Figure 1.
Illustrative representation of PT methodology. In this case, the number of tablets \( m = 12 \), first \( D_0 \), is calculated between the two profiles. Then, each vector is randomly located in new Reference or test subsets creating two new \((m \times n)\) Matrices \( R_i \) and \( T_i \). The same distance \( D \) is calculated between \( R_i \) and \( T_i \) and the value is stored as \( D_i \). This cycle is repeated 5000 times or more (500000 in this example) and an empirical distribution of the \( D_i \) values (all the 500000 values of \( D_i \)) is built. According to an established type I error (\( \alpha = 0.05 \)), a rejection value is indicated in this empirical distribution. A and B show distribution of \( D_i \) for similar and not similar profiles respectively, because it is an empirical distribution the shape is similar but not identical, it can be observed that in not similar profiles \( D_0 \) is bigger than the rejection value and therefore similarity hypothesis is rejected.

**TITLE: Methodology of PT.**

Figure 2.
Robustness Comparison of the presented tests under four dissolution models. In each model, pairs of similar batches were generated (batches with the same parameter values in equations 2-5) and the percentage of rejections is measured at different levels of variation (\( CV_{95} \)). Dotted line at 5% indicates the ideal percentage of rejections (\( \alpha = 0.05 \)). In Higuchi Model, according to equation 2, \( b_{\text{Reference}} = B_{\text{Test}} = 9 \) (\( T_{85} \approx 90 \) mins), In Korsmayer model, according to equation 3. \( k_{\text{Reference}} = k_{\text{Test}} = 7 \) and \( n_{\text{Reference}} = n_{\text{Reference}} = 0.5 \) (\( T_{85} \approx 150 \) mins). For Peppas Model, according to equation 4, \( k_{\text{r-Reference}} = k_{\text{r-Test}} = 0.6 \), \( k_{d-Reference} = k_{d-Test} = 4.4 \) and \( m_{\text{Reference}} = m_{\text{Reference}} = 0.45 \) (\( T_{85} \approx 130 \) mins). In Weibull model, according to equation 5, \( B_{\text{Reference}} = B_{\text{Test}} = 0.75 \) and \( a_{\text{Reference}} = a_{\text{Test}} = 0.03 \) (\( T_{85} \approx 250 \) mins).

Squares: TDT, circles: CI, stars: PT, triangles: f2. All of the tests have acceptable levels of Rejections for values of \( cv \leq 0.12 \). f2, and PT show ideal levels of rejection for values of \( cv \leq 0.3 \) in all the models.

**TITLE: Robustness Comparison of the four tests at different conditions of iid and batch size (Weibull Model).**

Figure 3.
Power Comparison of the presented tests. In A (Higuchi Model), Percentage of rejections (Power) Vs Difference (%) in \( b_{\text{Test}} \) according to equation 2. \( b_{\text{Reference}} \) was set at 9 (\( T_{85} \approx 90 \) mins) and \( b_{\text{Test}} \) varying from 7 (\( T_{85} \approx 150 \) mins) to 11 (\( T_{85} \approx 60 \) mins). In B (Korsmayer Model), Percentage of rejections (Power) Vs Difference (%) in \( n_{\text{Test}} \) according to equation 3. \( k_{\text{Reference}} \) was set at 7.5 and \( n_{\text{Reference}} \) at 0.5 (\( T_{85} \approx 130 \) mins) and \( n_{\text{Test}} \) varying from 0.5 to 0.56 (\( T_{85} \approx 130 \) mins to \( T_{85} \approx 75 \) mins). For Peppas Model (C), Percentage of rejections (Power) Vs Difference (%) in \( k_{\text{r-Test}} \), according to equation 4, \( k_{\text{r-Reference}} \) was set at 0.6 and \( k_{d-Reference} \) at 4.4 (\( T_{85} \approx 130 \) mins) and \( k_{d-Test} \) varying from 4.4 to 6.5 (\( T_{85} \approx 130 \) mins to \( T_{85} \approx 90 \) mins).

For Weibull Model (D), Percentage of rejections (Power) Vs Difference (%) in \( a_{\text{Test}} \), according to equation 5, \( B_{\text{Reference}} \) was set at 0.75 and \( a_{\text{Reference}} \) at 0.03 (\( T_{85} \approx 250 \) mins and \( a_{\text{Test}} \) varying from 0.03 to 0.045 (\( T_{85} \approx 250 \) mins to \( T_{85} \approx 145 \) mins).


**TITLE: Power comparison of the four tests at standard variability levels.**
Figure 4.
Contour plots of power ≥ 0.8 for the tests. Ability to detect simultaneous differences in two parameters is evaluated for the tests. The combination of differences in two parameters required by each test to reach a power ≥ 0.8 is represented by a point in the contour plot. In A (Korsmeyer Model), according to equation 3, \( k_{\text{Reference}} \) was set at 7.5 and \( n_{\text{Reference}} \) at 0.5 (\( T_{85} \approx 130 \text{ mins} \)) and \( k_{\text{Test}} \) and \( n_{\text{Test}} \) varying from 7.5 to 8.2 and 0.5 to 0.54 respectively (\( T_{85} \approx 150 \text{ mins} \) to \( T_{85} \approx 65 \text{ mins} \)). For Peppas Model (B), according to equation 4, \( k_{r-\text{Reference}} \) was set at 0.6 and \( k_{d-\text{Reference}} \) at 4.4 (\( T_{85} \approx 130 \text{ mins} \)) and \( k_{r-\text{Test}} \) and \( k_{d-\text{Test}} \) varying from 0.6 to 0.8 and 4.4 to 6 respectively (\( T_{85} \approx 130 \text{ mins} \) to \( T_{85} \approx 80 \text{ mins} \)). For Weibull Model (C), according to equation 5, \( B_{\text{Reference}} \) was set at 0.75 and \( a_{\text{Reference}} \) at 0.03 (\( T_{85} \approx 250 \text{ mins} \)) and \( a_{\text{Test}} \) and \( B_{\text{Test}} \) varying from 0.03 to 0.045 and 0.75 to 0.82 respectively (\( T_{85} \approx 250 \text{ mins} \) to \( T_{85} \approx 120 \text{ mins} \)). In D, Power Comparison of \( f_2 \) and TDT with two different values of \( \alpha \) and under iid and no-iid conditions under Peppas model (same conditions as B), Levels of rejection under iid and no-iid conditions were very similar (differences ≤ 5%).

Circles: CI, stars: PT, open squares: TDT with \( \alpha = 5 \), open triangles: \( f_2 \), filled squares: TDT with \( \alpha = 5 \) under iid conditions, filled triangles: \( f_2 \) under iid conditions, Open diamonds: TDT with \( \alpha = 10 \), filled diamonds: TDT with \( \alpha = 10 \) under iid conditions.

TITLE: Bidirectional power exploration of the tests.

Figure 5.
Power Comparison of \( f_2 \), CI and TDT with three different sampling schemes at typical variability conditions (CV\(_{95} \) =0.1). According to equation 3, \( k_{\text{Reference}} \) was set at 7 and \( n_{\text{Reference}} \) at 0.5 (\( T_{85} \approx 150 \text{ mins} \)) and \( k_{\text{Test}} \) varying from 7.5 to 8.2 and \( n_{\text{Test}} \) fixed at 0.5, Circles: standard sampling, crossings: equidistant sampling with 6 time points, stars: equidistant sampling with 5 time points.

TITLE: Effect of time sampling strategy on statistical power (Korsmeyer model).

Figure 6.
Diagram flow of the proposed strategy to Perform Optimal Dissolution Profile Comparisons, Each stage of the presented strategy corresponds to a stage of a typical experimental design illustrated in the right.

TITLE: Experimental Design Driven Strategy to Perform Optimal Dissolution Profile Comparisons.