

Formulation and Evaluation of Pulsatile Drug Delivery System of Pregabalin

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Abstract

Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Pregabalin is a new anticonvulsant drug indicated as an add on therapy for partial onset seizures and for certain types of neuropathic pain. It was designed as a more potent successor to a related drug, gabapentin. Pregabalin binds to the alpha2-delta subunit of the voltage-gated calcium channel in the central nervous system.

Keywords Pregabalin; Pulsatile drug delivery; Pvp k30; Ethylcellulose; USP type II dissolution apparatus

Introduction

Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Pregabalin is a new anticonvulsant drug indicated as an add on therapy for partial onset seizures and for certain types of neuropathic pain. It was designed as a more potent successor to a related drug, gabapentin. Pregabalin binds to the alpha2-delta subunit of the voltage-gated calcium channel in the central nervous system. While pregabalin is a structural derivative of the inhibitory neurotransmitter γ -aminobutyric acid (GABA), it does not bind directly to GABAA, GABAB, or benzodiazepine receptors, does not augment GABAA responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake [1,2].

Materials and Methods

Pregabalin is a gift sample from Hetero Drugs Hyderabad Andhra Pradesh, Polyvinyl pyrrolidone, Lactose, Dicalcium phosphate, ethylcellulose from S.D. Fine chemicals limited (Hyderabad) the entire chemicals of analytical grade and double distilled water used throughout the experiment [3].

Formulation of tablets

Tablets with drug (pregabalin) are prepared by the direct compression method in two layers. In first layer pregabalin, lactose, pvpk are used and in the second layer pregabalin, ethyl cellulose, isopropyl alcohol, dicalcium phosphate are used.

Technology Applied: Direct compression.

Diluent: lactose

Binder: polyvinyl pyrrolidone

Solvent: isopropyl alcohol

Hydrophobic polymer: ethyl cellulose

Diluent: dicalcium phosphate

This is prepared in two layers which releases in the form of two pulse. In first layer pregabalin, lactose, pvpk are used. Accurately weighed quantities of these polymers and drug are taken in mortar and pestle and triturated and passed through the sieve no # 20. In the second layer pregabalin, ethyl cellulose, isopropyl alcohol, dicalcium phosphate are used in this first the ethylcellulose was dissolved in a little quantity of isopropyl alcohol then this is taken in the mortar and pestle to this required quantities of pregabalin, dicalcium phosphate are added and triturated this is passed through the sieve no #10 and dried in a hot air oven for 15 min and this again passed through the sieve no # 20. The mixture equivalent to 250 mg was compressed into tablets with 10 mm round concave punches at a hardness of 6 kg/cm² [4-6].

Pre compressional parameters

Physical properties: The powder of excipients and drugs were characterized by angle of repose, bulk density, tapped density, % compressibility, and Hausner's ratio. The flow properties of powders have a great impact on tableting because non-uniform flow will result in variation in weight of the tablets. It also creates problem of hardness during compression of tablets.

Angle of repose: Angle of repose has been defined as the maximum angle possible between the surfaces of pile of powder and horizontal plane. It is performed to determine the flow rate of powder done by the funnel method. The powder mass was allowed to flow through the funnel orifice kept vertically to a plain paper kept on the horizontal surface, giving a heap angle of powder on paper. The angle of repose was calculated by substituting the values of the base Radius 'R' and pile Height 'H' in the following equation:

$\tan \Theta = H/R$ or

$\Theta = \tan^{-1} H/R$

Bulk density (Db): It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape, and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured, which is the initial bulk volume. Then it is expressed in g/mL and is given by;

$$Db = M/V_o$$

Where, M is the mass of powder, V_o is the bulk volume of the powder.

Tapped density (Dt): Ten gram of powder was introduced into a clean, dry 100 mL measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in g/mL and is given by,

$$Dt = M/V_t$$

Where, M is the mass of powder, V_t is the tapped volume of the powder.

Measures of powder compressibility: Carr developed an indirect method of measuring powder flow from bulk densities (Table 1). The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated by

$$\% \text{ Compressibility} = \frac{D_o - D_f}{D_o} \times 100$$

where, D_f =Fluff of poured bulk or bulk density and D_o =Tapped or consolidated bulk density.

Carr Index (Consolidation %)	Flow
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
33 – 38	Very poor
>40	Very very poor

Table 1: Grading of the powders for their flow properties according to Carr's Index.

Hausner's ratio: Hausner's ratio is the measure of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Hausner ratio [7-10].

which are calculated using the following formula.

$$\text{Hausner's ratio} = \frac{D_o}{D_f}$$

where, D_f =Fluff of poured bulk or bulk density and

D_o =Tapped or consolidated bulk density

Grading of the powders for their flow properties-Hausner ratio

Post compression parameters

The tablets prepared using the formula shown in the Table 2 was subjected to the following quality control tests.

Thickness and diameter: Control of physical dimensions of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of 20 tablets were measured using Vernier Calipers. Average and standard deviation of 20 tablets were recorded.

Hardness: The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. Average and standard deviation of 20 tablets were recorded. It is expressed in kg/cm^2 [11].

Uniformity of weight: This test is performed to ensure the uniformity of weight of each tablet which should be in the prescribed range. This was done by weighing 20 tablets and average and standard deviation were calculated. As per monograph, not more than two of the individual weights deviate from the average weight by more than the percentage shown in the Table 2 and none deviate by more than twice the percentage. The mean and standard deviation were determined [12].

Average weight of tablets (mg) (I.P.)	% Deviation allowed
Less than 80	10
80–250	7.5
More than 250	5

Table 2: Indian Pharmacopoeia specifications for tablet weight variation.

Content uniformity: This test was performed to ensure the uniformity of content of the drug which was considered to be in the 5% range. This test was performed by selecting 20 tablets randomly and powdered. A quantity of powder equivalent to 150 mg of pregabalin was dissolved in 100 mL of 0.1 N hydrochloric acid solution in 100 mL volumetric flask. The so formed sample was filtered and diluted and the absorbance was measured at 461 nm using 0.1 N hydrochloric acid solution as blank and the % drug content was calculated using equation for standard plot. The procedure was repeated on two more samples. Average and standard deviation of three readings were calculated [13].

Drug release study

In vitro release studies: The in vitro drug release studies were carried out using a USP Type II dissolution apparatus. 0.1N HCL pH 1.2 was used as a dissolution media for 2 h and phosphate buffer pH 6.8. The temperature was maintained at 37°C. Sample (6 mL) was withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. Samples were analyzed calorimetrically at 461 nm and the cumulative % drug release was calculated [14].

Accelerated stability studies: A study of stability of pharmaceutical product is essential. These studies were designed to increase the rate of chemical or physical degradation of the drug substance or product by

using exaggerated storage conditions. Stability studies are important to prevent the economic repercussions of marketing of an unstable product, since subsequent withdrawal and reformulation may lead to considerable financial loss. From the point of view of safety to patient, it is important that the patient receives a uniform dose of the drug throughout the shelf life of the product.

The optimized tablets were packed in a cover and stored in a stability chamber at 40±2°C and 75±5 % RH for 90 days. The tablets were evaluated for physical appearance, hardness, drug content, and in vitro dissolution characteristics and compared with the tablets evaluated immediately after manufacturing.

The results obtained in these methods and the discussion arrived from them are given in the following chapter "Results and Discussion" [15-20].

Results and Discussions

This is prepared in two layers which releases in the form of two pulse. In first layer pregabalin, lactose, pvpk are used. Accurately weighed quantities of these polymers and drug are taken in mortar and pestle and triturated, passed through the sieve no # 20. in the second layer pregabalin, ethyl cellulose, isopropylalcohol, dicalcium phosphate are used. In this first the ethylcellulose was dissolved in a little quantity of isopropylalcohol then this is taken in the mortar and pestle to this required quantities of pregabalin, dicalcium phosphate are added and triturated this is passed through the sieve no #10 and dried in a hot air oven for 15 min and this again passed through the sieve no # 20. The mixture equivalent to 300 mg was compressed into tablets with 10 mm round concave punches at a hardness of 6 kg/cm². Eight formulations F₁-F₈ were formulated by varying concentration of pvpk and ethylcellulose to study effect of release of pregabalin from the tablets effect of polymer concentration on the Thickness and diameter, hardness, uniformity of weight, uniformity of content and in vitro release studies.

To investigate the effect of release of pregabalin from the tablets eight batches F₁-F₈ were prepared. The release of the drug from all pulsatile release formulations can be observed. The higher drug release was observed with formulations F₈. F₁-F₈ indicates the different formulas prepared for better results. From 8 different formulations last formulation that is F₈ found to give better results in releasing the drug in pulse form.

Thickness and diameter: The results of thickness of formulations were in the range 4.84 ± 0.05 to 4.55 ± 0.25.

Hardness: The results of hardness of formulations were in the range 6.5 ± 0.3 to 5.9 ± 0.2.

Uniformity of content: The results of uniformity of content of formulations were in the range 98.23 to 98.65.

In-vitro drug release data and profiles

The dissolution conditions used for studying the drug release from the pulsatile release tablets.

Apparatus: USP Type 2 (paddle)

Agitation speed (rpm): 100

Medium: 0.1N HCl (pH 1.2), phosphate buffer (PH 6.8)

Temperature: 37.0 ± 0.5 C

Time: 5 min, 10 min, 15 min, 30 min, 1 h, 1.30 h, 2 h, 2.30 h, 3 h, 3.30 h, 4 h, 4.30 h, 5 h, 5.30 h, 6 h, 6.30 h and 7 h

Wavelength: 461 nm.

Accelerated stability studies: Significant changes were not noticed. The formulation F₈ was found to be stable after exposure to accelerated temperature and humidity conditions for a period of 3 months. No significant changes were seen in physical evaluation parameters.

Conclusion

The pulsatile tablets of pregabalin were prepared in two layers, containing the immediate release drug layer and hydrophobic rupturable polymer ethylcellulose which releases in the intestine in 3 h. Procedure to manufacture Pulsatile tablets of pregabalin by direct compression and wet granulation was established. The tablets were evaluated for pharmacopoeial and non-pharmacopoeial tests. Based on the results, F₈ was identified as better formulation amongst all formulation developed for Pulsatile tablets. An in vitro release profile of optimized formulation of Pulsatile tablets of pregabalin (F₈) was found to release the in 5 min and 3 h followed by 98% of release.

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