all the ingredients were sifted through #20 ASTM mesh and blended in a double cone blender at 15 rpm for 15 min. The Colloidal Silicon Dioxide and Talc were finally sifted through #40 ASTM mesh and blended with the bulk at 15 rpm for 5 min. The final blend was characterized with respect to bulk density, tapped density, angle of repose and blend uniformity. The final blend was then filled into hard gelatin capsule shells using manual capsule filling machine. Post filling, the filled capsules were evaluated for weight variation of filled capsules, weight variation of fill content, lock length variation, disintegration time and dissolution. The filled capsules were then packed in HDPE bottles capped with PP closures and evaluated for stability at 40°C / 75% RH for 3 months. During stability, the capsules were evaluated for Assay, Related Substances and Dissolution. Based on stability evaluation results of 25 mg strength, the composition was finalized and final composition and process was adopted and evaluated for other strengths.

Table. 1 API Characterization

Test	Result	Remarks
Bulk Density, g / mL	0.53	Interparticulate friction is minimal. Air permeability is good. Manageable flow. Compressibility is good.
Tapped Density, g / mL	0.78	
Angle of Repose, °	29	Flowable
Particle Size Distribution	d90 – 850 microns	Coarser grade

Table.2 Brand Product Characterization

Test	25 mg	50 mg	75 mg	100 mg	150 mg	200 mg	225 mg	300 mg
Description	Opaque white color imprint of Company name on cap and PGN Strength on body							
Composition	Lactose, Starch, Talc, Colloidal Silicon Dioxide, Sodium Lauryl Sulphate, Gelatin, Titanium dioxide, Shellac, Propylene Glycol, Potassium Hydroxide and Colored Iron Oxides.							
Packing Configuration	White High Density Polyethylene bottle with White Polypropylene Child Resistant closure							
Capsule Size, mm	4	3	4	3	2	1	1	0
Mean Capsule weight, mg	139	243	139	196	250	344	377	497
Mean Fill weight, mg	100	200	100	133	200	267	300	400
Mean Lock length, mm	14.3	15.7	14.3	15.8	17.7	19.3	19.3	21.5
Mean Disintegration Time, min	4	5	4	5	4	5	5	5
Dissolution	Time (min)	Mean % Drug Dissolved (n=6 units)						
USP-II (Paddle) 50 RPM, 900 mL, 0.06 N HCL	10	92	95	94	93	95	98	95
	15	95	97	95	95	95	98	97
	30	95	97	97	95	97	99	97
	45	95	98	97	98	99	99	97

Table.3 Drug-Excipient Compatibility Study

Particulars	40°C / 75% RH – 14 days (Open)			40°C / 75% RH – 14 days (Closed)		
	Assay	Related Compound (Lactam) RRT 5.55	C	Assay	Related Compound (Lactam) RRT 5.55	C
API	96	-		99	-	
API+Lactose Anhydrous	97	-		98	-	
API+Pregelatinized Starch	97	-		99	-	
API+Colloidal Silicon Dioxide	96	0.01		98	0.01	
API+Talc	96	-		98	-	

Table.4 Prototype Formulation

Particulars	Pregabalin Capsules, 25 mg (With Colloidal Silicon Dioxide)	Pregabalin Capsules, 25 mg (Without Colloidal Silicon Dioxide)
Composition	mg / capsule API – 25 Lactose Anhydrous – 30 Pregelatinized Starch – 27 Colloidal Silicon Dioxide – 5 Talc – 13 Fill weight – 100 Capsule Size – ‘4’	mg / capsule API – 25 Lactose Anhydrous – 30 Pregelatinized Starch – 32 Colloidal Silicon Dioxide – 0 Talc – 13 Fill weight – 100 Capsule Size – ‘4’
Blend Characterization	Bulk density, g / mL – 0.58 Tapped density, g / mL – 0.74 Carr’s Index, % – 22 Hausner Ratio – 1.28 Angle of Repose, ° – 28 Blend Uniformity, % Mean – 98 Minimum – 95 Maximum – 100	Bulk density, g / mL – 0.52 Tapped density, g / mL – 0.76 Carr’s Index, % – 32 Hausner Ratio – 1.46 Angle of Repose, ° – 34 Blend Uniformity, % Mean – 97 Minimum – 94 Maximum – 99
Capsule Characterization	Mean Caps Wt, mg – 141 Mean Fill Wt, mg – 99 Mean Lock Length, mm – 14.5 Mean DT, min – 5 % Mean Disso, 15 min – 95 Content Uniformity, % Mean – 98 Minimum – 94 Maximum – 99 Related Substances % Related Compound-C – 0.03	Mean Caps Wt, mg – 143 Mean Fill Wt, mg – 97 Mean Lock Length, mm – 14.2 Mean DT, min – 5 % Mean Disso, 15 min – 97 Content Uniformity, % Mean – 97 Minimum – 95 Maximum – 99 Related Substances % Related Compound-C – Not Detected
Stability Characterization (3rd Month – 40°C / 75% RH)	Assay – 95 Related Substances % Related Compound-C – 0.44 Mean DT, min – 5 % Mean Disso, 15 min – 93	Assay – 97 Related Substances % Related Compound-C – Not Detected Mean DT, min – 5 % Mean Disso, 15 min – 95

Table. 5 Composition of Pregabalin Capsules, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg & 300 mg

Ingredients		mg / capsule						
		50 mg	75 mg	100 mg	150 mg	200 mg	225 mg	300 mg
Pregabalin		50	75	100	150	200	225	300
Lactose Anhydrous		60	8.25	11	16.5	22	24.75	33
Pregelatinized Starch		64	8.37	11.13	16.75	22.67	25.12	33.5
Talc		26	8.38	11.17	16.75	22.33	25.13	33.5
Fill weight		200	100	133.3	200	267	300	400
Particulars		Blend Characterization						
Bulk density, g / mL		0.53	0.51					
Tapped density, g / mL		0.77	0.80					
Carr's Index, %		31.1	36.3					
Hausner Ratio		1.45	1.57					
Angle of Repose, °		27	32					
Blend Uniformity, %	Mean	98	97					
	Minimum	96	95					
	Maximum	99	100					
Particulars		Capsule Characterization						
Capsule size		3	4	3	2	1	1	0
Mean Capsule Fill Weight (mg)		246	137	174	248	331	365	499
Mean Fill Weight (mg)		203	98	135	198	264	304	402
Mean Lock Length (mm)		15.5	14.1	15.5	17.8	19.5	19.6	21.1
Mean Disintegration Time, min		5	5	4	5	5	4	5
Content Uniformity, %	Mean	97	98					
	Minimum	95	96					
	Maximum	99	99					
% Related Substances	Related Compound-C	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected
Dissolution		Mean % Drug Dissolved (n=6 Units)						
USP-II (Paddle) 50 RPM, 900 mL, 0.06 N HCL	Time, min							
	10	95	94	95	93	94	96	95
	15	97	96	96	94	95	97	98
	30	98	98	99	98	97	99	100
Stability	45	99	100	99	99	99	99	100
	Assay, %	98	97	98	97	98	98	97

Characterization (3 rd Month – 40°C / 75% RH)	% Related Compound-C	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected
Mean DT, min		5	5	5	5	5	5	5
% Mean Disso in 15 min		94	96	95	94	95	95	96

Figure.1 Schematic Representation of Pregabalin Incompatibility with Colloidal Silicon Dioxide

RESULTS & DISCUSSION

API Characterization

API was characterized with respect to Bulk Density, Tapped Density, Angle of Repose and Particle Size Distribution and the details as follows in the Table.1. From the data it is evident that the API has optimal flow and compressibility characteristics ideal for a direct blending process.

Brand Product Characterization

The brand product, was characterized with respect to Description of Capsule, Size of Capsule shell, Weight of capsule & content, Capsule fill weight, Lock length of capsule, Disintegration time, Dissolution, Composition and Packaging configuration and the details as follows in Table.2.

From the data it is evident that the brand has made scale-up / scale down or dose proportional design i.e. for 25 mg and 50 mg a common blend was made and for 75 mg to 300 mg a separate common blend was made. From the dissolution profile it is evident that the rate and extent of drug release is of “rapid and completely dissolving type”.

Drug-Excipient Compatibility Study

Based on the API and brand product characterization, excipients were selected for checking the compatibility with API and the details as follows in Table.3. From the tabulated data it is evident that there is a possible interaction of API with Colloidal Silicon Dioxide in the physical mixture itself. For the preliminary formulation work, Colloidal Silicon Dioxide was considered as part of composition and influence of the same on drug degradation was monitored during stability evaluation.

Formulation

The preliminary formulation work was initiated with 25 mg strength. Two (2) batches were made by direct blending process, one batch including Colloidal Silicon Dioxide and the other excluding Colloidal Silicon dioxide. The final blend of both the batches were completely characterized with respect to bulk density, tapped density, compressibility index, hausner ratio, angle of repose and blend uniformity in 10 different locations in blender. The final blend was then filled in hard gelatin capsule

shells using manual capsule filling machine, the filling operation was characterized with respect to Weight of capsule & content, Capsule fill weight, Lock length of capsule, Disintegration time, Uniformity of dosage units (in 10 different locations in encapsulated frame) and Dissolution. The filled capsules were then packed in high density polyethylene bottles equipped with polypropylene closures and stability evaluated at 40°C / 75% RH for 3 month and evaluated for Assay, Related Substances, Disintegration Time and Dissolution.

From the Table.4 it is evident that though the batches made with and without colloidal silicon dioxide showed good blend flow, good capsule fill characteristics and comparable disintegration and dissolution characteristics with the brand product but from the stability view point, the batch made with Colloidal Silicon Dioxide showed raise in drug degradation. There exists an incompatibility reaction possibly the degradation of API in the presence of Colloidal Silicon Dioxide which specifically resulted in rise of Pregabalin Related Compound-C (4-Isobutylpyrrolidin-2-one). Schematically the reaction is represented as follows in Fig.1

Based on the above evidence, the formulation was proceeded for other strengths without Colloidal Silicon Dioxide and for every strength blend, capsule and accelerated stability evaluation was done and found comparable to the brand product. In the following Table.5 the complete formulation, blend, capsule and stability characterization details of other strengths were provided.

CONCLUSION

A stable composition with a simple manufacturing process was arrived for Pregabalin Capsules, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg & 300 mg which showed comparable physico-chemical characteristics to that of the marketed brand product. All the formulated strengths showed ‘rapid and completely dissolving’ dissolution profile. Also the excipients used in the formulation were safe and were selected based on the API and brand characterization data and was further screened and selected based on the drug-excipient compatibility study. A simple direct blending process was followed in the formulation and was able to achieve optimal blend and encapsulation characteristics which were confirmed by blend uniformity and content uniformity evaluation. The finalized composition was found to be stable at accelerated stability condition of 40°C / 75%

RH for 3 months. One of the major finding during the prototype formulation is the identification of incompatibility of Pregabalin and Colloidal Silicon Dioxide.

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