CACHET PHARMA CONSULTING, LLC

Dissolution Capability & Risk Analysis - Confidential

4/2/2026, 12:48:37 PM

Simulation Parameters

Monte Carlo Iterations	1,000
Between-Dosage-Form Variance	75% of total SD^2 (see Appendix 2)
Correlation Decay Rate (lambda)	0.010 (see Appendix 3)
Acceptable Risk Threshold	< 0.3% predicted failure
Monitor Threshold	< 1% predicted failure
Action Required Threshold	< 2.5% predicted failure
Unacceptable Risk	>= 2.5% predicted failure

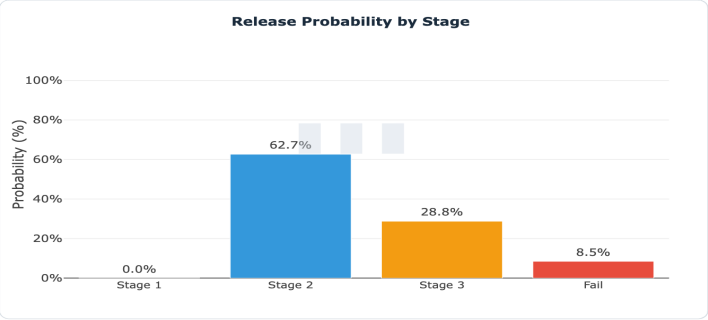
Dissolution Specification

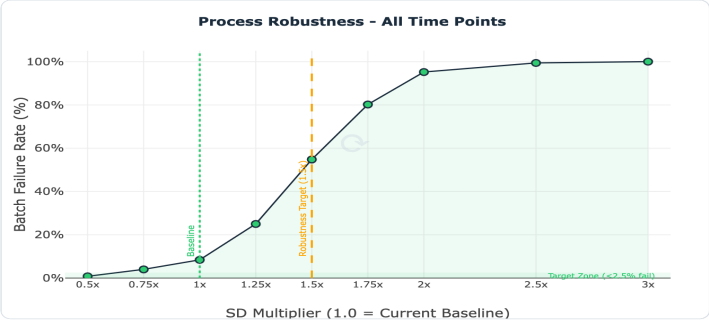
Time (min)	Spec Type	Limit / Q	Mean (%)	SD (%)
15 min	NMT	30	28%	8%
30 min	Range	40-60	55%	8%
45 min	NLT	80	83%	6%

PREDICTED FAILURE	STAGE 1 RELEASE	STAGE 2 RELEASE	STAGE 3 RELEASE	RISK RATING
8.50%	0.0%	62.7%	28.8%	Unacceptable

Capability & Risk Dashboard

Analysis performed: 4/2/2026, 12:48:36 PM | Iterations: 1,000 | Between-tablet variance: 75% | Decay lambda: 0.010





RISK INTERPRETATION & STRATEGIC GUIDANCE

UNACCEPTABLE *Overall predicted batch failure rate: **8.50%***

Predicted failure rate of 8.50% exceeds your unacceptable threshold (2.5%). Immediate intervention is required. Do not commit to this specification without a method-specification pivot or process improvement program.

*Across 1,000 simulated batches: **0.0%** release at Stage 1, **62.7%** at Stage 2, **28.8%** at Stage 3, and **8.50%** are predicted to fail.*

Failure Rate by Time Point:

- ***15 min (NMT 30%):*** *8.1% batch failure rate*
- ***30 min (Range 40-60%):*** *0.3% batch failure rate*
- ***45 min (NLT 80%):*** *0.3% batch failure rate*

*Failure risk exceeds your Action Required threshold (2.5%) at **0.75x** baseline variability, indicating limited process robustness headroom.*

Strategic Guidance: *If predicted failure risk exceeds your acceptable threshold, consider evaluating your Analytical Target Profile (ATP) to identify whether method variability is contributing to risk. A method-specification pivot - adjusting dissolution conditions to reduce analytical noise - can expand your effective operating window without changing the product. **Contact Cachet Pharma Consulting** for a full ATP-driven risk analysis.*

Consultant Strategic Recommendations:

Unacceptable results with 7.6% of batches expected to fail. Updates to the test method and potentially the process to reduce variability and tighten means is recommended.

1. Monte Carlo Simulation

This tool uses Monte Carlo simulation to estimate the probability of batch failure under USP <711> dissolution testing. Rather than making a single analytical prediction, the simulator generates 1,000 virtual batches. Each batch contains 24 simulated dosage units with values drawn from the specified statistical distribution and correlation structure. By tallying stage outcomes across all batches, the tool converts process mean and standard deviation data into actionable failure probability estimates.

2. Dosage Form Variance & Between-Unit Autocorrelation

A fundamental principle of dissolution testing is that each dosage unit is the same physical object throughout the entire test. A tablet that dissolves slowly at 15 minutes will, in all likelihood, still dissolve slowly at 30 and 45 minutes because the same physical properties - particle size, porosity, coating thickness, and compaction density - persist throughout the measurement. This phenomenon is called autocorrelation.

If dosage units were treated as statistically independent at each time point, the simulator could assign a 'slow' result at 15 minutes and a 'fast' result for that same unit at 30 minutes. This is physically impossible and leads to systematic overprediction of batch failure. The total observed standard deviation is decomposed into two components:

- **Between-Dosage-Form Variance (set to 75% of total SD^2):**

  Represents genuine unit-to-unit manufacturing differences that are persistent across all time points. A unit in the slow tail of this distribution will be slow at every time point. This is the primary driver of autocorrelation.

- **Residual Within-Unit Variance (25% of total SD^2):**

  Represents time-point-specific analytical noise and minor measurement fluctuations that are statistically independent between time points and do not contribute to autocorrelation.

The observed value for dosage unit i at time point t is modelled as:

$$X(i,t) = mu(t) + b(i,t) + e(i,t)$$

where mu(t) = population mean at t, b(i,t) = correlated between-unit offset, e(i,t) = independent residual noise

The between-unit offsets b(i,t) are drawn from a multivariate normal distribution with the exponential decay correlation structure described in Section 3, using Cholesky decomposition to ensure mathematical exactness. [Ref. 4, 5]

3. Correlation Decay Rate (lambda = 0.010)

Even for a slow-dissolving dosage unit, the strength of the autocorrelation weakens over longer time intervals as cumulative dissolution converges toward complete release. The correlation between two time points ti and tj is modelled using an exponential decay function:

$$corr(ti, tj) = exp(-lambda x |ti - tj|)$$

where lambda > 0 is the decay rate and |ti - tj| is the absolute time gap in minutes

This family of functions is widely used in longitudinal data modelling and geostatistics to represent processes where nearby observations are more strongly related than distant ones. [Ref. 4, 6] At the selected lambda = 0.010, the implied correlations are:

- 15-minute time gap: 86.1% correlation
- 30-minute time gap: 74.1% correlation
- 60-minute time gap: 54.9% correlation
- 90-minute time gap: 40.7% correlation

Higher lambda values reflect products where dissolution behaviour changes substantially over the profile, such as certain extended-release formulations. Lower values are appropriate for immediate-release products where early and late time point behaviour are tightly linked. The default value of 0.010 is a conservative and broadly applicable starting point for most solid oral dosage forms. Users with historical dissolution data are encouraged to estimate lambda by fitting the empirical correlation matrix to this functional form.

4. USP <711> Stage Testing Logic

The simulator applies the full three-stage USP <711> dissolution acceptance criteria to each simulated batch. [Ref. 2] The worst-case stage outcome across all time points determines the overall batch result:

- **Stage 1 (S1) - 6 units:**
  Each individual unit must meet Q + 5% (NLT) or Q - 5% (NMT). All 6 must pass. No failures permitted at this stage.
- **Stage 2 (S2) - 12 units total:**
  The mean of all 12 units must meet Q. No individual unit may fall below Q - 15% (NLT) or exceed Q + 15% (NMT).
- **Stage 3 (S3) - 24 units total:**
  The mean of all 24 units must meet Q. No more than 2 units may fall outside Q - 15%. No unit may fall outside Q - 25%.

A batch is recorded as a failure only if it does not satisfy the criteria at any of the three stages. The overall predicted failure rate reported in this document is the percentage of simulated batches that failed all three stages.

Regulatory & Compendial 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] United States Pharmacopeia. USP General Chapter <711> Dissolution. United States Pharmacopeial Convention. Current edition. Available at: https://www.usp.org

[3] International Council for Harmonisation. ICH Q2(R2): Validation of Analytical Procedures. ICH Harmonised Guideline, 2023. Available at: https://www.ich.org/page/quality-guidelines

Statistical & Methodological References

[4] Diggle, P.J., Heagerty, P., Liang, K.-Y., Zeger, S.L. Analysis of Longitudinal Data. 2nd ed. Oxford University Press, 2002. [Foundational text on correlated random effects models and the decomposition of between-unit and within-unit variance in repeated measures settings.]

[5] Gentle, J.E. Random Number Generation and Monte Carlo Methods. 2nd ed. Springer, 2003. [Covers Cholesky decomposition as the standard method for generating correlated multivariate normal random variates in Monte Carlo simulation.]

[6] Cressie, N.A.C. Statistics for Spatial Data. Revised ed. Wiley, 1993. [Establishes the exponential covariance function corr(h) = exp(-lambda x h) as a valid and widely used model for processes where correlation decays with separation distance or time, including applications to longitudinal pharmaceutical data.]

[7] 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. [Provides context for the f2 similarity factor and statistical approaches to comparing dissolution profiles, relevant to multi-point dissolution risk assessment.]

Guidance on Analytical Target Profile & Method Design Space

[8] International Council for Harmonisation. ICH Q14: Analytical Procedure Development. ICH Harmonised Guideline, 2023. [Establishes the Analytical Target Profile (ATP) framework and the use of design space concepts in analytical method development, directly informing the method-specification pivot strategy described in this report.]

[9] U.S. Food and Drug Administration. Guidance for Industry: Quality by Design for ANDAs - An Example for Immediate-Release Dosage Forms. CDER, 2012. [Illustrates how QbD principles, including the ATP and design of experiments, apply to dissolution method development and specification setting for solid oral dosage forms.]