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(54) Title: NOVEL STABILIZED INJECTABLE FORMULATION OF PREGABALIN

(57) Abstract: The present invention relates to an injectable pregabalin formulation which is stable in between pH 4.0 to 8.0. Further, the present invention relates to a process for manufacturing the said injectable pregabalin formulation. The injectable formulation of pregabalin according to the present invention is administered intravenously to the patients requiring pregabalin treatment.



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Field of the invention:

The present invention relates to stabilized injectable formulation of pregabalin and the process of preparing it. This injectable formulation is administered intravenously to the patient requiring Pregabalin treatment.

Background and Prior Art:

Pregabalin was first disclosed in US patent no. 5,563,175 by Richard B. Silverman et al of the Northwestern University for the treatment of seizure disorder. Chemically Pregabalin is (S)-(+)-3-aminomethyl-5-methyl hexanoic acids.

Pregabalin is a structural analogue of, but functionally unrelated to, the naturally occurring transmitter GABA (gamma-aminobutyric acid). Pregabalin acts by binding to the alpha-2-delta subunit of voltage-gated calcium channels and is related to the endogenous inhibitory neurotransmitter gamma-aminobutyric acid (GABA), which is involved in the regulation of brain neuronal activity.

In the United States, Pregabalin has been approved for the treatment of diabetic peripheral neuropathy, postherpetic neuralgia, and as an adjunctive treatment for partial onset seizures in adults.

In US patent no. 6,001,876 Pregabalin is claimed to be used for treating pain which can be related to any of inflammatory, neuropathic, cancer, postoperative pain etc.

Pregabalin is thought to be useful for treating physiological conditions associated with psychomotor stimulants, inflammation, gastrointestinal damage, alcoholism, insomnia, and various psychiatric disorders, including mania and bipolar disorder.

Pregabalin is marketed by Pfizer in United States of America under the brand name of Lyrica in capsule dosage form in various strengths from 25mg to 300mg.

Lyrica capsules are immediate release formulation and are administered to the patients two or three times daily.

PCT patent application no. WO2007052125 discloses matrix oral dosage form of pregabalin suitable for once a day administration whereas another PCT patent application no. WO2005063229 describes an oral liquid composition of Pregabalin.

Though solid oral and liquid oral dosage forms of pregabalin are known, injectable dosage form of pregabalin is still not reported. Injectable dosage form has its own advantage compared to other dosage forms. Injectable dosage forms provides quick onset of drug action compared to those administered orally. Also the therapeutic response of a drug is more readily controlled by injectable administration since the irregularities of intestinal absorption after oral administration of drug are circumvented.

Injectable dosage forms are normally administered by a professionally trained person, so it is expected that the dose is actually and accurately administered. Additionally when the patient is uncooperative or unconscious, it becomes difficult to administer the drug orally to the patient. In this case, an injectable dosage form is best suited for administration.

The inventors of the present invention have prepared an injectable dosage form of Pregabalin which is stable and well suited for administration to a patient. The injectable formulation is administered intravenously, so the drug directly reaches into the bloodstream via a vein. This causes quick onset of drug action and the therapeutic effect is achieved much quicker.

Object of the Invention:

The main object of the invention is to formulate an injectable dosage form of Pregabalin which is administered through intravenous, intramuscular, subcutaneous route or through infusion, preferably through intravenous route to a patient.

Additional object of the invention is to formulate iso-osmotic injectable dosage form of pregabalin.

One more object of the invention is to provide a process to formulate a stable injectable formulation of pregabalin using normal equipment for preparing injectable formulations.

Summary of the Invention:

The present invention provides a stable injectable formulation of pregabalin. Further, the present invention describes a process for the preparation of the said stable injectable formulation of pregabalin.

Detail Description of the Invention:

Formulating an injectable dosage form has many challenges compared to other dosage forms. As the drug is directly administered to blood circulation, it is essential that the formulation should be of high quality and should provide maximum safety to the patient. Choice of excipients and their quality is a critical factor in formulating an injectable dosage form.

The drug for present invention (Pregabalin) is susceptible to oxidation. Other challenges are with respect to the stability of the formulation. By maintaining a suitable pH condition Pregabalin injectable formulation remains stable. Considering these, the inventor of the present invention has formulated an injectable formulation of pregabalin which is stable and well suited for intravenous administration to a patient. It may also be diluted in commonly used intravenous fluids for infusion administration thereby allowing the drug to be administered with greater regularity in order to obtain a more precise and safer effect.

The injection prepared according to the present invention is a clear colourless solution. So any foreign particles, such as glass residues, fibers, undissolved substances and the like, inside the ampoule or vials is well controlled. This is particularly required while formulating an intravenous injection.

The formulation of the present invention apart from the active pharmaceutical ingredient (Pregabalin) comprises of pharmaceutically acceptable excipients like vehicle, tonicity

adjusting agent, buffering agent, anti-oxidants, pH adjusting agent and other excipients suitable to be used for an intravenous injection.

Vehicles are inert and non-toxic substances having no therapeutic activity. These are administered to provide an effective dose of the active ingredient. They present to body tissues the form of the active ingredient for absorption. Vehicles used in the present formulation can be selected from aqueous vehicle, water miscible vehicle and non-aqueous vehicle. Aqueous vehicle can be water whereas water miscible vehicles are solvents miscible with water. The water miscible vehicles can be ethyl alcohol, polyethylene glycol, propylene glycol and the likes. Non-aqueous vehicles can be fixed oils. The preferred vehicle used in the formulation of present invention is water for injection (WFI).

An intravenous injection is required to be isotonic with body fluids. The term isotonic means that the formulation has essentially the same osmotic pressure as human blood. To make the formulation isotonic, tonicity adjusting agent or tonicity modifiers are used. Tonicity modifiers suitable for this invention include salts and amino acids. The preferred tonicity modifier used is sodium chloride. Desired tonicity of the formulation is between 200 to 400, more preferably the desired tonicity of the formulation is 300.

Stability of the formulation of present invention is pH dependent. During the manufacturing process, the pH of the formulation of present invention is essentially maintained at a range of 5.8 to 6.2, preferably at pH 6.0. This enhances the stability of the injectable formulation. For pH adjustment, a pH adjusting agent is used which can be acid or base. The base can be oxides, hydroxides, carbonates, bicarbonates and the likes. The oxides can be metal oxides such as calcium oxide, magnesium oxide and the likes; hydroxides can be of alkali metals and alkaline earth metals such as sodium hydroxide, potassium hydroxide, calcium hydroxide and the likes and carbonates can be sodium carbonate, sodium bicarbonates, potassium bicarbonates and the likes.

The acid can be mineral acid and organic acids such as hydrochloric acid, nitric acid, phosphoric acid, acetic acid, citric acid, fumaric acid, malic acid tartaric acid and the likes. The preferred base and acid used in the formulation of present invention for pH adjustment are sodium hydroxide and hydrochloric acid respectively.

A buffering agent is also used in the formulation of present invention to stabilize the formulation against chemical degradation that might occur due to pH drift. The buffering agents used in the formulation of present invention can be citrates, acetates, phosphates other organic buffers and the likes. The preferred buffering agent used in present case is citric acid monohydrate.

Pregabalin is susceptible to oxidation and to prevent this, an antioxidant is used in the formulation. An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals, which start chain reactions that can have adverse effect on the purity and stability of the formulation. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions by being oxidized themselves. Sulfites like sodium sulfite, sodium bisulfite, sodium metabisulfite, sodium formaldehyde sulfoxylate, thiourea, sequestering agents such as sodium salt of ethylenediaminetetraacetic acid (EDTA) and acids such as citric acid and the likes can be used as antioxidant.

The process for the preparation of injectable pregabalin formulation according to the present inventions comprises the steps of:

Take water for injection (90% of batch size) in SS container and sparge with 0.2 μ filtered nitrogen until the levels of dissolved oxygen comes to less than 1ppm. Add and dissolve sodium chloride and citric acid monohydrate with continuous nitrogen sparging. Adjust pH to 6.0 (range 5.8 – 6.2) with 1N sodium hydroxide solution and / or hydrochloric acid solution. Add and dissolve pregabalin with continuous nitrogen sparging. Adjust pH to 6.0 (range 5.8 – 6.2) if required with 1N sodium hydroxide solution and / or hydrochloric

acid. Make up the volume to required batch size with nitrogen sparged water for injection. Continue nitrogen sparging for 30 minutes after batch manufacturing. Filter the bulk solution through 0.2 μ polyvinylfluoridine filter by using nitrogen gas. Fill the filtered bulk solution (3.1 ml (range 3.2ml $\pm$ 0.1ml)) into 5ml clear glass USP type I ampoules pre and post nitrogen gas flushing.

Nitrogen sparging helps in removing dissolved oxygen from the solution and hence minimizes oxidative degradation of oxidation susceptible drugs.

According to the present invention, the injectable pregabalin formulation is stable at pH between 4.0 to 8.0, more preferably between pH 5.0 to 7.0.

Throughout this specification it is to be understood that the words "comprise" and "include" and variations such as "comprises", "comprising", "includes", "including" are to be interpreted inclusively, unless the context requires otherwise. That is, the use of these words may imply the inclusion of an element or elements not specifically recited.

Example:

The present invention has been described by way of example only, and it is to be recognized that modifications thereto falling within the scope and spirit of the description, and which would be obvious to a person skilled in the art based upon the disclosure herein, are also considered to be included within the scope of this invention.

The formulation according to present invention can be illustrated by but not limited to following example(s).

Following example mentions about the formulation with excipients and its amount range which can be used in the formulation:

S. No.	Ingredient	Qty / mL
1.	Pregabalin	5-35 mg
2.	Sodium chloride	0-9 mg
3.	Citric acid monohydrate	0-10 mg
4.	Sodium hydroxide	q.s to pH
5.	Hydrochloric acid	q.s to pH
6.	Water for Injection	q.s to 1mL
7.	Nitrogen	q.s to sparge

Process of Preparation:

The process of preparation of formulation of the present invention does not require any particular or sophisticated apparatus. It is sufficient to use normal equipments to prepare the pharmaceutical formulations of present invention for injectable use.

Process of preparation comprise of following steps:

1. Water for injection (90% of batch size) was taken in stainless steel container. It was sparged with 0.2 micron filtered nitrogen until dissolved oxygen level comes to less than 1ppm.
2. After this, sodium chloride and citric acid monohydrate was added and dissolved with continuous nitrogen sparging.
3. The pH was adjusted in the range of 5.8 – 6.2 preferably at 6.0 with 1N sodium hydroxide solution and / or hydrochloric acid solution.
4. Pregabalin was then added and dissolved with continuous nitrogen sparging. If required the pH was adjusted to 6.0 (in the range of range 5.8 – 6.2) with 1N sodium hydroxide solution and / or hydrochloric acid.
5. The volume was made-up to require batch size with nitrogen sparged water for injection. Nitrogen sparging was continued for 30 minutes after batch manufacturing.
6. The bulk solution was then filtered through 0.2 micron polyvinylfluoridine (PVDF) filter by using nitrogen gas.

7. The filtered bulk solution was finally filled in manner as described below:

3.1 mL (Range $3.2\text{mL} \pm 0.1\text{mL}$) into 5mL clear glass USP Type I ampoules pre and post nitrogen gas flushing.

Formulation:

The following example mentions about stable injectable pregabalin formulation with stability data.

S. No.	Ingredient	Qty / mL
1.	Pregabalin	25 mg
2.	Sodium chloride	3 mg
3.	Citric acid monohydrate	2 mg
4.	Sodium hydroxide	q.s to pH*
5.	Hydrochloric acid	q.s to pH*
6.	Water for Injection	q.s to 1mL
7.	Nitrogen	q.s to sparge

* - Target pH range is in between 5.8 to 6.2

This formulation can be prepared by following the process mentioned in the earlier example.

Below mentioned table mentions about the data for stability studies conducted for the exemplified formulation.

Stability study data:

		Physical Appearance	pH	Pregabalin assay %
Initial		CCS	6.15	101.8%
1 month	30° C	CCS	6.21	101.4%
	40° C	CCS	6.22	101.4%
2 month	30° C	CCS	6.24	100.1%
	40° C	CCS	6.24	99.7%
3 month	30° C	CCS	6.29	100.2%
	40° C	CCS	6.35	100.1%

CCS – clear colourless solution

We claim:

1. An injectable formulation of pregabalin.
2. The formulation as claimed in claim 1, wherein the pH of the formulation is between 4.0 to 8.0, more preferable pH of the formulation is between 5.0 to 7.0.
3. The formulation as claimed in claim 1, wherein the vehicle of formulation can be aqueous, water miscible or non-aqueous.
4. The formulation as claimed in claim 1, further comprises of atleast one of pharmaceutical excipients; either tonicity adjusting agent, buffering agent, anti-oxidants, pH adjusting agent or mixtures thereof.
5. The formulation as claimed in claim 4, wherein the anti-oxidants can be sulfites, acids or sequestering agents.
6. The formulation as claimed in claim 1, wherein the amount of pregabalin is in the range of 5 to 35 mg/ml of the formulation.
7. A process for preparation of an injectable formulation of pregabalin stable at a pH in between 4.0 - 8.0 comprises the steps of:
 - a) Dissolving tonicity adjusting agent and buffering agent in formulation solvent,
 - b) Adjusting the pH in between 5.8 to 6.2 using pH adjusting agent,
 - c) Adding and dissolving pregabalin,
 - d) Adjusting the pH in between 5.8 to 6.2, if required,
 - e) Making up the required volume.

8. An injectable formulation of pregabalin stable at a pH between 4.0 to 8.0 comprises of:

Pregabalin – 5 - 35mg

Tonicity agent – q.s to adjust to desired tonicity

Buffering agent – 0 - 10mg

pH adjusting agent – q.s to pH

Formulation vehicle – q.s 1ml