

Understanding and evaluation of different degradation pathways and stability of drug product with active substance prone to chemical and physical degradation

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Introduction

Ensuring adequate stability of the active substance in its formulation in the final pharmaceutical dosage form is one of the key challenges in the pharmaceutical industry. Drug instability causes a decrease in the potency and the amount of drug substance delivered to the patient, but can also cause formation of undesirable degradation products (Sengupta et al., 2018). The possibility of predicting degradation products that may form from small-molecule organic pharmaceuticals is of a great importance. Particularly when the active component is prone to both chemically and physically induced degradation (Bhangare et al., 2022). If significant degradation takes place between manufacture and administration of the drug product then there is a risk of inadequate dosing. For treatment of hypertension and cardiovascular disease dosing accuracy is very important since ineffective treatment is likely to result in life-threatening complications. ACE inhibitors are among several antihypertensive drugs preferred for initial management of hypertension and/or cerebrovascular disease.

One of the most frequently prescribed angiotensin-converting inhibitors that has the broadest spectrum in terms of therapeutic indications relative to other drugs within the ACE inhibitor class, was subject of this study. Literature survey showed that this compound is very sensitive to light, moisture, heat, physical or chemical stress.

There are several methods described in the literature for preventing the decomposition of active substances prone to induced physical and chemical degradation (Grangeia et al., 2020; Hotha et al., 2016). In this study three approaches were tested and different degradation pathways of the active substance were observed.

Materials and methods

Tablet formulations and manufacturing

Laboratory trial N°1 for testing the first approach contains: pregelatinized maize starch (low moisture) microcrystalline cellulose (low moisture), silicon dioxide, and glycerol dibehenate. The active component was dry mixed with excipients with low water content. Laboratory trial N°2 for testing the second approach contains: hypromellose (HPMC), microcrystalline cellulose, pregelatinized maize starch, croscarmellose sodium and sodium stearyl fumarate. The polymer film can protect the active substance against external influences such as moisture and counteracts the mechanical deactivation. Laboratory trial N°3 for testing the third approach contains: hypromellose (HPMC), microcrystalline cellulose, sodium hydrogen carbonate, pregelatinized maize starch, croscarmellose sodium and sodium stearyl fumarate. In this approach, the active substance was mixed with a physiologically tolerated buffer which ensures that a pH in weakly alkaline range is set up, and is also coated with a polymeric protective coating. Laboratory trial tablets N°1

were manufactured by direct compression, and laboratory trial tablets N°2 and N°3 were manufactured by using a wet granulation process.

Tablet stability studies

Tablets were stored in cold forming aluminum/aluminum blister with proper number of tablets per blister as primary packaging and printed cardboard box as secondary packaging at 25 °C/60% relative humidity for 9 months and 40 °C/75% relative humidity for 6 months. The samples were tested for assay, related and degradation products, pH and water content.

High-performance liquid chromatography

HPLC analysis for determination of related and degradation products was performed by using a 5 µm, 250 x 4.6 mm i.d. Zorbax SB-CN column (Agilent Technologies, California, USA) at 65 °C with a mobile phase flow rate of 1.0 mL/min. The gradient elution used acetonitrile and phosphate buffer adjusted to pH 2.0 with ortho-phosphoric acid. The initial mobile phase composition of 5% acetonitrile after initial hold of 5 minutes was increased to 40% linearly over 25 minutes, followed by an increase to the final composition of 60% linearly over 7 minutes and held at this composition for 7 minutes. Degradants were routinely monitored at a wavelength of 210 nm. The sample and standard solutions were dissolved in 80:20 V/V mixture of phosphate buffer pH 2.0 and methanol and were passed through 0.45 µm regenerated cellulose filter. The HPLC system was Thermo Ultimate 3000 HPLC System consisted of LPG-3400SD Pump, WPS-3000TSL Autosampler, TCC3000SD Column Thermostat and DAD3000SD Detector, controlled by Thermo Scientific™ Dionex™ Chromeleon™ 7 Chromatography Data System, Version 7.2 SR5 MUI.

Results and discussion

Initial analysis for presence of related and degradation products in the laboratory trials didn't reveal any significant difference in the impurity profile among the different formulation approaches. Results from the analysis of laboratory trial N°1 and N°2 after 9 months at 25 °C/60% show that the assay of the active substance decreases, with formation of specified impurity D as main degradation product (3.04% and 1.88%, respectively). Contrasting this, results obtained for laboratory trial N°3 show formation of specified impurity E as main degradation product (3.37%). Total impurities for laboratory trials N°2 and N°3 were similar (app. 4%), which can be related with the manufacturing process of wet

granulation. While total impurities in laboratory trial N°1 are much lower (2.2%). Results for the samples stored at 40 °C/75% for 6 months confirm different degradation pathways among formulations, with additional increase of the amount of specified and total impurities.

The obtained results reveal that the degradation of the active substance follows parallel pathways of hydrolysis (impurity E) and intramolecular cyclization (impurity D), depending on the micro environment. Presence of sodium hydrogen carbonate in laboratory trial N°3 causes weakly alkaline environment compared to neutral environment in laboratory trial N°1 and N°2, thus catalyzing hydrolysis of the ester bond. Presence of HPMC in laboratory trial N°2 didn't show improved protection of the active substance compared to the low moisture excipients and dry mixing technology concept applied in laboratory trial tablets N°1.

Conclusion

The stability of sensitive pharmaceutical entities follows many rules defined by classic organic reaction mechanisms. It is of great importance to predict drug degradation in early steps of drug product development, increasing the knowledge about the product, minimizing the risk for patients and lowering the costs for excessive and long experiments. The first choice for a formulator to prevent hydrolysis is to avoid unnecessary or excessive contact of the active substance with water during the process of manufacture. As a result of the use of dry formulation techniques and the prevention of hydrolysis, stable formulation can be obtained.

References

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