CACHET PHARMA CONSULTING, LLC

Dissolution Similarity Analysis - Confidential

4/2/2026, 12:55:26 PM

Dissolution Profile Data

Time (min)	Ref Mean (%)	Test Mean (%)	|Diff| (%)	f_2 Contribution
15 min	20.00%	27.00%	7.00%	49.00
30 min	35.00%	42.00%	7.00%	49.00
45 min	72.00%	81.00%	9.00%	81.00
60 min	85.00%	95.00%	10.00%	100.00

Similarity Results

f_1 Value	f_1 Status	f_2 Value	f_2 Status	85% Rule
15.57	FAIL	53.76	PASS	OK

Dissolution Similarity Dashboard

Analysis performed: 4/2/2026, 12:55:18 PM | 4 time points

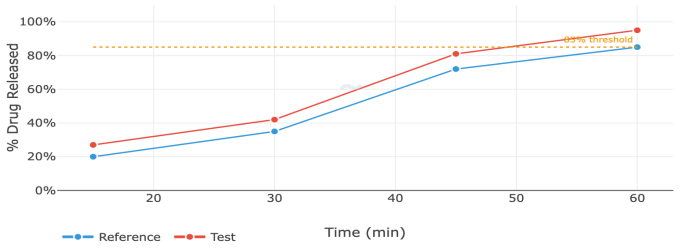
f_1 Dissimilarity Factor
15.57
FAIL
Target: < 15

f_2 Similarity Factor
53.76
PASS
Target: ≥ 50

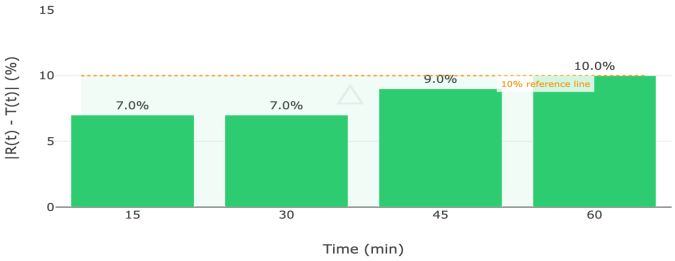
85% Rule
1 pt
PASS
Max 1 point ≥ 85%

Time Points Used
4
OK
Max 12 allowed

Dissolution Profile Overlay



Point-by-Point |Difference| (%)



REGULATORY INTERPRETATION & STRATEGIC GUIDANCE

f_2 (53.76) passes but f_1 (15.57) exceeds 15, indicating early time point differences. The elevated f_1 warrants discussion in the submission narrative, though f_2 is the primary regulatory metric.

POINT-BY-POINT SUMMARY

- ***15 min:*** *Ref 20.0% | Test 27.0% | |diff| 7.0%*
- ***30 min:*** *Ref 35.0% | Test 42.0% | |diff| 7.0%*
- ***45 min:*** *Ref 72.0% | Test 81.0% | |diff| 9.0%*
- ***60 min:*** *Ref 85.0% | Test 95.0% | |diff| 10.0%*

REGULATORY CONTEXT

- ***f_1 threshold:*** *≤ 15 (FDA 1997)*
- ***f_2 threshold:*** *≥ 50 (FDA 1997, ICH)*
- ***85% rule:*** *Max 1 point ≥85% in both profiles*
- ***Time points:*** *4 of 12 maximum used*

Strategic Guidance: *When f_2 is borderline (50-55), consider supplementing with model-dependent approaches such as the Weibull or Makoid-Banakar models, or request a pre-submission meeting with the Agency.* ***Contact Cachet Pharma Consulting*** *for dissolution strategy support.*

1. The f_1 Dissimilarity Factor

The f_1 factor measures the percent difference between two dissolution profiles, summed across all time points and normalized by the reference profile. Higher values indicate greater dissimilarity. f_1 is sensitive to early time point differences and is used as a supporting measure alongside f_2, which is the primary regulatory metric. FDA guidance (1997) specifies that f_1 values between 0 and 15 indicate similarity.

$$f_1 = \frac{\text{SUM} \mid R(t) - T(t) \mid}{\text{SUM } R(t)} \times 100$$

where SUM = sum over all n time points, R(t) = reference mean at time t, T(t) = test mean at time t

2. The f_2 Similarity Factor

The f_2 factor is the primary FDA-accepted metric for comparing dissolution profiles. It is a logarithmic transformation of the mean squared difference between profiles. Identical profiles give f_2 = 100; a consistent 10% mean difference gives f_2 = 50. An f_2 value >= 50 indicates similarity. When f_2 is borderline (50-55), model-dependent approaches or a pre-submission Agency meeting should be considered before filing.

$$f_2 = 50 \times \log_{10} \left\{ \frac{100}{\text{sqrt}(1 + \text{SUM}(R(t)-T(t))^2 / n)} \right\}$$

where n = number of time points, R(t) = reference mean, T(t) = test mean, sqrt = square root

3. The 85% Rule

FDA guidance specifies that no more than one time point should be included where both profiles have mean dissolution at or above 85%. Time points at near-complete release do not contribute meaningful discriminating power and can artificially inflate the f_2 value. Affected time points must be excluded before the result can be considered regulatory-compliant.

4. Regulatory Acceptance Criteria

- f_1:
  Values between 0 and 15 are considered acceptable. Values above 15 indicate dissimilarity.

- f_2:
  Values >= 50 indicate similarity. Values < 50 indicate the profiles are not similar per regulatory guidance.

- Number of time points:
  FDA guidance allows a minimum of 3 and a maximum of 12 time points.

- Applicability:
  Both metrics require that profiles are not flat - at least some time points should fall below 85% to provide discriminating information.

5. References

[1] U.S. Food and Drug Administration. Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. CDER, August 1997. Available at: https://www.fda.gov/media/70936/download

[2] Moore, J.W., Flanner, H.H. Mathematical comparison of dissolution profiles. Pharmaceutical Technology, 20(6): 64-74, 1996. [Original paper introducing the f1 and f2 similarity factors.]

[3] Shah, V.P., Tsong, Y., Sathe, P., Liu, J.P. In vitro dissolution profile comparison - statistics and analysis of the similarity factor, f2. Pharmaceutical Research, 15(6): 889-896, 1998.

[4] European Medicines Agency. Guideline on the Investigation of Bioequivalence. CPMP/EWP/QWP/1401/98 Rev. 1. EMA, 2010.

[5] International Council for Harmonisation. ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. ICH Harmonised Guideline, 2019.

[6] Yuksel, N., Kanik, A.E., Baykara, T. Comparison of in vitro dissolution profiles by ANOVA-based, model-dependent and -independent methods. International Journal of Pharmaceutics, 209(1-2): 57-67, 2000.