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METHOD DEVELOPMENT AND STABILITY STUDIES OF GABAPENTIN IN BULK AND PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

A Simple, new, accurate, precise, specific, robust and rapid RP-HPLC method was developed and validated for the estimation of Gabapentin in bulk and pharmaceutical dosage form. The separation of the drug was achieved on Symmetry ODS RP C_{18}, 5µm, 15mm x 4.6mm i.d. column with a mobile phase consisting of a mixture of ACN: 1.0% Orthophosphoric acid in the ratio of 75:25 v/v at a flow rate of 1ml/min, with detection at 218nm by using UV detector. The developed method was validated for different parameters such as linearity, accuracy, precision, limit of detection (LOD), limit of Quantization (LOQ), robustness and the results were found to be within the limits according to ICH guidelines. The retention time was found to be 3.742 min. Stability studies evaluate the effect of environmental factors on the quality of the drug product and they are developed to estimate the shelf life and the storage conditions. These studies should be designed following the guidelines issued by ICH. The results of the stability studies indicated the specificity of the method that has been developed. Gabapentin was stable in thermal and peroxide stress conditions.

KEY WORDS

Gabapentin, RP-HPLC, Method Development and Validation, ICH Guidelines.

1. INTRODUCTION

Gabapentin is an Anti-epileptic Agent. The physiologic effect of gabapentin is by means of Decreased Central Nervous System Disorganized Electrical Activity. Gabapentin[1] is a synthetic analogue of the neurotransmitter gamma-amino butyric acid with anticonvulsant activity. Although its exact mechanism of action is unknown, gabapentin appears to inhibit excitatory neuron activity. This agent also exhibits analgesic properties. Gabapentin is a unique anticonvulsant that is used as adjunctive therapy in management of epilepsy[2] and for neuropathic pain syndromes. Therapy with gabapentin is not associated with serum amino transferase elevations, but several cases of clinically apparent liver injury from gabapentin have been reported.

Gabapentin (brand name Neurontin) is a medication originally developed for the treatment of epilepsy. Presently, gabapentin is widely used to relieve pain, especially neuropathic pain. Gabapentin is well tolerated in most patients, has a relatively mild side-effect profile, and passes through the body unmetabolized. For the management[3] of postherpetic neuralgia in adults and as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy.

The Chemical Formula for Gabapentin is $C_9H_{17}NO_2$. The Molecular weight[4] of Gabapentin is 171.2368 g/mol. The IUPAC Name[5] of Gabapentin is 2-[1-(amino methyl) cyclo hexyl] acetic acid. The structure of Gabapentin is shown in Fig-1.

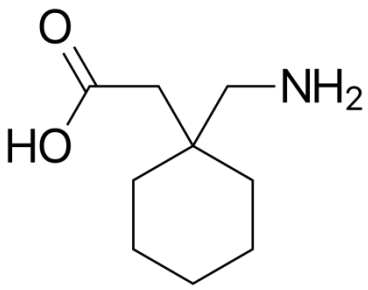

Fig-1: Structure of Gabapentin

2. METHODOLOGY

2.1. Materials and Chemicals:

The Gabapentin working standard was received from Pharmaceutical Industries Ltd. Gabapentin drug substance from AR Chemicals Pvt. Ltd. Gabapentin Tablets 100mg, Methanol, Acetonitrile, and Potassium dihydrogen phosphate of grade AR. HPLC Grade Water, orthophosphoric acid.

2.2. Chromatographic Conditions:

The analysis was carried on Symmetry ODS RP C_{18},5µm, 15mm x 4.6mm i.d. Column, with detection wavelength of 218nm. Injection volume of 20.0 µl and maintaining flow rate at 1ml/min.

2.3. Standard Solution preparation:

25 mg of Gabapentin standard was transferred into 25 ml volumetric flask, dissolved & make up to volume with mobile phase.

Further dilution was done by transferring 0.1 ml of the above solution into a 10ml volumetric flask and make up to volume with mobile phase.

2.4. Sample Solution preparation:

25 mg of Gabapentin sample was transferred into 25 ml volumetric flask, dissolved & make up to volume with mobile phase[6].

Further dilution was done by transferring 0.1 ml of the above solution into a 10ml volumetric flask and make up to volume with mobile phase.

2.5. Preparation of 1.0% Orthophosphoric acid Solution:

Take accurately 1ml of orthophosphoric acid and transferred into a 100 ml volumetric flask. Add 30 ml of HPLC Grade water and stir to dissolve the acid solution, and then complete the volume up to the mark with HPLC Grade water. The solution is then filtered[7] and degassed on a Sonicator for about 15 minutes to remove air bubbles.

2.6. Mobile Phase Preparation:

250mL (25%) of above 1.0% orthophosphoric acid solution and 750mL of Acetonitrile HPLC (75%) were mixed well and degassed[8] in ultrasonic water bath for 15 minutes. The solution was filtered through 0.45 µm filter under vacuum filtration.

2.6. Diluent Preparation:

Mobile phase can be used as diluent[9].

3. PROCEDURE FOR STABILITY STUDIES

3.1. STABILITY STUDIES:

Following protocol[10] was strictly adhered to for forced degradation[11] of Gabapentin Active Pharmaceutical Ingredient[12] (API).

The API (Gabapentin) was subjected to stress conditions[13] in various ways to observe the rate and extent of degradation that is likely to occur in the course of storage and/or after administration[14] to body.

This is one type of accelerated stability studies[15,16] that helps us determining the fate of the drug that is likely to happen after a long time storage, within a very short time as compare to the real time or long term stability testing.

The various degradation pathways[17] studied are acid hydrolysis, basic hydrolysis, thermal degradation, photolytic degradation and oxidative degradation.

3.1.1. ACID HYDROLYSIS:

An accurately weighed 25 mg of pure drug was transferred to a clean & dry 25 ml volumetric flask. To which 0.1 N Hydrochloric acid was added & make up to the mark & kept for 24 hrs. from that 0.5 ml was taken in to a 10 ml volumetric flask & make up to the mark with mobile phase[18], then injected into the HPLC system against a blank of HCl (after all optimized conditions).

3.1.2. BASIC HYDROLYSIS

An accurately weighed 10 mg. of pure drug was transferred to a clean & dry 10 ml volumetric flask. To which 0.5N Sodium hydroxide was added & make up to the mark & kept for 24 hrs. from that 0.1 ml was taken in to a 10 ml volumetric flask & make up to the mark with mobile phase, then injected into the HPLC system against a blank[19] of NaOH (after all optimized conditions).

3.1.3. THERMAL DEGRADATION

An accurately weighed 1 mg of pure drug was transferred to a clean & dry 100 ml volumetric flask, make up to the mark with mobile phase & was maintained at 50 ^{0}C. for 24 hrs. Then injected into the

HPLC system against a blank of mobile phase (after all optimized conditions).

3.1.4. Photolytic Degradation:

Approximately 10 mg. of pure drug was taken in a clean & dry Petri dish. It was kept in a UV cabinet at 254 nm wavelength for 24 hours without interruption. Accurately weighed 1 mg. of the UV exposed drug was transferred to a clean & dry 100 ml. volumetric flask. First the UV exposed drug[20] was dissolved in methanol & make up to the mark. Then injected into the HPLC system against a blank of mobile phase (after all optimized conditions[21]).

3.1.5. Oxidation with (3%) H_2O_2:

Accurately weighed 1 mg. of pure drug was taken in a clean & dry 100 ml. volumetric flask. 30 ml. of 3% H_2O_2 and a little methanol[22] was added to it to make it soluble & then kept as such in dark for 24 hours. Final volume was made up to 100 ml. using water to prepare 100 ppm solution. The above sample was injected into the HPLC system.

3.1.6. Results of Degradation (Stability) Studies:

The results of the stress studies indicated the specificity[23] of the method that has been developed. Gabapentin was stable in thermal and peroxide stress conditions. The result of forced degradation studies is given in the following Table-1.

Table-1: Results of forced degradation studies of Gabapentin API.

Stress condition	Time (hrs)	Assay of active substance	Assay of degraded products	Mass Balance (%)
Acid Hydrolysis (0.1 M HCl)	24Hrs.	62.18	37.82	100.0
Basic Hydrolysis (0.I M NaOH)	24Hrs.	57.84	42.16	100.0
Thermal Degradation (50 ^{0}C)	24Hrs.	89.48	10.52	100.0
UV (254nm)	24Hrs.	65.72	34.28	100.0
3 % Hydrogen peroxide	24Hrs.	86.54	13.46	100.0

4. RESULTS AND DISSCUTION

A simple, precise RP-HPLC method and stability studies for the estimation of Gabapentin in Tablet dosage form has been developed and validated according to ICH Guidelines. The drug was found to be highly Soluble in water (10 mg/mL), PBS pH7.2 (~10 mg/ml), and methanol. Sparingly soluble in ethanol, DMSO and DMF. Using these solvents with appropriate composition newer methods can be developed and validated. The retention time was 3.742min with run time of 7 min. The results of the stress studies indicated the specificity of the method that has been developed. Gabapentin was found to be stable in thermal and peroxide stress conditions.

5. CONCLUSION

The developed method can be used for routine quality control analysis of Gabapentin. A sensitive & selective RP-HPLC method has been developed & validated for the analysis of Gabapentin in bulk and Pharmaceutical dosage form.

The result shows the developed method is yet another suitable method for assay, purity which can help in the analysis of Gabapentin in different formulations. By the stability studies Gabapentin was found to be stable in thermal and peroxide stress conditions.

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