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"Comprehensive Review on Forced Degradation Studies of Rilpivirine: Implications for Pharmaceutical Development and Stability Assessment"

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ABSTRACT

Rilpivirine, a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), has been widely used in the treatment of HIV infection. The aim of this study was to develop a simple, efficient, and selective method for the determination of rilpivirine in pharmaceutical dosage forms. The method involved the forced degradation of rilpivirine under various conditions, including acid hydrolysis, basic hydrolysis, thermal degradation, photolytic degradation, and oxidation with hydrogen peroxide (H2O2). The results of these degradation studies were used to establish the stability-indicating nature of the developed method. The method was validated according to ICH guidelines and found to be accurate, precise, and linear over the concentration range. The limit of detection (LOD) and limit of quantification (LOQ). The method was successfully applied to the determination of rilpivirine in pharmaceutical dosage forms, and the results were in good agreement with the labeled content.

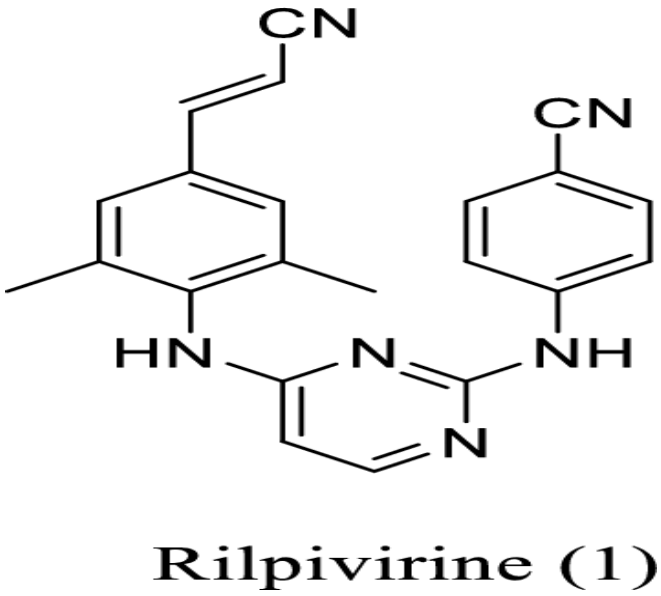
Keywords:

Rilpivirine, Forced degradation, HPLC, Stability-indicating assay, Validation, ICH guidelines.

INTRODUCTION

An antiviral is something that fights against viruses in your body. These can be medicines or treatments made to stop viruses from growing and spreading. They work by targeting different parts of the virus's life cycle, like its enzymes or proteins, to keep it from causing infections. Antivirals can help treat illnesses caused by viruses, like the flu, herpes, HIV/AIDS, and hepatitis [1]. They can either slow down the sickness or make its symptoms less severe. Sometimes, antiviral drugs are also used to prevent infections, especially in people who might be at a higher risk of getting sick from a particular virus [2].

Rilpirivine (RPV) is chemically known as 4[(4[(4-(1E) -2 cyanothenyl] -2, 6- dimethyl phenyl] amino] 2 pyrimidimyl] amino benzonitrile mono hydrochloride [3]. fig-1. Rilpirivine is the second generation of non-nucleoside reverse transcriptase inhibitors (NNRTIS) recently marketed for the treatment of HIV infection [4]. Rilpivirine is superior to first generation NNRTIS in that it is active against NNRTI resistant HIV-I [2-5]. Literature survey revealed analytical method for the determination of rilpivirine by HPLC method in dosage forms and its invitro dissolution assessment [5]. Simultaneous determination of existing and new antiretroviral compound is done by HPLC-MS/MS [6]. Literature survey reveals that, Rilpivirine is not official in any of the pharmacopeias like IP, BP, USP and European pharmacopeia. Hence an attempt has been made to develop a simple, efficient and selective method for the determination of Rilpirivine in pharmaceutical dosage forms [7].



Rilpivirine (1)

Fig 1- structure of Rilpirivine

- **Chemical name** - pyrimidine-2,4-diamine
- **Chemical formula** - $C_{22}H_{18}N_6$
- **Molecular Weight** - 368.385 g·mol−1
- **Melting Point** - 245 °C
- **Half-life –** 48 hr
- **Category –** Anti – Viral

Forced degradation studies may help facilitate pharmaceutical development as well in areas such as formulation development, manufacturing and packaging, in which knowledge of chemical behavior can be used to improve a drug product [8]. Stability testing of drug substance requires an accurate analytical method that quantitates active pharmaceutical ingredients (API) without interference from degradation products, process impurities and other potential impurities 1 [9]. With the advent of International Conference on Harmonization (ICH) guidelines, the requirement of establishment of stability-indicating assay method (SIAM) has become more clearly mandated [10]. The guidelines explicitly require conduct of

forced decomposition studies under a variety of conditions, like pH, light, oxidation, dry heat, etc. and separation of drug from degradation products

Objective of forced degradation studies [11]

Forced degradation studies are carried out to achieve the following purposes:

1. To establish degradation pathways of drug substances and drug products.
2. To differentiate degradation products that are related to drug products from those that are generated from non-drug product in a formulation.
3. To elucidate the structure of degradation products.
4. To determine the intrinsic stability of a drug substance in formulation.
5. To reveal the degradation mechanisms such as hydrolysis, oxidation, thermolysis or photolysis of the drug substance and drug product [1,2].
6. To establish stability indicating nature of a developed method.
7. To understand the chemical properties of drug molecules.
8. To generate more stable formulations.
9. To produce a degradation profile similar to that of what would be observed in a formal stability study under ICH conditions.
10. To solve stability-related problems [3]

FORCE DEGRADATION STUDIES [12]

The drug's stability profile was assessed through various degradation studies, including acid hydrolysis, basic hydrolysis, thermal degradation, photolytic degradation, and oxidation with hydrogen peroxide (H2O2). Here's a summary of each study in standard language:

Stress conditions are external factors that can mess with how well a medicine or drug holds up over time. These include things like:

- **pH**: Think of it like how acidic or basic something is. If it's too extreme, it can break down the medicine.
- **Temperature:** If it gets too hot or too cold, it can mess with the medicine's stability. Too hot can make it break down, while too cold might make it freeze or form crystals.
- **Light: Exposure** to light can make the medicine break down.
- **Humidity:** Moisture in the air can cause the medicine to break down or go bad.

1. Acid Hydrolysis:

- 25 mg of the pure drug was accurately weighed and transferred to a 25 ml volumetric flask.
- 0.1 M Hydrochloric acid was added with neutralize it 0.1M NaOH to the flask, and the volume was made up to the mark with water.
- The solution was allowed to stand for 24 hours.
- A 0.1 ml aliquot was taken from the solution and transferred to a 10 ml volumetric flask, and the volume was made up with the mobile phase.
- The resulting solution was injected into the HPLC system against an HCl blank, and the results were recorded.

2. Basic Hydrolysis:

- 10 mg of the pure drug was accurately weighed and transferred to a 10 ml volumetric flask.
- 0.1 M Sodium hydroxide was added with neutralize it with 0.1M HCL to the flask, and the volume was made up to the mark with water.
- The solution was allowed to stand for 24 hours.
- A portion of the solution was taken and diluted appropriately.
- The resulting solution was injected into the HPLC system against a blank of NaOH, and the results were recorded.

3. Thermal Degradation:

- 10 mg of the pure drug was accurately weighed and transferred to a 100 ml volumetric flask.
- The volume was made up to the mark with the mobile phase.
- The flask was maintained at 50°C for 24 hours.
- A portion of the solution was taken and injected into the HPLC system against a blank of the mobile phase, and the results were recorded.

4. Photolytic Degradation:

- Approximately 10 mg of the pure drug was exposed to UV light at 254 nm wavelength for 24 hours.
- 1 mg of the UV-exposed drug was accurately weighed and transferred to a 10 ml volumetric flask.
- The UV-exposed drug was dissolved in methanol, and the volume was made up to the mark.
- The resulting solution was injected into the HPLC system against a blank of the mobile phase, and the results were recorded.

5. Oxidation with H2O2:

- 10 mg of the pure drug was accurately weighed and transferred to a 100 ml volumetric flask.
- 30 ml of 3% H2O2 solution and a small amount of methanol were added to the flask to make the drug soluble.
- The solution was kept in the dark for 24 hours.
- The final volume was made up to 100 ml with water to prepare a 100-ppm solution.
- The resulting solution was injected into the HPLC system, and the results were recorded.

Conclusion:

The developed method for the determination of rilpivirine in pharmaceutical dosage forms was found to be simple, efficient, and selective. The method was validated according to ICH guidelines and was successfully applied to the determination of rilpivirine in pharmaceutical dosage forms. The results were in good agreement with the labeled content, confirming the accuracy and precision of the method. The forced degradation studies conducted under various conditions helped to establish the stability-indicating nature of the developed method.

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