

COMPARISON OF DISSOLUTION PROFILES: CURRENT GUIDELINES

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Introduction

Comparison of therapeutic performances of two medicinal products containing the same active substance is a critical means of assessing the possibility of alternative using between the innovator and any essentially similar medicinal product. Assuming that in the same subject an essentially similar plasma concentration time course will result in essentially similar concentration at the site of action and thus in an essentially similar effect, pharmacokinetic data instead of therapeutic results may be used to establish equivalence: bioequivalence.

A bioequivalence study is basically a comparative study designed to establish equivalence between test and reference products. In vivo bioequivalence studies are needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence. But it's also possible to request a waiver of in vivo bioavailability and/or bioequivalence studies for solid oral dosage forms based on an approach termed the Biopharmaceutics Classification System (BCS) (1).

Comparison of dissolution profiles

® FDA guidelines:

Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability

across the gastrointestinal tract. Because of the critical nature of the first two steps, in vitro dissolution may be relevant to the prediction of in vivo performance.

The BCS can be used as a basis for setting in vitro dissolution specifications and can also provide a basis for predicting the likelihood of achieving a successful in vivo-in vitro correlation (IVIVC). Based on drug solubility and permeability, the BCS is recommended: (2):

- Case 1: High Solubility – High Permeability.
- Case 2: Low Solubility – High Permeability.
- Case 3: High Solubility – Low Permeability.
- Case 4: Low Solubility – Low Permeability.

The BCS suggests that for high solubility, high permeability drugs and in some instances for high solubility, low permeability drugs, 85 % dissolution in 0.1 N HCl in 15 minutes can ensure that the bioavailability of the drug is not limited by dissolution. In the case of low solubility / high permeability drugs, drug dissolution may be the rate limiting step for drug absorption and an IVIVC may be expected. A dissolution profile in multiple media is recommended for drugs products in this category. In the case of high solubility / low permeability drugs, permeability is the rate controlling step and a limited IVIVC may be possible. Drugs in case 4 present significant problems for oral drug delivery.

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The dissolution profile comparison may be carried out using model independent or model dependent methods: (3) A simple model independent approach uses a *difference factor* (f_1) and a *similarity factor* (f_2) to compare dissolution profiles.

$$f_1 = \{ [S_{t=1}^n (R_t - T_t)] / [S_{t=1}^n R_t] \} \cdot 100$$

$$f_2 = 50 \cdot \log \{ [1 + (1/n) S_{t=1}^n (R_t - T_t)^2]^{0.5} \cdot 100 \}$$

There is a specific procedure to determine difference and similarity factors as follows:

1. Determine the dissolution profile of two products (12 units each) of the test and reference products.
2. Using the mean dissolution values from both curves at each time interval, calculate the difference factor (f_1) and similarity factor (f_2) using the above equations. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves.

This model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. The following recommendations should also be considered:

- The dissolution measurements of the test and reference batches should be made under the same conditions. The dissolution time points for both the profiles should be the same. The reference batch used should be the most recently manufactured prechange product.
- Only one measurement should be considered after 85 % dissolution of both the products.
- To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20 %, and at other time points should not be more than 10 %.

® EMEA guidelines: (4)

Dissolution studies can serve several purposes as, for example, to be used as a tool in quality control to demonstrate consistency in manufacture, to demonstrate similarity between reference products from different Member States, to demonstrate similarity between different formulations of an active substance (variations and new, essentially similar products included) and the reference medicinal product.

If an active substance is considered highly soluble, it is reasonable to expect that it will not cause any bioavailability problems. A bioequivalence study may in those situations be waived based on case history and similarity of dissolution profiles. The similarity should be justified by dissolution profiles, covering at least three time points, using three different buffers.

If an active substance is considered to have a low solubility and a high permeability, the rate limiting step for absorption may be the dosage form dissolution. In those cases a variety of test conditions is recommended and adequate sampling should be performed until 90 % of the drug is dissolved or an asymptote is reached. Any methods to prove similarity if dissolution profiles are accepted as long as they are justified.

The similarity may be compared by model-independent or model-dependent methods e.g. by linear regression of the percentage dissolved at specified time points, by statistical comparison of the parameters of the Weibull function or by calculating a similarity factor as f_2 :

$$f_2 = 50 \cdot \log \{ [1 + (1/n) S_{t=1}^n (R_t - T_t)^2]^{0.5} \cdot 100 \}$$

In this equation f_2 is the similarity factor, n is the number of time points, $R(t)$ is the mean percent drug dissolved of e.g. a reference product, and $T(t)$ is the mean percent drug dissolved of e.g. a test product. The evaluation of similarity is based on the conditions of:

- A minimum of three time points (zero excluded).

- 12 individual values for every time points for each formulation.
- Not more than one mean value of > 85 % dissolved for each formulation.
- That the standard deviation of the mean of any product should be less than 10 % from second to last time points.

An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. In cases where more than 85 % of the drug are dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.

A new approach on the use of the similarity factor f_2

In researchments carried out in our department (5), it has been demonstrated that similarity factor (f_2) is a simple measure for the comparison of two dissolution profiles, but f_2 factor is a slanted and conservative estimator of similarity factor real value. The statistical distribution of the f_2 metrics has been simulated using the Bootstrap method. A relatively robust distribution and a statistical correction of the slant were obtained.

In conclusion, it is plain that the use of Bootstrap confidence intervals is an useful tool in order to simulate the confidence the confidence interval for similarity factor f_2 .

References

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