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Short communication

Application of Bootstrap as an alternative statistical approach for assessing dissolution profile similarity in the presence of significant variability

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Introduction

Dissolution profile comparison plays a pivotal role in drug development and regulatory evaluation, particularly as a surrogate for bioequivalence under certain conditions. Regulatory authorities, including the FDA and EMA, endorse its use in supporting biowaivers, evaluating minor formulation or manufacturing changes, and establishing therapeutic equivalence for specific dosage forms (EMA, 2010; FDA, 1997; Islam & Begum, 2018;).

The choice of an appropriate comparison method is largely driven by the variability of the dissolution data. In low-variability scenarios—commonly defined by a coefficient of variation (CV) of less than 20% at early time points and less than 10% at later stages the similarity factor (f_2) is the standard metric (Moore & Flanner, 1996; FDA, 1997). An f_2 value of 50 or higher is generally interpreted as evidence of comparable dissolution profiles (Moore & Flanner, 1996; Shah et al., 1998).

However, when dissolution data exhibit high variability, the reliability of the f_2 metric diminishes (Muselík et al., 2021; Shah et al., 1998). In such cases, alternative statistical approaches—both model-independent and model-dependent—are recommended (Muselík et al., 2021). More recently, bootstrap methodologies have gained traction as a robust tool for addressing variability, allowing for the estimation of confidence intervals around the f_2 value (Boddu et al., 2023; Islam & Begum, 2018; Noce et al., 2020). Consequently, the use of a 90% confidence interval derived from bootstrap analysis is increasingly recognized as a preferred approach for demonstrating dissolution similarity under variable conditions (Boddu et al., 2023; Muselík et al., 2021).

Materials and methods

The dissolution profiles of orodispersible tablets as test and film-coated tablets as reference, both containing the same BCS Class II active pharmaceutical ingredient, were evaluated for similarity. Dissolution testing was conducted using USP Apparatus II (paddle) at 50 rpm in 900 mL of compendial buffer media (pH 1.2, 4.5, and 6.8). To improve in vivo predictability and support *in vitro–in vivo* correlation (IVIVC), additional studies were performed in biorelevant media (FaSSGF, pH 1.6, 300 mL; FaSSIF, pH 6.5, 500 mL). Mini vessels with paddles at 100 rpm were used for FaSSGF, while standard vessels at 50 rpm were used for FaSSIF.

In vitro dissolution similarity between the test and reference products was evaluated using the

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similarity factor (f_2) and a bootstrap approach. Where standard criteria for direct f_2 application were not met, bootstrap methodology was applied to estimate the distribution of f_2 values and assess the worst-case scenario via the lower bound of the confidence interval (CI) (Davit et al., 2016; EMA, 2010). Data analysis was performed in R (RStudio) using the *Bootf2_BCA* script. A decision rule based on bootstrap-derived CIs was implemented, where similarity is concluded if the lower bound of the 90% CI for the expected f_2 is $\geq$ 50 (FDA, 1997). Four CI types were calculated to ensure robustness: Normal approximation, Basic (Bootstrap-t), Percentile, and Bias-Corrected and Accelerated (BCa). The bootstrap model employed 5000 resamples, 90% CI, and profile truncation at 85% dissolution, in accordance with EMA recommendations (EMA, 2010).

Results and discussion

Dissolution profiles of the test and reference products were evaluated in compendial and biorelevant media (12 units, 7 time points, 5–60 min). The f_2 values across all dissolution media (56- 62) indicate dissolution profile similarity.

The similarity factor (f_2), calculated from the mean dissolution profiles in pH 6.8, FaSSGF and FaSSIF, was 60; 57 and 56, respectively, all exceeding the conventional acceptance threshold of 50. However, due to increased variability (RSD > 10%) at 15 and 20 min (pH 6.8, FaSSGF, FaSSIF), at 30 min (pH 6.8, FaSSGF), and at 10 and 60 min (FaSSGF), the criterion that variability should be <20% at the first time point and <10% thereafter was not fulfilled, necessitating the use of a bootstrap approach. The obtained E(f_2) values were 59.71 (pH 6.8), 57.34 (FaSSGF) and 56.17 (FaSSIF), with symmetric distributions and 90% confidence intervals whose lower limits remained well above 50, confirming similarity.

Conclusion

The test and reference products showed similar and consistent dissolution profiles, with all f_2 values above the acceptance threshold. The bootstrap analysis further supported the robustness and reproducibility of these findings, demonstrating stable f_2 estimates with confidence intervals within regulatory limits.

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