F2 - Similarity Factor (A Deficiency)

Saeed A. Qureshi, Ph.D. (www.drug-dissolution-testing.com)

The similarity Factor or F2 is a parameter commonly used to show similarity or equivalence of two dissolution profiles. The F2-value is often calculated using the formula described here (link). The values of F2 range from 0 to 100. Commonly, a value between 50 and 100 is considered to reflect the similarity of two dissolution profiles which ***implies*** that the products will have similar in vivo drug release characteristics as well.

It is critical to note that the similarity factor (F2) is a made-up parameter, with the 50-100 range arbitrarily assigned. It is like requiring stylish packaging of some arbitrary dimensions to indicate the quality of the product inside. Point being, there is no link of the similarity factor (F2) in reflecting in vivo characteristics of the product which are established by comparing blood drug conc.-time (C-t) profiles.

There are at least two reasons for this lack of link between F2 and in vivo characteristics: (1) the dissolution tests are commonly conducted using apparatuses, in particular paddle and basket, which often do not provide bio- or in vivo relevant results. Therefore, using such data to draw inferences regarding in vivo characteristics would be incorrect. (2) Often one obtains highly variable and unpredictable in vitro results, because of poor hydrodynamics within vessels, which may provide a false negative conclusion about the characteristics (quality) of the test products (link).

The following example illustrates such a false negative situation.

Dissolution characteristics of two bio-equivalent marketed products were evaluated as described in the literature (link). The tested products are combination products containing 160 mg of trimethoprim (TMX) and 800 mg of sulfamethoxazole (SMX). Dissolution tests were conducted in different media, however, for this article the results obtained using pH 6.8 medium are considered. The reason for selecting these results, i.e. obtained using the medium having pH 6.8, is because of its physiological relevance. For further discussion in this regard see link.

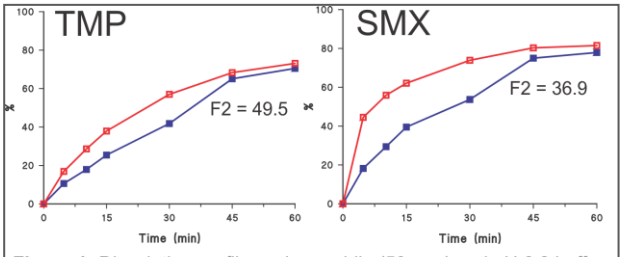

Figure 1: Dissolution profiles using paddle (50 rpm) and pH 6.8 buffer as medium. Different color profiles represent the two different tested products.

The dissolution tests were conducted with paddle apparatus (50 rpm) using 900 mL of the medium. The dissolution profiles of the two drugs (TMX and SMX) are shown in Figure 1, along with F2 values as reported in the publication. The dissolution test results and the corresponding F2-values were considered erroneous as the products are bioequivalent.

On the other hand, however, if the dissolution data are transferred to blood-drug concentration-time profiles using a convolution methodology (link), one obtains the corresponding predicted C-t profiles as shown in Figure 2. The predicted profiles look quite similar for the tested products. For PK parameters which were used to calculate the C-t profiles, please see the link. The derived parameters C_{max} and AUC for these profiles also look quite similar. Therefore, based on the predicted C-t profiles these products may be considered bioequivalent as expected. However, the F2 approach provided a false negative conclusion.

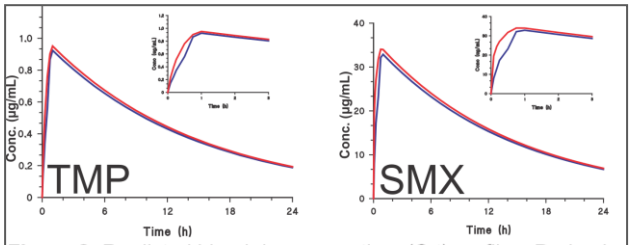

Figure 2: Predicted blood drug conc.-time (C-t) profiles. Derived parameters for TMX (AUC= 11.6 and 11.2; Cmax=0.95 and 0.92) and for SMX (AUC=419.7 and 400.70; Cmax=34.0 and 32.9).

The reason for this discrepancy may be explained as follows: It is possible that the results obtained, using paddle apparatus at 50 rpm, are typical with expected high variability in the results (profiles). This variability that appears in these results is in fact most likely a reflection of the variability of testing using paddle apparatus and may not be because of the products themselves. On the other hand, when the same data (dissolution results) are transferred to C-t profiles using exponential factor (using the exponential elimination rate equation and their summation), it "smoothes out" the observed differences. It is a data transformation effect. That is why one often sees differences in in vitro results which may not be observed in vivo. Therefore, it is very important to note that if one likes to evaluate potential in vivo drug dissolution characteristics, one must consider this exponential data transfer effect, otherwise they may observe a false negative as in this case using the F2 approach.