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Short communication

Assessment of the impact of excipients on the stability of ramipril, including a comparison of low-moisture and conventional excipients

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Introduction

The development of a robust pharmaceutical formulation requires a thorough understanding of interactions between the active pharmaceutical ingredient (API) and excipients (Hotha et al., 2016).

As an initial step, a pre-formulation study was performed to select suitable excipients through stress testing of binary mixtures with ramipril under various conditions (Bhangare et al., 2022). Special focus was placed on low-moisture excipients, given the susceptibility of ramipril to hydrolytic degradation, leading to the formation of diketopiperazine and ramipril diacid impurities.

To assess the protective effect of excipients against temperature and moisture-induced degradation, both standard and low-moisture grades of key fillers—microcrystalline cellulose and starch—were evaluated. The results of this screening form the basis for subsequent DoE-based optimization, supporting the selection of excipients that enhance both stability and overall product performance (Grangeia et al., 2019).

Materials and methods

Selection of Excipients and Preparation of Binary Mixtures

Several excipients were evaluated for compatibility with the active substance to confirm their suitability for tablet formulation, including microcrystalline cellulose (Avicel PH 112), low-moisture microcrystalline cellulose (Avicel PH 200 LM), low-moisture pregelatinized starch (Starch 1500 LM), pregelatinized starch (Starch 1500) glycine hydrochloride, hydrated silicon dioxide (Syloid AL-1 FP), sodium stearyl fumarate and glycerol dibehenate (Compritol 888 ATO).

Binary mixtures of the active substance, ramipril, with the selected excipients were prepared by dry blending.

Stress Testing of Binary Mixtures

Each binary mixture, was exposed to several stress conditions in Petri dishes covered with perforated aluminum foil: in a dry oven at 40 °C, in a stability chamber at 25 °C/65% RH, and in a stability chamber at 40 °C/75% RH for a period of 30 days. Samples from each binary mixture were analyzed initially and after 30 days of exposure to the specified conditions.

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Pure ramipril was subjected to the same conditions and analyzed as a control to assess the extent of the excipient's impact. All samples were tested for related substances and degradation products.

Chromatographic Conditions

High-performance liquid chromatography (HPLC) was employed for the determination of related substances and degradation products. Analyses were performed using a Dionex Ultimate 3000 HPLC system (Thermo Fisher Scientific Inc., Waltham, MA, USA). Instrument control, data acquisition, and processing were carried out using Chromeleon™ 7 software (version 7.2 SR5 MUI).

Separation was achieved on a Zorbax SB-CN column (Agilent Technologies, CA, USA), 250 × 4.6 mm, 5 µm, maintained at 65 °C. The mobile phase flow rate was 1 mL/min, using gradient elution with phosphate buffer (pH 2.0) and acetonitrile. Chromatograms were recorded at a wavelength of 210 nm. Sample and standard solutions were prepared in a mixture of phosphate buffer (pH 2.0) and methanol (80:20, v/v).

Results and discussion

After 3 months, analysis of the active substance ramipril showed a slight increase in impurity D under elevated temperature and humidity conditions (40 °C/75% RH). This increase was particularly pronounced in binary mixtures with Avicel 112, Avicel 200 LM, and Syloid under the same conditions. The highest level of degradation was observed with Avicel 200 LM (8.9%), approximately twice that of Avicel 112 (4.3%) and Syloid (4.3%). A minor increase was also observed in the binary mixtures with Starch 1500 (0.34%) at 40 °C/75% RH; no significant difference was noted between regular and low-moisture starch.

Impurity E was not detected in the pure active substance after 3 months under any stress condition. However, the formation of impurity E was observed in binary mixtures, most notably with Syloid at 25 °C/60% RH (0.81%) and especially at 40 °C/75% RH (2.7%). Smaller but notable increases were also observed with Avicel 112 (0.17%) and Avicel 200 LM (0.38%) under the same stress conditions.

These findings indicate that ramipril degradation is accelerated by elevated temperature and humidity and follows different pathways depending on the excipient used, likely due to the specific microenvironments within the mixtures. Notably, despite its low moisture content, Avicel 200 LM appears to promote intramolecular cyclization, possibly due to its higher porosity and moisture retention capacity which increases molecular mobility.

Conclusion

These results demonstrate that excipient selection significantly influences the stability of ramipril, with certain excipients, such as Avicel 200 LM and Syloid, potentially promoting degradation under conditions of elevated temperature and humidity. Low-moisture excipients do not consistently provide improved stability for ramipril. Their impact depends on overall physicochemical properties, and some, such as Avicel 200 LM, may even promote cyclization under stress conditions. Therefore, excipient selection should be based on a comprehensive evaluation rather than moisture content alone. To fully understand their combined effects within the final formulation, a detailed evaluation using a Design of Experiments (DoE) approach is required. This will enable assessment of both the individual and interactive effects of excipients on ramipril stability, as well as identification of optimal conditions to minimize degradation.

References

Bhangare, D. et al., 2022. Systematic strategies for degradation kinetic study of pharmaceuticals: an issue of utmost importance concerning current stability analysis practices. J. Anal. Sci. Technol. 13, 7. https://doi.org/10.1186/s40543-022-00317-6

Grangeia, H.B. et al., 2020. Quality by design in pharmaceutical manufacturing: a systematic review of current status, challenges and future perspectives. Eur. J. Pharm. Biopharm. 147, 19–37. https://doi.org/10.1016/j.ejpb.2019.12.007

Hotha, K.K. et al., 2016. Drug-excipient interactions: case studies and overview of drug degradation pathways. Am. J. Anal. Chem. 7, 107–140. https://doi.org/10.4236/ajac.2016.71011