Dissolution Technologies

www.dissolutiontech.com Volume 32, Issue 4 | November 2025


JetX —
Automated
Sample Preparation.
sotax
Traditional
Sample Preparation
is slow. Complicated.
And expensive.
It is time
for a change.
JetX™
Coming in
March 2025.
Solutions for Pharmaceutical Testing
sotax.com/jetX

# Table of Contents

## In This Issue



## Advertisers



## To Submit Articles

Please check the website for instructions, the articles are peer-reviewed and are submitted through the PeerTrack™ website, https://www.editorialmanager.com/dt.

The scope of articles is limited to dissolution or disintegration topics as the major focus. Articles on formulation development where dissolution is just one test of many should not be submitted.

For inquiries and prescreening, e-mail vagray@rcn.com

***Dissolution Technologies* is indexed in:**

**Science Citation Index Expanded®**
**Journal Citation Reports®/ Science Edition**
**International Pharmaceutical Abstracts**
**Chemical Abstracts (CAS)**
**SCOPUS**
**EMBASE**
**CrossRef**
**Google Scholar**

## *Topics for the Next Issue*

The February 2026 issue will include research articles on sulindac tablets, dissolution prediction of salt formulations, and dolutegravir–para amino benzoic acid cocrystal method as well as the Q and A feature.

Research Editor
Vivian Gray
vagray@rcn.com

# Publisher's Information


**PURPOSE:** *Dissolution Technologies* is a peer-reviewed quarterly publication reporting current information on dissolution testing. It provides an international forum for open exchange of information on various dissolution topics.

**CORRESPONDENCE:** Send all correspondence to: *Dissolution Technologies*, Inc., 9 Yorkridge Trail, Hockessin, DE 19707. Phone (302) 235-0621, e-mail: vagray@rcn.com. Website: www.dissolutiontech.com (SSL certified).

**STAFF:** Founder, Cynthia Brown; Managing Director, Vivian Gray; Associate Editor, Valerie Clark; Research Editor, Vivian Gray; Research Editor, William Brown; Communications, Michael Larson; Circulation Manager, Sandra Larson; Layout, Michele Arnold; Publication, Printing, and Distribution Services, Archer Print Group, Sellersville, Pennsylvania.





ISSN 1521-298X

**Dissolution Technologies is indexed in:**
**Science Citation Index Expanded®**
**Journal Citation Reports®/ Science Edition**
**International Pharmaceutical Abstracts**
**Chemical Abstracts (CAS)**
**SCOPUS**
**EMBASE**
**CrossRef**
**Google Scholar**

# Test right. Dose right.

Trusted providers of pharmaceutical testing solutions for over 75 years.


## Pharmaceutical dosage form testing specialists:

- Disintegration
- Dissolution
- Powder Flowability
- Friability
- Hardness
- Diffusion

COPLEY

INNOVATIVE
COMPLIANT
TRUSTED

+44 (0)115 961 6229 | copleyscientific.com | sales@copleyscientific.co.uk

dx.doi.org/10.14227/DT320425P166

# Parametric Tolerance Interval Test for Dissolution Testing of Immediate-Release Solid Oral Dosage Forms

**Steven J. Novick[1*], David LeBlond[2], and Stan Altan[3]**
[1]*Takeda Pharmaceuticals, Cambridge, MA, USA.*
[2]*Robert Singer Consulting, Sonora, CA, IL, USA.*
[3]*Johnson & Johnson Innovative Medicine, Titusville, NJ, USA.*

*email: steven.novick@takeda.com*

## ABSTRACT

**Introduction:** The compendial method specified in the *United States Pharmacopeia* (*USP*) General Chapter Dissolution <711> serves as a standard for batch quality. Although it has been commonly used by industry as a batch release test, it lacks any statistical underpinning. This study proposes the parametric tolerance interval test (PTIT) as a robust risk-based procedure for batch release decisions. The PTIT approach can be calibrated to match the operating characteristics of USP <711> under specific test settings to allow for flexible decision criteria, multiple stages, varying sample sizes, and alpha-spending adjustments if needed. **Methods:** PTIT compares a one-sided, beta-content, gamma-based confidence tolerance limit against a testing limit. Monte Carlo simulations were used to calculate the operating characteristics of USP <711> and PTIT across different testing parameters. The robustness of PTIT was evaluated for deviations from normality, and a Bayesian PTIT variant is introduced, with inference through posterior probabilities. **Results:** Implementing PTIT is recommended by comparing a 95% confidence/85% content tolerance limit to the $Q - 5$ testing limit. This approach allows for other confidence and content levels, as considered appropriate. The operating characteristics align well with USP <711> when the SD of the mean is 3%. PTIT remains robust to slight departures from normality. The Bayesian approach is equally viable while also providing the ability for prior information inclusion as well as consideration of non-normal data distributions. **Conclusion:** The PTIT offers a practical solution for customizing dissolution release testing to specific product and process needs. This underscores the importance of sophisticated statistical approaches to enhance decision-making, transparency, and maintain drug product quality.

**KEYWORDS:** USP <711>, Q testing, parametric tolerance interval test (PTIT), dissolution, in vitro release

## INTRODUCTION

Dissolution or in vitro release testing of solid dose products (e.g., tablets, capsules) is a regulatory and commercial necessity. Regulations mandate that drug product batches meet compendial dissolution specifications prior to distribution, and post-marketing commercial testing tracks batch quality consistency. In vitro release testing also provides insights into the disintegration and release rate of the active pharmaceutical ingredient, which can indicate bioavailability and therapeutic effects.

The *United States Pharmacopeia* (USP) general chapter <711> specifies equipment, media, protocols, and acceptance limits applicable to immediate, extended, modified, and delayed release dosage forms requiring dissolution testing (*1*). As companion sets of guidelines, USP <1092> advises on assay development, and USP <724> extends the concept of standards to transdermal dosage forms (*2*, *3*). Companies are advised to develop their own tailored batch release procedures, ensuring the USP standards are met with high confidence. The United States FDA has explicitly noted that USP <711> and, similarly, USP <905> (uniformity of dosage units) is not intended to provide statistical assurance of quality for the broader batch release testing of dose units (*4*, *5*). Consequently, manufacturers are advised to implement more stringent and statistically grounded release

*Corresponding author

tests, taking into consideration the Biopharmaceutics Classification System properties of the formulation or compound (*6*).

For immediate-release products, USP <711> follows a three-stage zero-tolerance decision rule in which the summary statistics and limits vary across the stages. Because it lacks any underlying parametric model that permits hypothesis-driven inference, it cannot characterize batch quality. Consequently, there have been efforts to develop statistically grounded release tests. The parametric tolerance interval testing (PTIT) was proposed by Tsong and Shen as a consistent underlying model and hypothesis-based batch population inference approach (*7*). Subsequent works by Hauck et al., Dong et al., and Otava et al., refined the PTIT operating characteristics, with calibration enabling alignment with USP <711> stringency (*8–10*).

The FDA supports statistical approaches like PTIT for batch release testing of dissolution and broader quality assurance, as evidenced in its guidance for inhalation and nasal drug products. The current work builds upon the endeavors of Hauck et al., Dong et al., and Otava et al. to provide definitive recommendations for the use of PTIT for hypothesis-driven batch release testing (*8–10*). This study assesses the statistical power of PTIT under a variety of scenarios and illustrates its robustness to deviations from normality. Finally, this study aims to provide a modernized PTIT via Bayesian method to accommodate the possibility of prior information or non-normal distributions.

## METHODS

### Parametric Tolerance Interval Test (PTIT)

Consider the population of solid oral dosage units (without loss of generality, tablets) in a batch. Let $Y$ denote the percent dissolution of a tablet at a predefined time point and let $Q$ denote the dissolution criterion from USP <711>. Assume that $Y \sim N(\mu, \sigma^2)$ are independent normally distributed random variables, where $\mu$ = mean, and $\sigma$ = standard deviation (SD). Because the percent dissolution must fall above 0% and (roughly) below 100%, some care must be taken in making the normality assumption. It is our experience that, over a wide range of time points chosen to describe the dissolution profile, the normality assumption is reasonable. This is frequently the case in the region of $Q$ = 70–80%. Solutions for non-normal distributions will be discussed later.

For lower testing limit $L$, (i.e., $L \leq Q$) and for proportion $p$, a reasonable null ($H_0$) and alternative ($H_A$) hypothesis for batch release testing is given by H1 and visualized in Figure 1.

$H_0$: Less than 100$p$% of tablets > $L$ (H1)

$H_A$: At least 100$p$% of tablets > $L$

Let $q_p(\mu, \sigma^2) = \mu - \Phi^{-1}(p)\sigma$ denote the lower 100(1 – $p$)% quantile of $Y$, and $\Phi^{-1}(p)$ is the inverse of the standard normal cumulative distribution function. To declare $H_A$ in H1, we must have $q_p(\mu, \sigma^2) > L$. If tolerance limit $T_L$ is a lower 100(1 – $\alpha$)% confidence limit for $q_p(\mu, \sigma^2)$ and $T_L > L$, we can state that at least 100$p$% of tablets in the batch are > $L$ with 100(1 – $\alpha$)% confidence. To test the hypotheses in H1, we declare $H_A$ if $T_L > L$.

A lower 100(1 – $\alpha$)% confidence limit for $q_p(\mu, \sigma^2)$ is also called a 100(1 – $\alpha$)%/100$p$% Beta-content tolerance limit for $Y$. Under the normal distribution assumption, a 100(1 – $\alpha$)%/100$p$% tolerance limit is given in Chapters 2 (frequentist) and 11 (Bayesian) by Matthew and Krishnamoorthy (*11*). The procedure of testing H1 with a tolerance interval is called a one-stage parametric

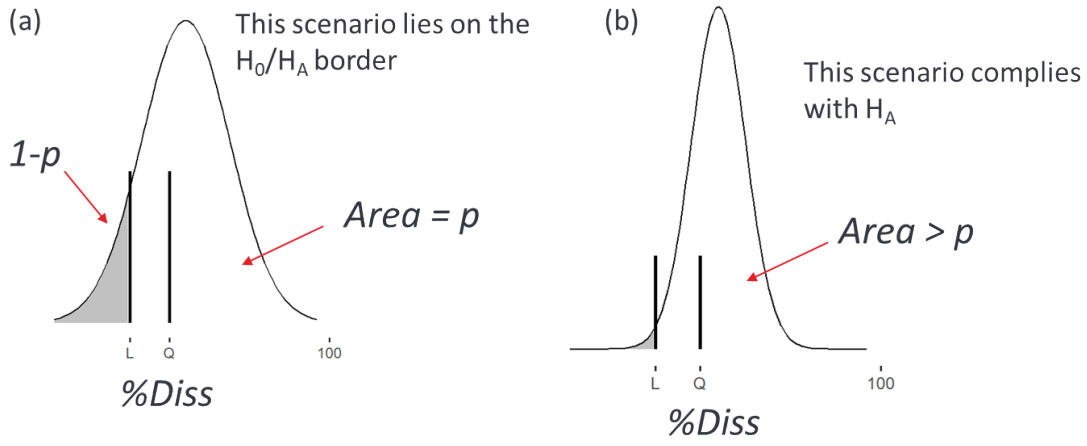



*Figure 1. (**a**) Normal distribution on the $H_0/H_A$ border for testing hypothesis 1 (H1). (**b**) Normal distribution that meets with $H_A$ of $H_1$. Diss: dissolution; $H_0$: null hypothesis; HA: alternative hypothesis; L: lower limit.*

tolerance interval test (PTIT-1). As an alternative test statistic, a Bayesian rule can be applied to accept $H_A$ if the posterior probability that $q_p(\mu, \sigma^2) > L$ is at least 1 - α. The Bayesian paradigm proves especially useful when a non-normal distributional assumption is imposed on the dissolution data. For now, the standard classical statistical approach is explored.

Because USP <711> is a three-stage test, consider a three-stage PTIT (PTIT-3) with sample sizes $n_1 = 6$ for stage 1, $n_2 = 12$ for stage 2, and $n_3 = 24$ for stage 3. Let $Y_j$ denote the percentage of dissolution for the $j^{th}$ tablet, with $Y_j \sim N(\mu, \sigma^2)$; $j = 1, \ldots, 24$. Let $\bar{y}_i$ and $s_i$ denote the sample mean and SD of the full sample at the $i^{th}$ stage, respectively. Testing of multiple stages is adjusted for alpha-spending ($\alpha_1$, $\alpha_2$, $\alpha_3$) to achieve an overall type 1 error, α. The lower 100(1 – α)%/100*p*% tolerance limit for the $i^{th}$ stage is given by Eq. (1).

$$T_L(i) = \bar{y}_i - t^{-1}\left(1 - \alpha_i,\ n_i - 1,\ ncp = \sqrt{n_i}\,\Phi^{-1}(p)\right)\frac{s_i}{\sqrt{n_i}}, \quad (1)$$

where $t^{-1}$ ($\eta$, $\lambda$, $\phi$) is the 100$\eta$% quantile of the non-central T distribution with $\lambda$ degrees of freedom and non-centrality parameter (*ncp*) $\phi$.

Different alpha-spending calculations may be explored and employed, depending on costs, risks, and stage of development considerations. We follow Tsong and Shen, who implemented the alpha-spending approach of O'Brien and Fleming with an overall α = 0.05 so that $\alpha_1 = 0.00009$, $\alpha_2 = 0.00554$, and $\alpha_3 = 0.04824$ (*7, 12*). Another reasonable choice, as performed by Novick et al., is the DeMets and Lan and Pocock alpha-spending function, which yields $\alpha_1 = 0.0179$, $\alpha_2 = 0.0189$, and $\alpha_3 = 0.0279$ and more evenly distributes the risk across testing stages (*13–17*). While O'Brien and Fleming put a larger burden on testing in stages 1 and 2 and may be seen as well-aligned with USP <711>, both alpha-spending methods share an overall type 1 error rate of 0.05. The choice of alpha spending adjustment may also be linked to stage of process validation, as defined by the 2011 process validation FDA guidance (*18*). It makes sense to apply the O'Brien and Fleming adjustment during process validation stages 1, 2, and early 3 (not to be confused with testing stages), when the historical knowledge of the process is still limited (*12*). But later in process validation stage 3, when the historical knowledge of the process has accumulated, relaxing the adjustment to the DeMets and Lan method may be justified (*16*).

At the $i^{th}$ testing stage, $H_A$ in H1 may be accepted if $T_L(i) > L$; otherwise, testing proceeds to the next stage. In this work, if $H_A$ is not accepted at stage 3, the test results in a failure and the batch cannot be released to market.

Without loss of generality, let $Q = 80\%$ for the remainder of this paper. Dong et al. and Otava et al. examined the PTIT under the assumptions laid out in this section, with $L = Q$ across various choices for p (*9, 10*). This PTIT is considered to be overly conservative compared to the operating characteristics specified in USP <711>, given that, for the empirical requirements of stage 3, about 92% (22 out of 24) of dosage units must exceed $Q - 15$. Instead, we consider a PTIT with $L = Q - \delta$ for some $\delta \geq 0$. In the Results section, a Monte Carlo study will explore the values δ and *p* so that, under selected conditions, the PTIT-3 operating characteristic (i.e., probability to declare $H_A$ in Eq. 1) will be similar to USP <711> (i.e., probability to satisfy USP <711> requirements). By careful selection of *Q*, δ, and *p*, the user may ensure that the probability to declare $H_A$ in H1 is not larger than the probability to meet the requirement of USP <711>.

**Confidence Interval Test (CIT)**

For lower testing limit *M* (i.e., $M \leq Q$), a reasonable hypothesis for batch release testing is given by H2.

$$H_0: \mu \leq M \qquad (H2)$$

$$H_A: \mu > M$$

A lower 100(1 – α)% confidence limit for the batch mean is given in Chapter 7 by Ross (*19*).

To test the hypotheses in H2, we declare $H_A$ if confidence limit $C_L > M$. As a comparator to USP <711>, in which one must show that the sample mean $\bar{y} > Q$, because $C_L < \bar{y}$, it follows that it is desirable for $M < Q$.

As with the tolerance limit, the lower 100(1 – α)% confidence limit is modified with alpha-spending for the three stages, as shown in Eq. (2).

$$C_L(i) = \bar{y}_i - t^{-1}(1 - \alpha_i,\ n_i - 1)\frac{s_i}{\sqrt{n_i}}, \qquad (2)$$

where $t^{-1}$ ($\eta$, $\lambda$) is the 100$\eta$% quantile of the central *T* distribution with $\lambda$ degrees of freedom.

In this method, the three-stage procedure of testing H2 with Eq. (2) is called the confidence interval test (CIT). Because USP <711> places requirements on both individual dosage units and the sample mean, it makes sense to require both the PTIT and CIT. That is, one must claim $H_A$ in both H1 and H2 by showing $T_L(i) > L$ and $C_L(i) > M$ at some stage $i = 1$, 2, or 3. Because this is an example

of intersection-union testing, no adjustment to the type 1 error (except for the alpha-spending) is made (*19*). A Bayesian rule can also be applied to jointly accept $H_A$ in H1 and H2 if the posterior probability that $q_p$ ($\mu$, $\sigma^2$) > $L$ and $\mu > M$ is at least 1 - $\alpha$. As with the PTIT, we consider a CIT with $M = Q - \gamma$ for some $\gamma \geq 0$.

### Monte Carlo Simulations for Normally Distributed Data

Monte Carlo simulations were performed to investigate the operating characteristics for meeting the requirements of USP <711> (Table 1), the PTIT alone, and the combined PTIT and CIT (PTIT+CIT). It will be shown in this section that the added value of the CIT is debatable, so the focus of this work will be on the PTIT. Although the sample size in USP <711> is fixed with three stages, the operating characteristics of the PTIT were investigated with larger sample sizes and separately, with only one or two stages.

*Table 1. Operating Characteristics for USP <711> Requirements*

| Stage | Sample size | USP <711> Criteria |
|---|---|---|
| 1 | $n_1 = 6$ | All 6 values > $Q + 5$ |
| 2 | $n_2 = 12$ (6 additional) | Mean of 12 values > $Q$<br>All 12 values > $Q - 15$ |
| 3 | $n_3 = 24$ (12 additional) | Mean of 24 values > $Q$<br>At least 22 of 24 values > $Q - 15$<br>All 24 values > $Q - 25$ |

*Based on information from USP <711> (1).*
*USP: United States Pharmacopeia.*

Unless otherwise noted, $Q = 80\%$ and data were generated as independent $Y_j \sim N$ ($\mu$, $\sigma^2$) ($j$ = 1, …, 24), with 75 < $\mu$ < 90 and $\sigma$ = 0.5, 1, 3, 4.5, 6. For the PTIT with $T_L(i) > Q - \delta$, testing parameters were varied according to $p$ = (0.80, 0.85, 0.90, 0.95), and $\delta$ = (0, 5, 10, 15). For the CIT with $C_L(i) > M - \gamma$, we examined $\gamma$ = (0, 3).

To determine the operating characteristics for the PTIT with $T_L(i) > Q - 5$ as a function of sample size, the sample size was increased at each stage by 1x ($n_1 = 6$, $n_2 = 12$, $n_3 = 24$), 2x ($n_1 = 12$, $n_2 = 24$, $n_3 = 48$) , and 3x ($n_1 = 18$, $n_2 = 36$, $n_3 = 74$). O'Brien and Fleming alpha spending is a function of the relative sample size of stage, so the values of ($\alpha_1$, $\alpha_2$, $\alpha_3$) remain unchanged (*12*). Because the operating characteristics of the PTIT and USP <711> can be matched at $\sigma = 3$, $p = 0.85$, and $\delta = 5$, the main interest is to examine the operating characteristic for 3 < $\sigma$ < 6% to determine if the PTIT can recover its disadvantage for $\sigma > 3\%$.

To study the effect of staged testing on the PTIT, single-stage testing (PTIT-1) was performed with $n_1 = 24$; two-stage testing (PTIT-2) was performed with $n_1 = 12$ and $n_2 = 24$; and PTIT-3 was performed with $n_1 = 6$, $n_2 = 12$, $n_3 = 24$. With an overall $\alpha = 0.05$, there is no alpha-spending adjustment for PTIT-1. For PTIT-2, the O'Brien and Fleming alpha-spending adjustment is $\alpha_1 = 0.000687$ and $\alpha_2 = 0.049771$. For PTIT-3, $\alpha_1$, = 0.00009, $\alpha_2 = 0.00554$, and $\alpha_3 = 0.04824$. The CIT was only examined in three-stage testing with the same sample sizes and alpha-spending adjustments as PTIT-3. Each simulated scenario was run 10,000 times.

### Monte Carlo Simulations for Non-Normal Data

Although the normal distribution may be a reasonable choice for most dissolution data, it is plausible that dissolution distribution for some products may deviate from this assumption. We examine the robustness of the PTIT with $T_L(i) = Q - 5$ ($\delta = 5$) and $p = 0.85$ to such deviations by characterizing the operating characteristics of the PTIT under a skew normal (SN) and a T distribution (see supplemental material for functional forms). In the SN probability density function, $\beta$ controls the skewness, $\epsilon$ is the location parameter, and $\omega$ is the scale parameter (*20*). In the T probability density function, $n$ denotes the degrees of freedom, $\epsilon$ is the location parameter, and $\omega$ is the scale parameter (*21*). Relative to the normal distribution, the SN with a negative skew parameter is skewed to the left, which places more probability in the left tail, and the T distribution puts more probability in both tails.

To illustrate the skew and extra tail probability, a Monte Carlo simulation was performed to explore the robustness of the proposed PTIT-3 to the SN and T distributions relative to the normal distribution. The means and tail probabilities less than $Q = 80\%$ were matched across all three distributions for each scenario. Means ranged from ($Q + 1$) < $\epsilon$ < 90%, and tail probabilities are 0.01, 0.1, 0.2, and 0.3. The skewness settings for the SN distribution were $\beta$ = –4, –3, –2, –1, 0 (where –4 = large skew and 0 = no skew). The degrees of freedom for the $T$ distribution are $\gamma$ = 3, 5, 10, 25, $\infty$ (where 3 = larger tail probabilities, $\infty$ = normal tail probabilities). In all cases, the scale parameter was derived from the other parameters.

### Bayesian Method for PTIT and CIT

Equations (2) and (4) provide a lower 100(1 – $\alpha$)%/100$p$% tolerance limit and a lower 100(1 – $\alpha$)% confidence limit for the mean, respectively, using a frequentist construct specifically for the normal distribution. Although Bayesian analysis may directly calculate the posterior distribution to meet $H_A$ in H1 and H2, for a Bayesian analogue to the frequentist system, one may construct a lower 100(1 – $\alpha$)%/100$p$% Bayesian tolerance limit by calculating the lower 100$\alpha$% quantile of the posterior distribution $T_L = \mu - \sigma\Phi^{-1}(p)|\boldsymbol{Y}$, where $\Phi^{-1}(p)$ is the inverse

cumulative distribution function of the standard normal, and ***Y*** denotes the sampled dissolution data. A lower 100(1 – α)% credible limit ($C_L$) for μ may substitute for the confidence limit. With the Jeffreys' prior, Matthew and Krishnamoorthy show that $T_L$ is equal to H2 and $C_L$ is equal to Eq. (3) (*11*). However, depending on applications and justifiable prior knowledge, Bayesian analysis may leverage different prior distributions, which would then affect the values of $T_L$ and $C_L$.

For PTIT-3, one might use the alpha-spending procedure suggested for frequentist testing and calculate the lower 100(1 – $\alpha_i$)% quantile $T_L(i) = \mu - \sigma\Phi^{-1}(p)|\boldsymbol{Y}_i$ and a $C_L(i)$, a lower 100(1 – $\alpha_i$)% credible limit for μ, where $\boldsymbol{Y}_i$ denotes the cumulative sampled dissolution data at the $i^{th}$ stage. It may be antithetical to use an alpha-spending schema because Bayesian probabilities, unlike *p*-values, are not calculated with conditioning on $H_0$ (Bayes factors are a notable exception).

For consistency with the frequentist approach, an analogous test can be constructed using the Bayesian versions of $T_L(i)$ and, if desired, $C_L(i)$. From these, one may construct Bayesian PTIT and PTIT+CIT procedures. Note that for the PTIT+CIT, the Berger and Hsu intersection-union procedure does not extend to Bayesian hypothesis testing (*22*). Bayesian analysis would instead calculate the joint posterior probability (*Pr*) of $H_A$ directly via Eq. (3).

$$p_i = Pr\,(\mu - \sigma \times \Phi^{-1}(p) > L \text{ and } \mu > M|\boldsymbol{Y}_i) \qquad (3)$$

Then, at the $i^{th}$ stage, if $p_i > 1 - \alpha_i$, $H_A$ is declared; otherwise, move to the next stage.

Bayesian statistics may also extend the PTIT and CIT to other distributions. Let $Y_j \sim F(\boldsymbol{\theta})$, for some distribution *F*(.) with parameter vector **θ**, *j* = 1, 2, …, 24 (or some other sample size) and let $g(\boldsymbol{\theta})$ denote the mean of the distribution. For the PTIT, a lower 100(1 – α)/100*p*% Bayesian tolerance limit is given by the lower 100(1 – α)% quantile of the posterior distribution $T_L = F^{-1}(\boldsymbol{\theta}, p)|\boldsymbol{Y}$ and $C_L$ may be given as the lower 100(1 – α)% posterior quantile of $g(\boldsymbol{\theta})$. Thus, the generalization of Eq. (3) is given by Eq. (4).

$$p_i = Pr\,(F^{-1}(\boldsymbol{\theta}, p) > L \text{ and } g(\boldsymbol{\theta}) > M|\boldsymbol{Y}_i) \qquad (4)$$

As before, if $p_i > 1 - \alpha_i$, $H_A$ is declared at the $i^{th}$ stage; otherwise, move to the next stage.

For normally distributed data and vaguely informative priors, the Bayesian method should perform similarly to the frequentist procedures described in earlier sections. The Bayesian method is demonstrated in the results with SN and T-distributed computer-generated data with (β = -3, ϵ = 88, ω = 4) and (γ = 5, ϵ = 85, ω = 2), respectively.

## RESULTS

### Monte Carlo Simulations

#### *USP <711> and PTIT*

To determine the operating characteristics for satisfying the requirements USP <711> and the PTIT alone using Eq. (1) to test H1, a Monte Carlo simulation was conducted. The operating characteristics for stage 3 (overall probability) are provided in Figure 2.

From Figure 2, calibration of the PTIT with USP <711> can be determined in several places. For example, the operating characteristics match up well when σ = 3, *p* = 0.85 and δ = 5. From our experience, σ = 2–3% stands as a typical range, with 1–2% and 3–5% representing tight and variable dissolution methods, respectively. Producers with an SD that falls outside of the range of these simulations are encouraged to conduct their own set of simulations to examine the operating characteristics for their specific analytical circumstances. In this work, the PTIT with σ =3, *p* = 0.85, δ = 5 stands as a reasonable point of comparison against USP <711>. Given the set of parameters, the PTIT procedure rewards lower SD and penalizes larger SD compared to USP <711>. This is a desirable feature of the PTIT. Another potential PTIT choice is σ = 2.5, *p* = 0.90, δ = 5. Earlier, *p* = 0.92 and δ = 15 was suggested to be a reasonable choice, but, from Figure 2, one can infer that this scenario would be far too liberal to match with USP <711> until σ = 6, which represents a highly variable dissolution method. In practice, for batch release characterization and testing, one should choose a PTIT that is more conservative than the USP <711> criteria (Table 1).

The operating characteristics for each stage of the PTIT with *p* = 0.85 and δ = 5 are shown in Supplementary Figure S1. Across all stages, relative to USP <711>, the PTIT is more liberal with small SD values and more conservative with larger SD values.

#### *USP <711> and PTIT + CIT*

To determine the operating characteristics for satisfying the requirements of USP <711> and the PTIT+CIT, using Eq. (1) to test H1 and Eq. (2) to test H2, a Monte Carlo simulation was conducted. The operating characteristics for stage 3 (overall probability) are provided in Figure S2 with $C_L(i) > Q$ (γ = 0). As expected, one cannot calibrate the PTIT+CIT to match with USP <711> for any value of *p* or δ when σ ≥ 2.5. In Figure 3, the operating characteristic of the PTIT+CIT with $C_L(i) > Q - 3$ (γ = 3) is compared to the PTIT alone, with δ = 5, 10. When δ = 5, there is no

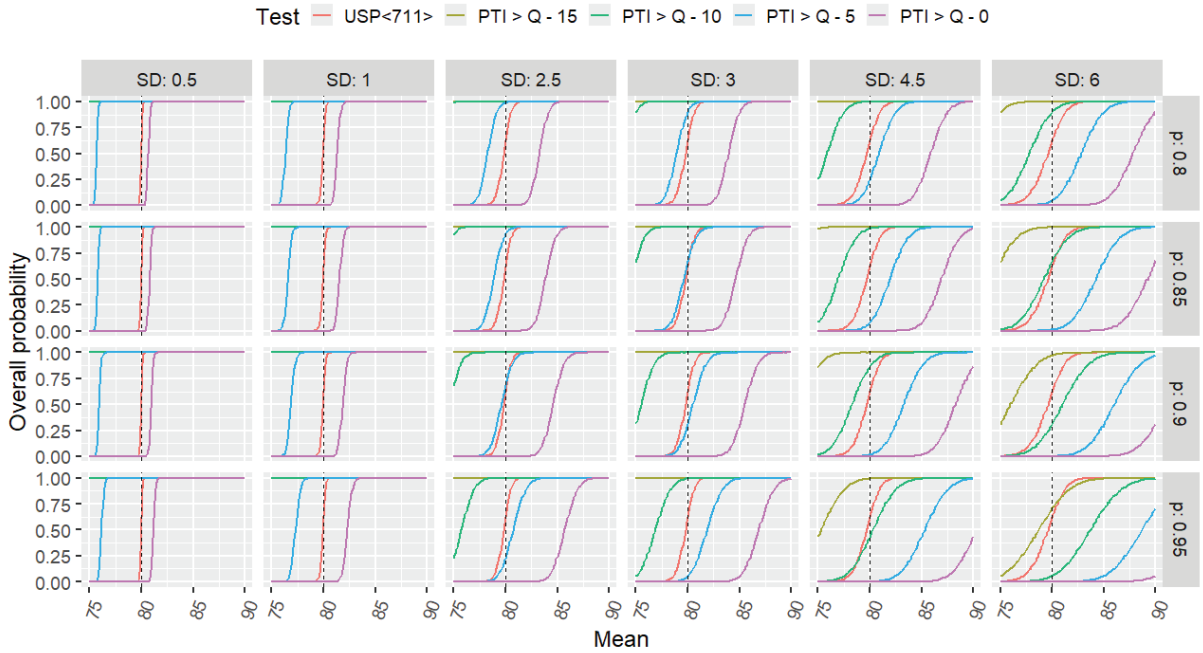



*Figure 2. Overall operating characteristics for satisfying USP <711> and three-stage parametric tolerance interval (PTI) tests for normally distributed data with a population mean and standard deviation.*

significant difference between the PTIT+CIT and PTIT alone except when σ ≥ 1, which represents a rare tight dissolution assay. The differences are made clear when δ = 10, with decreasing preference for the PTIT alone as the SD increases. Considering the recommended PTIT settings of $p$ = 0.85 and δ = 5, the CIT does not contribute to the stringency of the test procedure, so it is an unnecessary test; however, it also appears to do little harm.

### *PTIT as a Function of Sample Size*

The sample size for USP <711> is $n_1$ = 6, $n_2$ = 12, and $n_3$ = 24. The operating characteristics for PTIT as a function of

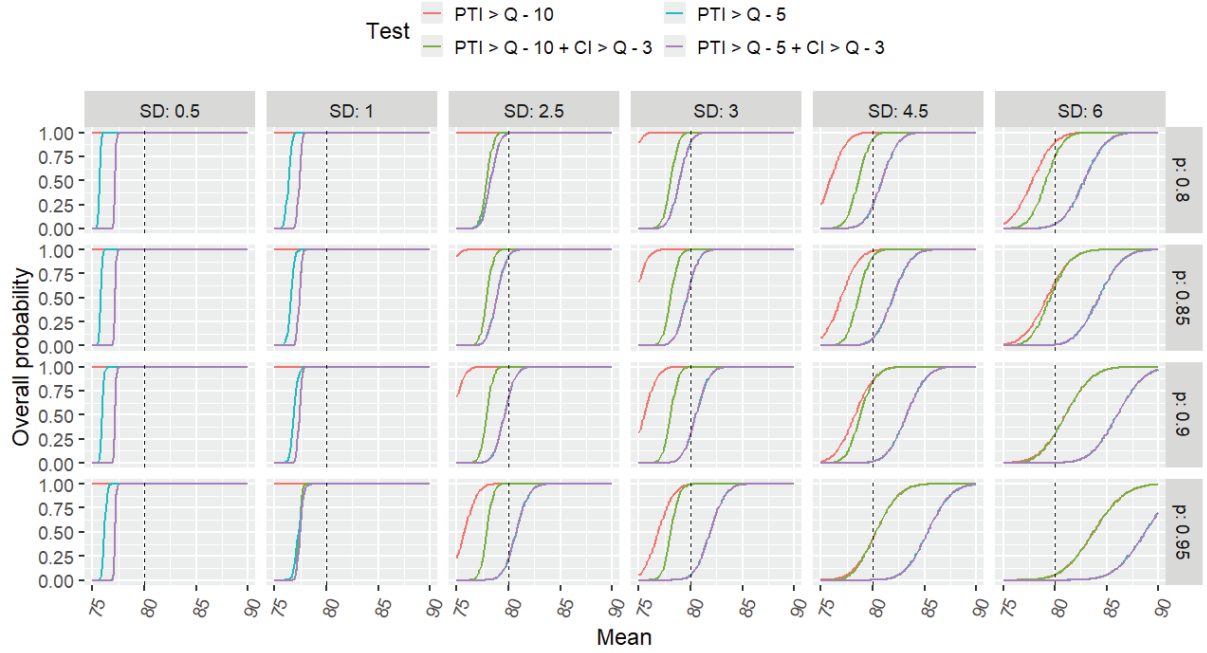



*Figure 3. Overall operating characteristics for satisfying three-stage parametric tolerance interval (PTI) test alone and combined with the confidence interval (CI) test ($C_L$ (i) > Q -3) for normally distributed data with a population mean and standard deviation.*

sample size are shown in Figure S3. Doubling and tripling the sample size improves the operating characteristic of the PTIT but cannot match that of USP <711> for σ ≥ 4.5%.

***PTIT with Multi-Stage Testing***

As shown in Figure S4, the number of stages does not appear to affect the probability to satisfy H1 with the PTIT. Because staging may affect efficiency, the expected number of dosage units was calculated. For single-stage testing, the number of units is always 24. For two-stage testing, the expected number of units is $12 + 12 \times (1 - p_1)$, where $p_1$ is the probability to meet the requirements of the PTIT in stage 1. For three-stage testing, the expected number of units is $6 + 6 \times (1 - p_1) + 12 \times (1 - p_2)$, where $p_i$ is the probability to meet the requirements of the PTIT in stage *i*, (*i* = 1 or 2). The expected number of dosage units are shown in Figure S5, which indicates that multi-stage testing generally requires fewer dosage units, making it the more efficient option. This advantage must be balanced against the requirement of representativeness.

**Robustness of the PTIT to Non-Normality**

Figure S6 shows a normal distribution with parameters μ = 85 and σ = 3.04; an SN distribution with parameters β = –4, ϵ = 88.3, and ω = 4.2; and a T distribution with parameters γ = 3, ϵ = 85, and ω = 2.1, each possessing a tail probability below *Q* = 80% of 0.05. The scenarios β = 0 for SN and γ = ∞ for T represent the normal distribution. The operating characteristics are shown in Figure S7. It appears that skewness and excess tail probability both drive operating characteristic probabilities lower. Thus, for the SN and T distributions, it may be inferred that the PTIT shows robustness to deviations from normality.

**Bayesian Methods for Non-Normality**

To demonstrate the Bayesian method, 24 observations were generated and split into three stages, respectively, from the SN (β = -3, ϵ = 88, ω = 4) and T (γ = 5, ϵ = 85, ω = 2) distributions. The results are provided in Table S1 and Figure S8. The mean for both distributions is 85%, and the 5% and 95% quantiles of the two distributions are similar.

The PTIT, CIT, and probability $p_i$ from Eq. (4) were calculated by correctly assuming the SN and T distributions. For model fitting, vaguely informative prior distributions are given by the following, where HC = half-Cauchy, Γ is the gamma distribution with parameters shape (sh) and scale (sc), and *Q* = 80%.

- SN: $\beta \sim T(\gamma = 3, \epsilon = 0, \omega = 1)$; $\epsilon \sim N(\mu = Q, \sigma = 10)$; $\omega \sim HC(0, 1)$
- T: $\gamma \sim \Gamma(sh = 2, sc = 0.1)$; $\epsilon \sim N(\mu = Q, \sigma = 10)$; $\omega \sim HC(0, 1)$

Parameter estimates (posterior medians) with 95% credible limits for the SN and T distributions are provided in Tables S2 and S3, respectively. Results of testing are given in Table 2, which shows that the SN-generated data fails stages 1 and 2 but passes in stage 3. The T-generated data would fail stage 1 but pass at stage 2. The same conclusion was drawn using PTIT+CIT and Eq. (3) for the assessment.

## DISCUSSION

Dissolution testing for the purpose of assuring drug product quality has a long history as part of pharmaceutical company's overall control strategy. USP <711> sets forth a compendial standard of quality and has often been used for batch release testing (*1*). Although this practice has been criticized by both the scientific community and the FDA, the limited literature on the topic has had little influence in changing industry practices. Consequently, this study provides an updated view of an existing statistically based decision procedure.

The PTIT statistical approach for batch release has been previously proposed for content uniformity and more recently, for dissolution. The current study was built upon this approach and proposes a flexible PTIT statistical procedure that permits varying the decision rule criterion, the number of stages and sample sizes, and proposed a Bayesian counterpart with a decision criterion supported by a posterior probability.

*Table 2. Results of Bayesian PTIT, CIT, and Posterior Probability for Batch Release Testing with Q = 80%*

| Distribution | Stage | $\alpha_i$[a] | $1-\alpha_i$ | $T_L(i)$ Must be > $Q - 5$ | $C_L(i)$ Must be > $Q - 3$ | $p_i$ Must be > $(1 - \alpha_i)$ |
|---|---|---|---|---|---|---|
| SN | 1 | 0.00009 | 0.99991 | 58.9 (fail) | 72.3 (fail) | 0.957 (fail) |
| | 2 | 0.005544 | 0.994456 | 74.5 (fail) | 79.9 | 0.992 (fail) |
| | 3 | 0.048242 | 0.951758 | 78.6 | 83.2 | > 0.999 |
| T | 1 | 0.00009 | 0.99991 | 63.3 (fail) | 76.0 (fail) | 0.988 (fail) |
| | 2 | 0.005544 | 0.994456 | 79.1 | 82.9 | > 0.999 |
| | 3 | 0.048242 | 0.951758 | 81.4 | 84.5 | > 0.999 |

[a]*alpha-spending values from O'Brien and Fleming (11).*

It is encouraging to observe the increasing regulatory acceptance of Bayesian approaches. A Bayesian PTIT approach can offer three advantages:

1. The Bayesian perspective supports patient-centric risk-based release decisions by quantifying batch quality probabilistically.

2. When prior knowledge about underlying model parameters (e.g., mean and SD) can be justified from representative historical studies, the Bayesian paradigm provides distributional tools for expressing that knowledge quantitatively and incorporating it seamlessly into the decision process.

3. For products that require more complex modeling (e.g., non-normal, hierarchical, or nonlinear models), non-Bayesian approaches may require approximations or even be intractable. Bayesian methods are less dependent on analytical derivations and provide exact solutions to any desired degree of Monte Carlo accuracy.

An alpha spending adjustment based on the O'Brien and Fleming method was implemented in the multiple stage testing to accommodate sequential testing (*12*). For convenience and for comparative purposes, this study assessed operating characteristics using the same sample sizes as given in the USP <711> three-stage test with $Q$ = 80% at chosen values of σ and $p$ (proportion above $Q$). Given the set of parameters, the PTIT procedure rewards lower variability and penalizes larger variability compared to USP <711>. For typical parameter values, it is a more stringent test procedure than the USP <711> rules. The addition of a simultaneous test on the batch mean value was found to provide little, if any, advantage in forming a more informative or more stringent test. Robustness of the PTIT procedure was studied through the assessment of mild skewness and wide tails. For both cases, the PTIT procedure showed robustness to departures from normality, especially in those cases where the mean was close to $Q$. Finally, a Bayesian version of the proposed test was detailed, with the possibility of the incorporation of appropriate prior information and non-normal data distributions. Inference is then provided in terms of the posterior probabilities.

Although PTIT procedures have been proposed previously, we are not aware of any approved drug product that employs this approach to assure conformance to the USP <711> standard. It is important to understand that there is always some probability that a given dataset passes the PTIT as we have described it but fails to meet USP <711> criteria (*1*). The operating characteristic curves in this work demonstrate that the probability to declare HA with the PTIT can be no larger than the probability to meet the USP requirements.

This study is not proposing to change or replace the USP <711> compendial standard. The intent is to propose a coherent statistical framework for batch release decisions that, if passed, will provide assurance that the test batch meets the existing compendial standard with similar or smaller probability. This PTIT test is framed as a batch release decision tool, but it seems reasonable that a similar PTIT, with appropriately adjusted parameters, may also be useful for other purposes, such as developmental or investigational decision making.

## CONCLUSION

The need for a statistically based decision procedure for dissolution release testing was the motivation for developing this procedure, especially in view of the widespread but inappropriate application of USP <711> for batch release by companies. The proposed Bayesian PTIT approach promotes patient centric decision-making by allowing customizable criteria, direct risk control, and the ability to integrate historical data. It provides strict evaluation standards, ensuring a rigorous risk control strategy with good performance characteristics relative to the USP <711> criteria. The proposed PTIT method offers a robust statistical framework for reliable drug product quality assurance and is easily adapted to conform to companies' risk tolerance practices specific to the product and the process.

## DISCLOSURES

The authors received no financial support for this work and have no conflicting interests.

## SUPPLEMENTAL MATERIAL

Supplemental material is available for this article and may be found at https://osf.io/k2s85/files/52yft.

## REFERENCES

1. <711> Dissolution. In *USP–NF*. United States Pharmacopeia, 2023. DOI: 10.31003/USPNF_M99470_03_01.
2. <1092> The dissolution procedure: development and validation. In *USP–NF*. United States Pharmacopeia, 2023. DOI: 10.31003/USPNF_M643_05_01.
3. <724> Drug release. In *USP–NF*. United States Pharmacopeia, 2023. DOI: 10.31003/USPNF_M99490_05_01.
4. <905> Uniformity of Dosage Units. In *USP–NF*. United States Pharmacopeia, 2022. DOI: 10.31003/USPNF_M99694_01_01.
5. Questions and Answers on Current Good Manufacturing

Practice Regulations: Production and Process Controls. U.S. Food and Drug Administration. May 22, 2024. https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practice-regulations-production-and-process (accessed Oct 16, 2025).
6. M9 Biopharmaceutics Classification System-Based Biowaivers; Guidance for Industry. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 2021.
7. Tsong, Y.; Shen, M.; Shah, V. P. Three-stage sequential statistical dissolution testing rules. *J. Biopharm. Stat*. **2004**, *14* (3), 757–779. DOI: 10.1081/BIP-200025689.
8. Hauck, W. W.; Foster, T.; Sheinin, E.; Cecil, T.; Brown, W.; Marques, M.; Williams, R. L. Oral dosage form performance tests: new dissolution approaches. *Pharm. Res*. **2005**, *22* (2), 182–187. DOI: 10.1007/s11095-004-1184-4.
9. Dong, X.; Tsong, Y.; Shen, M.; Zhong, J. Using tolerance intervals for assessment of pharmaceutical quality. *J. Biopharm. Stat*. **2015**, *25* (2), 317–327. DOI: 10.1080/10543406.2014.972512.
10. Otava, M., Jacquart, S.; Altan, S. Dissolution testing strategies for large sample sizes and applications in continuous manufacturing. *Dissolut. Technol*. **2024**, *31* (3), 128–134 DOI: 10.14227/DT310324P128.
11. Mathew, T.; Krishnamoorthy, K. *Statistical Tolerance Regions: Theory, Applications, and Computations*; John Wiley & Sons: Hoboken, NJ, 2009.
12. O'Brien, P. C.; Fleming, T. R. A multiple testing procedure for clinical trials. *Biometrics* **1979**, *35* (3), 549–556. DOI: 10.2307/2530245.
13. Novick, S.; Christopher, D.; Dey, M.; Lyapustina, S.; Golden, M.; Leiner, S.; Wyka, B.; Delzeit, H. J.; Novak, C.; Larner, G. A two one-sided parametric tolerance interval test for control of delivered dose uniformity. Part 1--characterization of FDA proposed test. *AAPS PharmSciTech* **2009**, *10* (3), 820–828. DOI: 10.1208/s12249-009-9270-x.
14. Novick, S.; Christopher, D.; Dey, M.; Lyapustina, S.; Golden, M.; Leiner, S.; Wyka, B.; Delzeit, H. J.; Novak, C.; Larner, G. A two one-sided parametric tolerance interval test for control of delivered dose uniformity--part 2--effect of changing parameters. *AAPS PharmSciTech* **2009**b, *10* (3), 841–849. DOI: 10.1208/s12249-009-9269-3.
15. Novick, S.; Christopher, D.; Dey, M.; Lyapustina, S.; Golden, M.; Leiner, S.; Wyka, B.; Delzeit, H. J.; Novak, C.; Larner, G. A two one-sided parametric tolerance interval test for control of delivered dose uniformity--part 3--investigation of robustness to deviations from normality. *AAPS PharmSciTech* **2009**c, *10* (3), 829–840. DOI: 10.1208/s12249-009-9271-9.
16. DeMets, D. L.; Lan, K. K. G. In *Recent Advances in Clinical Trial Design and Analysis*; Thall, P. F., Ed.; Kluwer Academic Publishers: Boston, 1995.
17. Pocock, S. J. Group sequential methods in the design and analysis of clinical trials. *Biometrika* **1977**, *64* (2), 191–199.
18. Process Validation: General Principles and Practices; Guidance for Industry. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Veterinary Medicine, 2011.
19. Ross, S. M. Introduction to probability and statistics for engineers and scientists, 6th ed.; Academic Press: London, 2020.
20. Azzalini, A. A class of distributions which includes the normal ones. *Scand. J. Statist*. **1985**, *12*, 171–178.
21. Hill, G. W. ACM Algorithm 395: Student's t-Distribution. *Comm. ACM*, **1970**, *13* (10), 617–619.
22. Berger, R. L.; Hsu, J. C. Bioequivalence trials, intersection–union tests and equivalence confidence sets. *Statist. Sci*. **1996**, *11* (4), 283–319. DOI: 10.1214/ss/1032280304.

ERWEKA
a VERDER company

DIGITAL

# Dissolution Testing with On-Device Audit Trail


*More infos:*

## *New DT 950/9510 Series software updates:*

- Audit Trail with filter
- No external PC or software needed
- Method approval

*www.erweka.com*

dx.doi.org/10.14227/DT320425P176

# Paradoxical Effects of Superdisintegrants on Dissolution Performance in Ibuprofen Orodispersible Tablets

**Nemanja B. Todorović[1*], Aleksandra D. Ćoškov[1], Jelena M. Čanji Panić[1], Dejana D. Bajić[3], Gordana D. Švonja Parezanović[1], Nataša P. Milošević[1], and Mladena N. Lalić-Popović[1,2]**

[1]*Department of Pharmacy, Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad, Serbia.*
[2]*Center for Medical Pharmaceutical Research and Quality Control, Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad, Serbia.*
[3]*Department of Biochemistry, Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad, Serbia.*

*e-mail: nemanja.todorovic@mf.uns.ac.rs*

## ABSTRACT

**Introduction:** Pharmacopoeial tests for the characterization of solid drug forms may not be sufficiently discriminatory when applied to orally dispersible tablets (ODTs), primarily due to the requirement for rapid disintegration. The aim was to examine the influence of mannitol and disintegrant content on the results of selected pharmacopoeial and non-pharmacopoeial methods for the characterization of ibuprofen ODTs. **Methods:** Eight different formulations of 100-mg ibuprofen ODTs were prepared with different proportions of mannitol in the filler (25% and 75%) and varying the type and concentration of superdisintegrant (SSG at 2% and 8% or CCS at 0.5% and 5%). The tablets were obtained by direct compression and had similar resistance to crushing ($p < 0.01$). The effects of the ODT composition on the results of disintegration, dissolution, wettability, medium absorption rate, and hygroscopicity were measured. **Results:** All eight formulations disintegrated in less than 3 minutes. Those with 5% CCS and 25% or 75% mannitol and the formulation with 0.5% CCS and 75% mannitol had disintegration times less than 30 seconds. With an increase in the proportion of CCS, the dissolution rate decreased in the formulations with a low proportion of mannitol. Increased disintegrant content enhanced medium absorption. The hygroscopicity test was most discriminatory, showing lower values in formulations with higher mannitol. **Conclusion:** The dissolution test is not discriminatory for formulations containing a high proportion of mannitol, if the first sampling is at 5 minutes. The disintegrant proportion must be considered to ensure proper disintegration times and achieve rapid dissolution rates.

**KEYWORDS:** sodium starch glycolate, croscarmellose sodium, dissolution, wettability, orally dispersible tablets

## INTRODUCTION

Ibuprofen (IBU) is a widely used active pharmaceutical ingredient (API) known for its anti-inflammatory, analgesic, and antipyretic effects. Due to its inherent properties, including low solubility and high permeability, IBU is classified in the second group of the Biopharmaceutical Classification System (BCS II) (*1*).

Solid dosage forms, such as orodispersible pharmaceutical formulations, are increasingly present in the pharmaceutical market due to their advantages, including easy administration without the need for additional water, rapid disintegration, and suitability for patients with swallowing difficulties (*2*). Although liquid forms of drugs are most suitable for children under 2 years of age, orodispersible tablets (ODTs) can be used from the second year of life. During the development of ODT formulation, the selection of excipients and disintegrants plays an important role. The desired properties of excipients are high physiological tolerability, non-toxicity, compatibility with other excipients and APIs, good taste and mouthfeel (which is especially important for ODT), good compressibility and flowability, and low hygroscopicity (*3*, *4*).

*Corresponding author

Mannitol as an excipient stands out for its physicochemical characteristics such as low hygroscopicity and high inertness. These properties result in good compressibility, allowing for production of highly durable tablets. Furthermore, mannitol is well-suited for oral pharmaceutical dosage forms because of its excellent solubility and compatibility with individuals who have lactose or fructose intolerance (*4*).

Superdisintegrants, such as sodium starch glycolate (SSG) and croscarmellose sodium (CCS), are commonly used to increase the rapid dissolution of solid drug formulations. SSG is typically used at concentrations ranging from 2–8%, and CCS is utilized in concentrations between 0.5% and 5% in tablet formulations (*5*). The mechanism of action of both superdisintegrants is similar, as both promote swelling to facilitate tablet disintegration (*6*).

In this study, IBU ODTs were formulated and produced using the direct compression method, with a dose of 100 mg and varying concentrations of mannitol (25% and 75%) and superdisintegrants (SSG at 2% and 8% or CCS at 0.5% and 5%). The objective was to evaluate the effects of these modifications using both non-pharmacopoeial test methods, such as wettability, medium absorption rate, and hygroscopicity, as well as pharmacopoeial procedures, including disintegration and dissolution tests. Additionally, a comparison was made between the results of ODT testing using pharmacopoeial and non-pharmacopoeial methods.

## METHODS

### Materials

IBU, which complies with the *European Pharmacopoeia* 11 (EP) requirements, was sourced from Farmalabor (Italy). Spray-dried α-lactose monohydrate (LAC, Supertab 21AN, DFE Pharma, Germany) and mannitol (Farmalabor) were used as fillers. SSG (Primojel, DFE Pharma, Germany) and CCS (Galenika AD, Serbia) served as superdisintegrants. Colloidal silicon dioxide (Centrochem, Serbia) and magnesium stearate (Farmalabor) were employed as a glidant and lubricant, respectively.

For the content uniformity test, the tablets were dissolved in a sodium hydroxide solution (Lachner, Czech Republic) at a concentration of 4 g/L (*7*). A phosphate buffer with a pH of 7.2, prepared using potassium phosphate and potassium dihydrogen phosphate salts (Lachner, Czech Republic) according to United States Pharmacopeia (USP) recommendations, was used for the dissolution test (*8*).

Methylene blue (Fluka, Biochemika, Germany) at a concentration of 1 mg/mL and filter paper (ø 110 mm, Macherey-Nagel, Germany) were employed for the tablet wettability test.

### Preparation of Ibuprofen Orodisposable Tablets (ODTs)

The composition of the investigated formulations was characterized by a fixed proportion of IBU (20%), silicon dioxide (0.5%), and magnesium stearate (0.5%). The proportion of mannitol in the filler varied (25% or 75%), as did the proportions of the superdisintegrants used - SSG (2% or 8%) or CCS (0.5% or 5%) (Table 1). A total of 100 g of tablet blend was prepared. All components, except for magnesium stearate, were blended in a powder mixer (Farmalabor) for 25 minutes at a speed of 130 rpm (blending intensity 5/5) in a plastic box filled to approximately 50% of its volume. After the initial blending, magnesium stearate was added, and blending continued for an additional 2 minutes under the same conditions. The preparation of IBU ODTs (100 mg) was carried out using an eccentric tablet press (EK0, Korsch, Germany). The tablet blend contained 20% IBU, and the lower punch was adjusted to fill the tablet blend with a mass of 0.50 g, providing the desired dose. The position of the upper punch was adjusted to achieve satisfactory tablets with the lowest possible compression. After preparing, the tablets were stored in plastic boxes until testing.

*Table 1. Composition of Tested Formulations*

| Component | Formulation | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| Ibuprofen | 20% | 20% | 20% | 20% | 20% | 20% | 20% | 20% |
| LAC:MAN (75:25) | 77% | 71% | 78.5% | 74% | – | – | – | – |
| LAC:MAN (25:75) | – | – | – | – | 77% | 71% | 78.5% | 74% |
| SSG | 2% | 8% | – | – | 2% | 8% | – | – |
| CCS | – | – | 0.5% | 5% | – | – | 0.5% | 5% |
| Silicon dioxide | 0.5% | 0.5% | 0.5% | 0.5% | 0.5% | 0.5% | 0.5% | 0.5% |
| Magnesium stearate | 0.5% | 0.5% | 0.5% | 0.5% | 0.5% | 0.5% | 0.5% | 0.5% |

*Dash (–) indicates not applicable.*
*LAC: lactose; MAN: mannitol; SSG: sodium starch glycolate; CCS: croscarmellose sodium.*

### *Experimental Design*

A $2^2$ factorial design (Design Expert 13, StatEase) was utilized to investigate the impact of formulation composition on the outcomes of selected tests. The independent variables were as follows: $X_1$, the proportion of mannitol in the filler, with levels set at –1 (25%) and +1 (75%), and $X_2$, the proportion of superdisintegrants, with levels at –1 (2% for SSG and 0.5% for CCS) and +1 (8% for SSG and 5% for CCS). The dependent variables analyzed included disintegration, IBU drug release at 5 minutes, wettability, medium absorption rate, and hygroscopicity.

### *Pre-Formulation Testing*

The solubility of IBU was determined in phosphate buffer (pH 7.2) and 0.1 M sodium hydroxide solution (pH 13). The test was conducted in a thermostatic water bath equipped with a shaker (Witeg, Germany). The temperature was maintained at 37 °C, and the shaking speed was set to 200 rpm. Sampling from the saturated solutions was carried out after 2 and 24 hours. The samples were then filtered through a 0.45-µm membrane filter (Sartorius Lab Instruments, Germany), diluted, and analyzed spectrophotometrically.

The bulk and tapped volumes of pure substances and prepared tablet blend were determined using a jolting volumeter (Stav II, J. Engelsmann AG, Germany). A 50-mL measuring cylinder was used, with a sample mass of approximately 30 g. Bulk volume and the volume after 10, 100, 500, 900, and 1250 impacts were recorded. All measurements were performed in triplicate, and the results are presented as mean values ± SD. The index of compressibility, Hausner ratio, and flow categorization were calculated according to EP guidelines (2.9.36.) (*9*).

The angle of repose was determined for pure substances and tablet blends. A glass funnel was positioned on a laboratory stand such that its outlet was 3 cm above the workbench and paper. The test powders were allowed to fall freely through the funnel in the amount required to form a cone 3 cm in height. The diameter of the cone's base was measured, and the angle of repose was calculated according to EP 2.9.36 (*9*). The test was performed in triplicate, and the results are presented as mean values ± SD.

### Physiochemical Assessment of IBU ODT Formulations

Disintegration (2.9.1), uniformity of mass (2.9.5) and content (2.9.6 Test A), friability (2.9.7), and hardness (2.9.8.) were evaluated in accordance with EP 11 (*9*). A disintegration (Erweka ZT54, Germany) and friability tester (Erweka TA) were used. Hardness was assessed using a durometer tester (Farmalabor). Additionally, the diameter and thickness of each tablet were measured with a Vernier caliper 24 hours after tablet preparation. The dissolution test was performed using a dissolution tester (Erweka DT800). Test conditions were set according to the United States Food and Drug Administration (FDA) recommendations for IBU chewable tablets (*10*). The test medium consisted of 0.05 M phosphate buffer with a pH of 7.2 (900 mL). The apparatus with paddles was operated at 50 rpm and 37 °C. Samples were withdrawn at 5, 15, 25, 35, 45, and 60 minutes. Prior to analysis, the samples were filtered using 0.45-µm membrane filters (Sartorius Lab Instruments).

The wettability and medium absorption rate were determined by placing one tablet in a prepared plastic Petri dish with a diameter of 3.5 cm. The preparation of the Petri dish involved placing three layers of filter paper, which were soaked with 550 µL of methylene blue solution (volume determined by pilot testing). The time required for the tablet to turn blue, indicating wetting of the surface, was recorded. The mass of the tablet before and after the wettability test was also measured, and the medium absorption rate was calculated. All tests were performed in triplicate.

The hygroscopicity of the tablets was evaluated under conditions of increased humidity (75% ± 2%) in a desiccator, using a saturated aqueous solution of sodium chloride. The weight of the tablets was measured before the test and after 2 and 7 days of exposure to increased humidity.

### UV/Vis Spectrophotometry

Spectrophotometric determination of IBU in the solubility, uniformity of content, and dissolution testing was performed by measuring the absorbance at 264 nm using the previously applied method (*11*). A UV-Vis spectrophotometer (8453, Agilent Technologies, USA) was used for the measurements. Linearity was confirmed within the concentration range of 3.90625–250 µg/mL ($R^2$ = 0.9989).

### Statistical Analysis

To examine the discriminative power of the methods, a one-factor analysis of variance (ANOVA) was performed. Pearson correlation coefficient was used to compare the results of the conducted tests. Preliminary analyses were conducted to assess normality, linearity, and homogeneity of variance. Statistical analysis was performed using IBM SPSS Statistics 26 software package.

## RESULTS AND DISCUSSION

The results of the IBU solubility test in two different media (phosphate buffer at pH 7.2 and 0.1 M sodium hydroxide solution at pH 13) at 37 °C were evaluated to determine the sink conditions for the dissolution test and to assess the suitability of each medium for the content determination test. After 24 hours at 37 °C, IBU solubility was 4.71 and 12.25 mg/mL at pH 7.2 and 13, respectively. IBU is a weak acid, with a pKa value in the range of 4.5–4.6 (*12*). Based on the obtained solubility values, it can be concluded that IBU solubility increases with increasing pH. The highest solubility is observed at pH 13, which can be explained by the increased dissociation of weak acids with rising pH, leading to IBU predominantly existing in its ionized, more soluble form. Similar results from an IBU solubility test were reported by Levis et al., i.e., solubility was similarly influenced by the pH of the tested media (at pH 6.8 and 7.4 at 37 °C) (*13*). The results confirm the presence of sink conditions when 900 mL of phosphate buffer at pH 7.2 (as per FDA recommendations) is used as the medium for testing the dissolution of 100-mg IBU ODTs.

Before tableting, the flowability of the IBU tablet blends was assessed, and it was found that the addition of a glidant improved the flowability compared to the filler (both individually and in blends) and pure IBU. However, the Hausner ratio, compressibility index, and angle of repose indicated better flowability for the formulations with 25% mannitol (F1–F4) compared to those with a 75% mannitol (F5–F8). Furthermore, the flowability results influenced the mass variation test, with formulations F1–F4 exhibiting less mass variation compared to formulations F5–F8. Formulations F5 and F7 contained 75% mannitol and did not meet EP 11 requirements for mass variation, but IBU content in individual tablets ranged from 91.11–111.93% (mean values) in all eight formulations.

Results of the tablet hardness test, tablet thickness measurements, friability, and disintegration times are shown in Figure 1. All measured tablet diameters were consistently 12.0 mm with no observed variation across all formulations (12.0 ± 0.0 mm). As shown in Figure 1A, the tablets were formulated to have similar hardness values ($p < 0.01$) to avoid biasing the test results. Low values were chosen to ensure rapid disintegration of the ODT. However, formulations with high mannitol content (F5–F8) had significantly higher friability values due to capping (Fig. 1B) compared formulations containing 25% mannitol. Therefore, future studies should focus on development and optimization of formulations with high mannitol content.

The longest disintegration time was required for formulations F1, F2, and F5 (Fig. 1C). Formulations F1 and F5 had 2% SSG. Having a higher proportion of SSG (8%) shortened the disintegration time in the formulation with 75% mannitol (F6) compared with the 25% mannitol formulation (F2). Formulations with CCS led to faster disintegration of the tested ODTs. Formulations F4, F8 (5% CCS) and F7 (0.5% CCS and 75% mannitol) had a disintegration time shorter than 30 seconds. Although USP and EP do not provide precise disintegration criteria specifically for ODTs, regulatory guidelines offer relevant recommendations. An in vitro disintegration time of approximately 30 seconds or less is generally considered appropriate for ODTs, as it supports administration without the need for water or chewing. Dosage forms with disintegration times exceeding 30 seconds are more suitably classified as chewable tablets or oral tablets (*14*). The results of similar studies suggest that mannitol is the recommended excipient for ODT, as is the superdisintegrant CCS, but it is necessary to optimize its proportion to avoid poor dissolution test results (*15*).

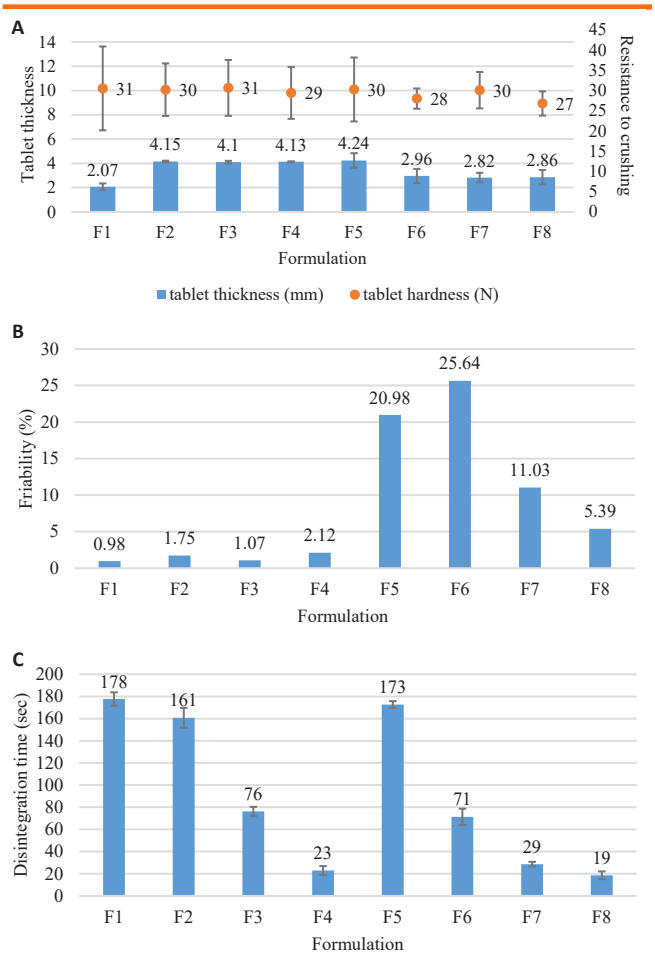



*Figure 1. Assessment of (**A**) tablet thickness and hardness, (**B**) friability, and (**C**) disintegration of the tested formulations.*

In this study, all formulations dominated by mannitol (F5–F8) released the entire content and were considered similar to each other, and the type and proportion of superdisintegrant had no significant effect on the dissolution test results (Fig. 2B). On the other hand, differences in the dissolution profiles for formulations with low mannitol content (F1–F4) were observed according to the type and amount of superdisintegrant present (Fig. 2A). An increase in the proportion of SSG from 2% to 8% resulted in faster dissolution content (F2 vs. F1). Paradoxically, an increase in CCS from 0.5% to 5%, resulted in a slower release of IBU (F4 vs. F3). The dissolution method used showed discriminative power in differentiating the dissolution profiles of formulations with low mannitol content (F1–F4). Previously published studies have identified a reduction in dissolution rate associated with higher concentrations of CCS. Partial gelation may occur, which can form a viscous barrier and limit the dissolution rate (*15*).

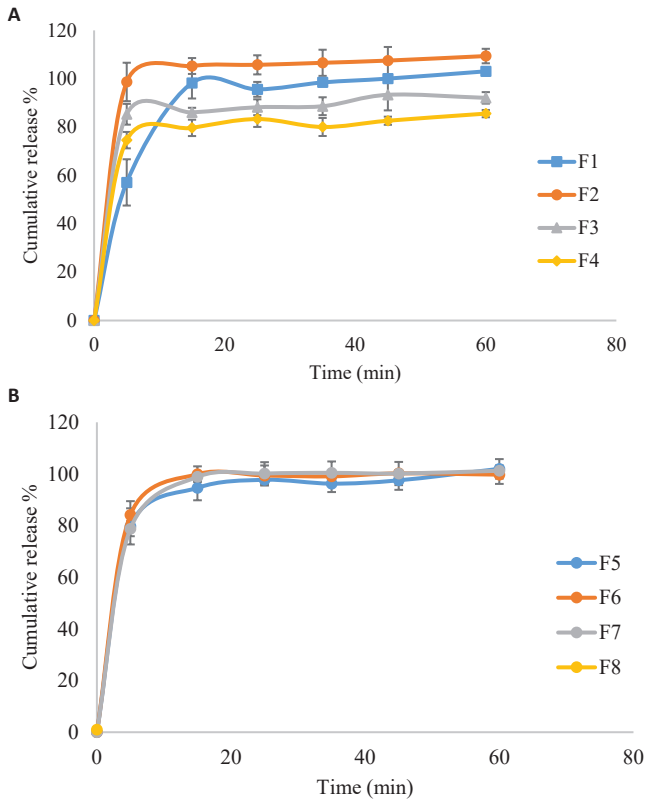



*Figure 2. Dissolution profiles of tested tablet formulations F1–F4 (**A**) and F5–F8 (**B**).*

Wettability measurement can be employed as an additional test for the characterization of ODT since disintegration and wettability have a positive linear correlation, as this study demonstrated (Fig. 3A). Wettability did not significantly change with 5% CCS compared with 0.5% CCS (F4 vs. F3 and F8 vs. F7). In any case, wettability of formulations with CCS (F3, F4, F7, and F8) was significantly faster than those with SSG (F1, F2, F5, and F6). Tsabita et al. reached the same conclusion. In their study of acetosal ODTs, the formulation containing CCS exhibited shorter wettability time compared to that with SSG (*16*).

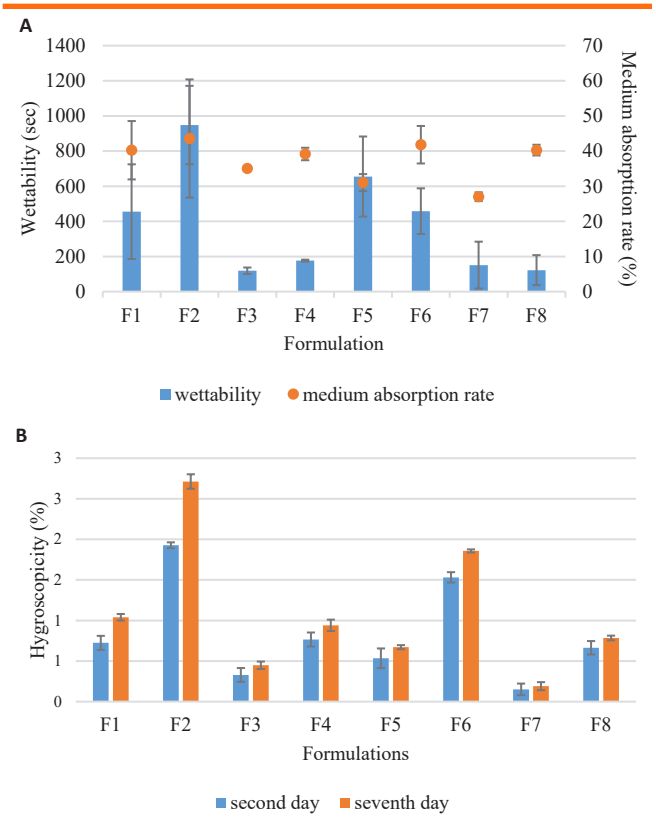



*Figure 3. Assessment of (**A**) wettability and medium absorption rate and (**B**) hygroscopicity of the tested formulations*

Medium absorption rate and wettability reflect the swelling capacity of superdisintegrants in the presence of a small amount of liquid (*17*). A higher medium absorption rate was observed for formulations with SSG, which also required a longer wettability compared to CCS (Fig. 3A). These results indicate a correlation between the medium absorption rate and hygroscopicity (Fig. 3B), i.e., a formulation that is more hygroscopic has a higher medium absorption rate. Data reported by Aglawe et al. suggest that SSG has a higher medium absorption rate than CCS (*18*).

Figures 4 and 5 illustrate the impact of mannitol and superdisintegrants on disintegration, cumulative release in 5 minutes, wettability, medium absorption rate, and hygroscopicity. Superdisintegrants have a dominant positive influence on hygroscopicity, which is reduced

by the negative influence of mannitol as a filler, and is further reduced by their interaction. The highest hygroscopicity level was observed in formulation F2 (Fig. 3B), which is characterized by 8% SSG. This outcome was expected based on the work of Faroongsarng et al., where higher hygroscopicity of SSG was observed compared with CCS under the same temperature and humidity conditions (*19*). According to the results of our study, the hygroscopicity test gave the most discriminatory results for the characterization of ODTs (Figs. 4 and 5) as well as a positive linear correlation with dissolution, wettability, and medium absorption rate.

## CONCLUSION

This study examined the influence of mannitol and superdisintegrants SSG and CCS on disintegration, dissolution, wettability, medium absorption rate, and hygroscopicity of IBU ODTs. All eight tested formulations disintegrated within 3 minutes. The strict regulatory requirement of disintegration within 30 seconds was met by formulations with 25% mannitol and 5% CCS (F4) as well as 75% mannitol with 0.5% and 5% CCS (F7 and F8). Friability testing highlighted the superiority of formulations with low mannitol (F1–F4), whereas those with high mannitol (F5–F8) require further optimization of process parameters. Paradoxically, in formulations with low mannitol content, increasing the proportion of superdisintegrant CCS (F4 vs. F3) led to slower dissolution of IBU. Among all evaluated tests, hygroscopicity proved to be the most discriminative, showing a positive linear correlation with dissolution, wettability, and medium absorption rate. The complex interplay of multiple factors affecting these results highlights the need for comprehensive consideration in future research focused on ODT development.

## DISCLOSURES

The authors acknowledge Galenika AD for kindly providing the pharmaceutical excipients used in this study. This study was supported by the Ministry of Science, Technological Development, and Innovation of the Republic of Serbia (grant no. 451-03-136/2025-03/200114). The authors received no other financial support for this work and have no conflicting interests.

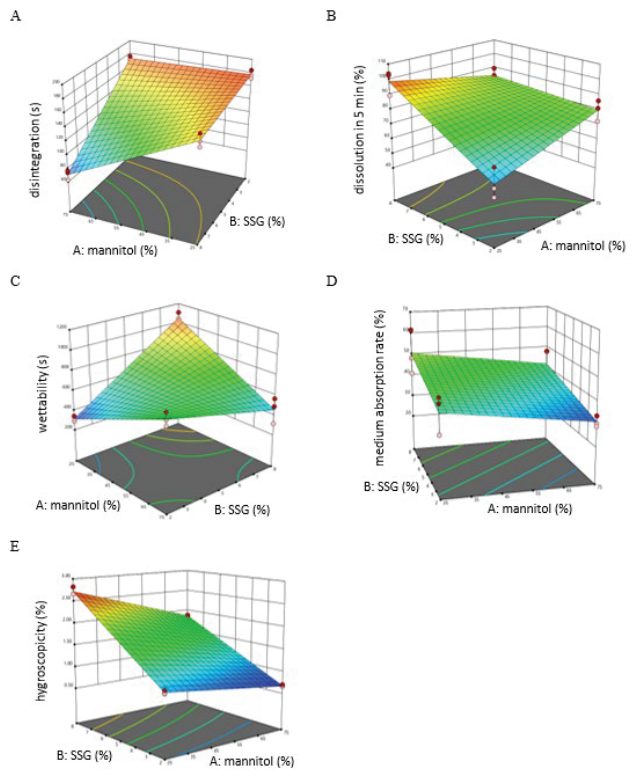



*Figure 4. Three-dimensional representation of the influence of formulation composition on (**A**) disintegration, (**B**) dissolution rate in 5 minutes, (**C**) wetting time, (**D**) degree of medium absorption, and (**E**) hygroscopicity of formulations F1–F4.*

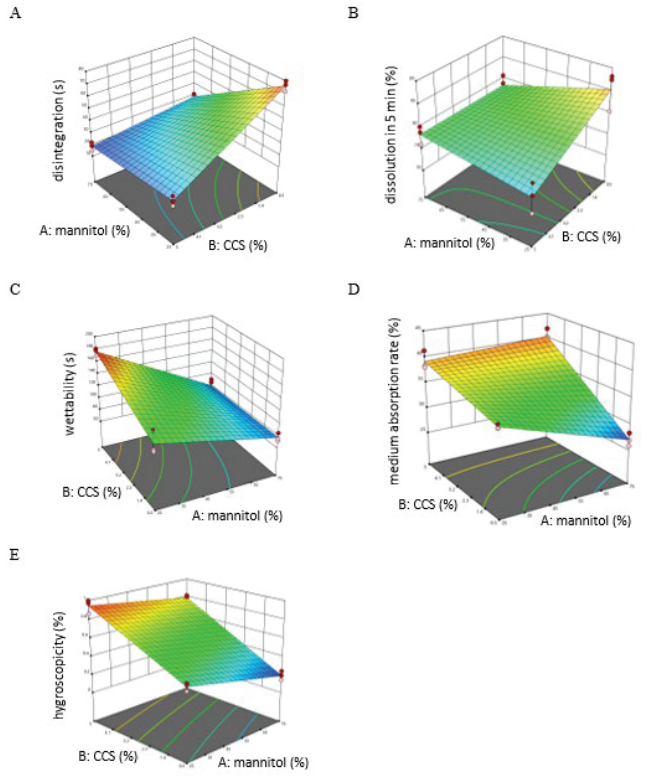



*Figure 5. Three-dimensional representation of the influence of formulation composition on (**A**) disintegration, (**B**) dissolution rate in 5 minutes, (**C**) wetting time, (**D**) degree of medium absorption, and (**E**) hygroscopicity of formulations F5–F8.*

## REFERENCES


1. Zarzoso-Foj, J.; Cuquerella-Gilabert, M.; Merino-Sanjuan, M.; Reig-Lopez, J.; Mangas-Sanjuán, V.; Garcia-Arieta, A. Physiologically-based biopharmaceutics modeling for ibuprofen: identifying key formulation parameter and virtual bioequivalence assessment. *Pharmaceutics* **2025**, *17* (4), 408. DOI: 10.3390/pharmaceutics17040408.
2. Pepić, I.; Lovrić, J. Challenges in patient-centric oral dosage form design – the example of sumamed. *Medicus*. **2018**, *27* (2), 171–175.
3. Alderborn, G.; Frenning, G. Tablets and compaction. In *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, 5th ed.; Aulton, M. E., Ed.; Elsevier, 2018; pp 517–563.
4. Liu, J.; Klinzing, G. R.; Nie, H. Effect of material properties and variability of mannitol on tablet formulation development. *Pharm. Res*. **2023**, *40* (8), 2071–2085. DOI: 10.1007/s11095-023-03577-y.
5. Sheskey, P. J., Cook, W. G., Cable, C. G., Eds. *Handbook of Pharmaceutical Excipients*, 8th ed.; Pharmaceutical Press, 2017.
6. Berardi, A.; Janssen, P. H. M.; Dickhoff, B. H. J. Technical Insight into potential functional-related characteristics (FRCs) of sodium starch glycolate, croscarmellose sodium and crospovidone. *J. Drug Deliv. Sci. Technol*. **2022**, *70*, 103261. DOI: 10.1016/j.jddst.2022.103261.
7. Buffer solutions. In *USP 43–NF 38*. United States Pharmacopeia, 2020.
8. Ibuprofen. In *European Pharmacopoeia*, 11th ed. European Directorate for the Quality of Medicines and HealthCare, Council of Europe, 2023.
9. *European Pharmacopoeia*, 11th ed. European Directorate for the Quality of Medicines and HealthCare, Council of Europe, 2023.
10. Dissolution Methods Database. U.S. Food and Drug Administration website. www.accessdata.fda.gov/scripts/cder/dissolution (accessed Feb 10, 2023).
11. Marković, A.; Spasić, M.; Savić, V.; Sunarić, S.; Tasić-Kostov, M. [Spectrophotometric method in comparative in vitro dissolution test of branded and generic ibuprofen tablets] [Article in Bosnian]. *Acta Fac. med. Naiss*. **2021**, *38* (2), 147–155. DOI: 10.5937/afmnai38-28337.
12. Higgins, J. D.; Gilmor, T. P.; Martellucci, S. A.; Bruce, R. D. Analytical profiles of drug substances and excipients. In *Analytical Profiles of Drug Substances and Excipients*; Brittain, H. G., Ed.; Academic Press, 2001; pp 265–330. DOI: 10.1016/S1075-6280(01)27008-6.
13. Levis, K. A.; Lane, M. E.; Corrigan, O. I. Effect of buffer media composition on the solubility and effective permeability coefficient of ibuprofen. *Int. J. Pharm*. **2003**, *253* (1-2), 49–59. DOI: 10.1016/S0378-5173(02)00645-2.
14. Orally Disintegrating Tablets; Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 2007.
15. Desai, P. M.; Er, P. X. H.; Liew, C. V.; Heng, P. W. S. Functionality of disintegrants and their mixtures in enabling fast disintegration of tablets by a quality by design approach. *AAPS PharmSciTech* **2014**, *15* (5), 1093–1104. DOI: 10.1208/s12249-014-0137-4.
16. Tsabita, S.; Ikasari, E. D.; Sari, W. K. Optimization of sodium croscarmellose and sodium starch glycolate in orally disintegrating tablets (ODT) acetosal. *Med. Farm. Indones*. **2025**, *20* (1), 15–23. DOI: 10.53359/mfi.v20i1.289.
17. Ghourichay, M. P.; Kiaie, S. H.; Nokhodchi, A.; Javadzadeh, Y. Formulation and quality control of orally disintegrating tablets (ODTs): recent advances and perspectives. *BioMed Res. Int*. **2021**, *2021* (1), 6618934. DOI: 10.1155/2021/6618934.
18. Aglawe, S. B.; Gayke, A. U.; Sancheti, V. P.; Metkar, P. S. Formulation and evaluation of mouth dissolving tablets of oxcarbazepine. *World J. Pharm. Res*. **2017**, *6* (10), 1130–1137.
19. Faroongsarng, D.; Peck, G. E. Thermal porosity analysis of croscarmellose sodium and sodium starch glycolate by differential scanning calorimetry. *AAPS PharmSciTech* **2003**, *4* (4), 67. DOI: 10.1208/pt040467.

Pion


# Pion. Powers Dissolution

## Introducing the DissoSpec™ QC Dissolution Monitoring System.

- In situ UV-Vis dissolution testing system.
- Efficient, compliant, real-time method development.
- Dosage to data, simplified. No pumps, filters or user bias.
- Simplified workflow: Add your sample, press start, and walk away.
- DissoPro Software with 21 CFR Part 11 Compliance.
- Compendial USP 1/2/5/6 Apparatus.


**Learn more at: https://info.pion-inc.com/dissospec**

Pion

Pion Inc. | 10 Cook St. | Billerica, MA 01821 | MA | 01821 | +1 978.528.2020
Pion Inc. (UK) Ltd | Forest Row Business Park | Station Road, Forest Row | East Sussex RH18 5DW | +44 (0) 1342 820720
www.pion-inc.com | sales@pion-inc.com | techsupport@pion-inc.com

dx.doi.org/10.14227/DT320425P184

# Comparative Assessment of 1% Luliconazole Cream Release Profile Through Franz Diffusion Cells – A Way Towards Qualification and Validation of Critical In Vitro Parameters

**Yogesh Upadhyay*, Sanjeev Mishra, Sanjay Jagannath Gurule, and Arshad H. Khuroo**
*Department of Clinical Pharmacology and Pharmacokinetics, Sun Pharmaceutical Industries Ltd., Gurugram, Haryana, India.*

*e-mail: Yogesh.Upadhyay@sunpharma.com*

## ABSTRACT

**Introduction:** The in vitro release test (IVRT) is an established method used to characterize the rate of active pharmaceutical ingredient (API) release and assess the sameness in product quality attributes. This study aims to present a systematic approach for validating critical IVRT parameters, alongside high-performance liquid chromatography (HPLC) method validation and qualification of the IVRT procedure for estimating luliconazole (LCZ) from semisolid formulations. **Methods:** The comparative release profile of LCZ from its cream formulations was evaluated using vertical Franz diffusion cells. Samples collected during the in vitro studies were analyzed using a HPLC system equipped with an ultraviolet detector. **Results:** The drug release demonstrated linearity, with a coefficient of determination ($R^2$) ≥ 0.90, indicating a strong correlation between the amount of drug released and the square root of time (√t) through the LCZ semisolid matrices. Statistical analysis confirmed equivalence between reference formulations when IVRT was performed on 2 separate days; however, non-equivalence was observed between the reference and test formulations, as the 90% confidence interval exceeded the acceptable range of 75–133.33%, according to SUPAC-SS guidelines. **Conclusion:** These results confirm that the developed IVRT method is sensitive, selective, and specific for evaluating the product sameness of LCZ formulations.

**KEYWORDS:** In vitro release testing, dissolution, Franz diffusion cell, apparatus qualification, luliconazole

## INTRODUCTION

Luliconazole (LCZ), an imidazole antifungal agent, has demonstrated potent activity against a variety of fungi. Fungal infections are generally classified into two categories: superficial and invasive. Superficial fungal infections are often associated with poor quality of life and neglect of treatment and affect approximately 25% of the world's population. Invasive fungal infections, which typically occur in patients who are critically ill or immune-compromised, are a significant cause of hospitalization.

The R-enantiomer of LCZ exhibits strong antifungal activity by inhibiting the enzyme lanosterol demethylase, thereby disrupting the synthesis of ergosterol. This inhibition results in decreased levels of ergosterol and an accumulation of lanosterol (*1*). LCZ cream is approved for topical use in the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis, caused by *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients aged 18 years and older (*2*).

Draft guidance published by the United States Food and Drug Administration (FDA) on LCZ states that the test product and reference standard should exhibit equivalent LCZ release rates as demonstrated through an acceptable IVRT bioequivalence study (*3*). This study should compare

*Corresponding author

at least one batch of the test product with one batch of the reference standard using a properly validated IVRT method (*3*).

The physical and structural properties of a semisolid topical formulation can significantly influence the release rate of the active pharmaceutical ingredient (API). Characterizing the release behavior of an API is essential throughout the drug development process. The IVRT method serves as a critical tool for determining the release rate and diffusion behavior of an API from topical formulations. For semisolid dosage forms, it is imperative to evaluate drug release characteristics using IVRT techniques.

The IVRT method offers several advantages, including its application in the quality control of drug formulations, prediction of in vivo performance, evaluation and confirmation of formulation design intent, and assessment of formulation quality and product equivalence following post-approval changes (*4*). IVRT is also a valuable tool for optimizing formulations during the early stages of development, serving as a cost-effective means of generating predictive insights into a drug product's in vivo behavior. In each IVRT experiment, certain validated parameters—such as temperature, sample application technique, membrane preparation, stirring efficiency, Franz diffusion cell (FDC) dimensions, and sampling intervals—are maintained consistently to ensure the robustness and reproducibility of the study. In contrast, variables such as the type of synthetic membrane and the choice of receptor fluid can significantly influence the drug release characteristics of the dosage form.

An extensive literature review revealed a previously reported comparative IVRT study of LCZ, which primarily focused on validation of the IVRT and HPLC methods; however, it lacked comprehensive methodology and relevant data for conducting an in-depth comparative release study (*5*). Another study focused on the application of mathematical models, but similarly did not provide adequate comparative release data (*6*). Although additional literature was identified for LCZ HPLC analysis, no well-qualified and validated IVRT and HPLC method has been reported (*7*).

This study aims to develop and validate an IVRT method for LCZ cream with high sensitivity, specificity, selectivity, and reproducibility. This study also outlines a procedure for determining product equivalence or non-equivalence using the test/reference (T/R) ratio calculation. Moreover, this study presents a comprehensive evaluation of IVRT parameters, resulting in a simple and reliable method that can be applied to the characterization of other topical dosage forms as well.

## METHODS

### Chemicals and Reagents

LCZ (working standard) was obtained from Clearsynth Labs Ltd. (Mumbai, India). Brij O20 and HPLC-grade methanol were sourced from Sigma Aldrich Chemical Pvt. Ltd. (Bengaluru, India). Ammonium bicarbonate was acquired from Fluka, Honeywell (Mumbai, India), and phosphate buffer saline (PBS) was procured from Sisco Research Laboratories Pvt. Ltd. (Mumbai, India).

### Drug Products

Lulifin cream (LCZ 1% w/w, batch no. SXB0257C, Sun Pharmaceutical Industries Ltd., Gurugram, India) was employed as the reference formulation, while LCZ cream (LCZ, 1% w/w, batch no. F51/PRS/175) served as the test formulation. Additionally, to evaluate IVRT selectivity, specificity, and sensitivity, two other test formulations were included: LCZ 0.5% cream (LCZ, 0.5% w/w, batch no. F88/ASR/001) and LCZ 1.5% cream (LCZ, 1.5% w/w, batch no. F88/ASR/003).

### High-Performance Liquid Chromatography (HPLC) Method Validation

The reverse phase (RP)-HPLC method validation was performed over a concentration range of 0.200–200.244 µg/mL at a detection wavelength of 295 nm using a Zorbax SB CN column (150 × 4.6 mm, 5 µm) from Agilent (Mumbai, India). A gradient elution technique was employed, where mobile phase A consisted of buffer 1 and methanol (40:60, v/v), and mobile phase B contained buffer 1 and methanol (10:90, v/v). Buffer 1 was prepared as 20 ± 1 mM ammonium bicarbonate. The flow rate was maintained at 1.000 mL/min, following the gradient program outlined in Table 1.

*Table 1. HPLC Time Program for Luliconazole Estimation.*

| Time (min) | Mobile Phase | Flow (%) |
|---|---|---|
| 0.01 | A | 100 |
| | B | 0.0 |
| 3.00 | A | 100 |
| | B | 0.0 |
| 3.01 | A | 0.0 |
| | B | 100 |
| 5.01 | Stop | - |

*HPLC: high performance liquid chromatography; mobile phase A: Buffer 1: Methanol; 40:60, v/v; mobile phase B: Buffer 1: Methanol; 10:90, v/v; and buffer 1 was 20 ± 1 mM ammonium bicarbonate.*

The injection volume was set to 10 µL, and the column oven temperature was maintained at 45 °C. A stock solution of LCZ was prepared in methanol at a

concentration of 1 mg/mL, which was used to construct the calibration curve and prepare quality control (QC) samples. This stock solution was further diluted with the mobile phase A to obtain the following calibration standards: 0.200, 0.501, 4.005, 20.024, 40.049, 80.098, 160.196, and 200.244 µg/mL.

During each analytical run for IVRT samples, eight calibration standards and one blank were injected. The calibration curve was generated based on these standards. Additionally, three QC samples at low, medium, and high concentrations (0.586, 79.220, and 158.440 µg/mL, respectively) were included in each IVRT run to ensure analytical accuracy and reliability.

***Linearity and Range***

Method linearity was evaluated by analyzing an eight-point standard calibration curve. The curve demonstrated excellent linearity over the concentration range of 0.200 µg/mL (limit of quantitation, LOQ) to 200.244 µg/mL (upper limit of quantitation, ULOQ), with a regression equation of $y = 1.0019x + 0.1183$ and a $R^2$ of 0.9998. This calibration curve was then used to back-calculate the concentrations of LCZ in unknown samples.

***Selectivity and Specificity***

The synthetic membrane Ultipor N66 was immersed in the receptor medium for 6 hours. Simultaneously, 300 µL of placebo was mixed with 20 mL of receptor solution, vortexed, and allowed to stand at room temperature for the same duration to simulate the experimental conditions. This procedure was performed in triplicate. After processing the selectivity samples, the peak area response at the analyte's retention time was evaluated.

***Precision and Accuracy***

In this study, both intra-batch (within-batch) and inter-batch (between-batch) precision and accuracy were evaluated. Intra-batch assessments involved six replicates of QC samples at three concentration levels: 0.562 µg/mL (low), 61.069 µg/mL (medium), and 156.588 µg/mL (high), all prepared in receptor solution and analyzed on the same day. For inter-batch evaluation, 18 replicates at each QC level were analyzed across three precision and accuracy runs conducted over 2 consecutive validation days.

**In Vitro Release Test (IVRT) Method**

The IVRT system was qualified by evaluating all critical parameters of the FDC, including receptor chamber capacity, cell diameter, membrane surface area, receptor solution temperature, stirring speed, dispensing volume, and environmental conditions (*8*). These parameters were measured using standard techniques for assessing length, weight, and temperature. The results are summarized in Table 2.

The IVRT experiment was carried out using an FDC system (PermeGear, PA, USA) with a receptor chamber volume of 20 mL. The experimental setup included the donor and receptor chambers, clamp, magnetic stirrer, and synthetic membrane, all properly assembled. A magnetic stir bar was placed in the receptor chamber, which was filled with receptor medium composed of 0.5% Brij O20 (w/v) in a mixture of 10× PBS and water (10:90, v/v).

The membrane was carefully placed over the receptor chamber to ensure full contact with the junction between the donor and receptor chambers. The donor chamber was aligned on top of the membrane, and a clamp was used to secure the assembly. The underside of the membrane was checked for air bubbles, which were eliminated by gently tilting the FDC assembly, if needed.

The entire setup was mounted in the cell holder, and the water jacket was connected to a recirculating system using flexible tubing. A heating circulator bath was activated to maintain the membrane temperature at 32 ± 1 °C. The magnetic stirrer was operated at a consistent speed of 560 ± 20 rpm throughout the experiment. The membrane was allowed to equilibrate for at least 30 minutes, with its surface temperature monitored using a calibrated infrared thermometer.

*Table 2. Results of Apparatus Qualification Test*

| Parameter | Acceptance Criteria | Result | Acceptable |
|---|---|---|---|
| Franz diffusion cell capacity (mL) | 20 ± 1.0 | 20 ± 0.16 | YES |
| Orifice diameter (mm) | 15 ± 0.75 | 15 ± 0.2 | YES |
| Temperature of receptor solution (°C) | 32 ± 1 | 32 ± 0.5 | YES |
| Temperature on membrane surface (°C) | 32 ± 1 | 32 ± 0.6 | YES |
| Speed of magnetic stirrer (rpm) | 600 ± 60 | 565 ± 5 | YES |
| Dispensed sampling volume (µL) | 300 ± 9 | 302 ± 5 | YES |

*Values are presented as mean ± SD (n = 6).*

Before application of the test formulation, pre-dose samples (300 µL) were collected from the center of the receptor chamber in each FDC and stored in sample vials. After each sampling, the receptor chamber was refilled with fresh receptor solution to maintain consistent volume and conditions.

Quantification of IVRT samples was carried out with a Shimadzu HPLC system coupled to a UV detector, along with Analyst 1.6.3 software for data analysis.

***Laboratory Qualification***

Laboratory qualification was conducted by evaluating the release rates of LCZ reference formulations using the developed and validated IVRT and HPLC-UV methods. Release rates from two reference formulations were measured over 2 separate days using six FDCs per day ($n$ = 6). Reproducibility, along with intra- and inter-run variability, was calculated as the percent coefficient of variation (%CV), which was required to remain below 15%.

The intra-run %CV for the first and second IVRT runs was 5.06% and 4.09%, respectively, while the inter-run %CV ($n$ = 12 FDCs) was 3.89%. Product equivalence was evaluated using the 90% CI method in accordance with SUPAC-SS guidelines (*9*). Individual test-to-reference (T/R) ratios were expressed as percentages, with Day 1 considered the reference and Day 2 the test run. The 90% CI was calculated from the ordered T/R ratios, with the $8^{th}$ and $29^{th}$ ranked ratios representing the lower and upper confidence limits, respectively (*9*). The resulting 90% CI ranged from 100.94–112.51%, which falls within the acceptable equivalence range of 75–133.33%, indicating successful qualification and reproducibility of the IVRT system.

***Receptor Solution Selection***

Various receptor solutions and synthetic membranes were evaluated in this study to optimize the drug release rate. The receptor solutions tested included different ratios of methanol-water and isopropyl alcohol-water mixtures. Cumulative drug release percentages were measured using hydro-alcoholic solutions containing 5–50% isopropyl alcohol or methanol in water. Notably, even with as little as 5% organic content, the cumulative drug release exceeded 30%, indicating a deviation from Higuchi theory (*10*). Additionally, these hydro-alcoholic receptor solutions showed high inter-cell variability ($n$ = 6), with release rates exceeding 15% and a coefficient of determination ($R^2$) below 0.90 across the FDCs.

Subsequently, PBS was considered as a receptor solution. However, due to the lipophilic nature of LCZ, with a Log P value of 4.07, inadequate solubility and inconsistent release results were observed in PBS alone. To address this issue, various concentrations (0.1%, 0.25%, 0.5%, and 1.0%) of a hydrophilic-lipophilic balance (HLB) surfactant, Brij O20, were added to the PBS receptor solution to enhance drug solubility and maintain sink conditions (*11–13*).

Surfactant concentrations above 0.5% were effective in maintaining sink conditions throughout the experiment; however, a concentration of 1.0% Brij O20 resulted in excessive bubble formation in the receptor solution (*14*). Therefore, the optimal concentration was determined to be 0.5% Brij O20 in 10-mM PBS. This composition maintained sink conditions, provided consistent results, minimized variability between cells, and yielded an $R^2$ value close to 1. The solubility of LCZ in the selected receptor solution was further confirmed by dissolving 1 mg of LCZ in 1 mL of the solution.

***Synthetic Membrane Selection***

A suitable membrane should be selected to ensure consistent drug release, providing inertness and minimal resistance to diffusion from the dosage form. In this study, three different synthetic membranes were evaluated: Supor 200, Ultipor Nylon 6,6 [N66], and Tuffryn HT200, procured from Pall Life Sciences (Mumbai, India). All membranes had a pore size of 0.2 µm and a diameter of 25 mm. Temperature monitoring of the synthetic membranes was performed using an infrared thermometer (Metravi MT4, West Bengal, India).

To assess drug binding to the membranes, each was immersed in a known concentration of LCZ prepared in the receptor solution for over 6 hours. Following the incubation period, the peak area responses of the LCZ solutions (after membrane immersion) were measured and compared with the peak area response of a control stock solution. This comparison allowed for the evaluation of drug loss due to membrane binding.

***Drug Application and Sample Collection***

Approximately 300 µL of the formulation was evenly applied to the synthetic membrane via the donor chamber of the FDC. After application, the donor chamber was occluded with parafilm to prevent evaporation. According to regulatory guidance, a minimum of six sampling time points is required to establish linearity (*8*). In this study, the sampling time points were set as: pre-dose, 0.5, 1, 2, 3, 4, 5, and 6 hours.

The maximum duration of the IVRT was limited to 6 hours, which is sufficient to distinguish the release rates between different strengths of LCZ. At each designated

time point, approximately 300 µL of receptor solution was withdrawn and transferred into HPLC vials for analysis. The receptor chamber was immediately replenished with pre-warmed receptor solution to maintain volume consistency and sink conditions.

**Estimation and Comparison of Release Rates**

Concentration of collected samples was estimated through HPLC-UV analysis. For calculating the amount of drug released at each time point (µg/cm$^2$), the cumulative concentration (µg) obtained at each sampling time point was multiplied by the FDC volume (20 mL) and by the volume of sample removed at each time point, which was then divided by the effective surface area of membrane (i.e., surface area of orifice = 1.77 cm$^2$). The cumulative amount removed in the previous sampling was calculated by adding the volume of sample removed (mL) from the FDC at each sampling time.

For calculation of release rate, the slope of a straight line (which denotes release rate) was obtained by plotting the cumulative amount of drug release per unit area (µg/cm$^2$) versus time ($h^{1/2}$). Mass balance was evaluated by dividing the cumulative amount of drug released (µg) by the concentration of the applied formulation.

Comparison of the in vitro release rate was conducted following the SUPAC-SS guidelines. Six individual release rate slopes were obtained for both the test and reference formulations. From these slopes, 36 individual T/R ratios were calculated and expressed as percentages (i.e., T/R ratio × 100). These T/R ratios were then ordered from lowest to highest. The 8$^{th}$ and 29$^{th}$ values in the ordered list were used to define the lower and upper limits, respectively, of the 90% CI for the calculated T/R ratios. According to the guidelines, the 90% CI must fall within the acceptance range of 75–133.33% (*9*).

All statistical analyses were performed using Microsoft Excel 2021.

## RESULTS

### HPLC Method Validation

***Selectivity and Specificity***

The results showed no significant interference at the analyte's retention time in any of the blank selectivity samples, confirming that the method is specific for detecting LCZ in its cream formulation.

***Precision and Accuracy***

Method precision reflects the reproducibility of results, and accuracy indicates how close the measured values are to the true value. Precision is typically expressed as the percentage coefficient of variation (%CV), and accuracy is reported as the percentage deviation from the nominal concentration at each level. The percentage accuracies ranged from 91.00–97.01% for intra-batch and from 95.89–98.16% for inter-batch. The mean %CV for intra-batch precision ranged between 0.14–1.28%, and inter-batch precision ranged from 1.03–1.20%.

### IVRT Method Validation

***Solubility of Drug in Receptor Solution***

The receptor medium must maintain sink conditions, meaning it should be able to dissolve at least three times the amount of drug present in the dosage form. In this study, 300 µL of a formulation containing 1% w/w LCZ was applied, so the receptor medium needed to dissolve at least 450 µg/mL of LCZ. Experimental results showed that the solubility of LCZ in the chosen receptor medium was 464.398 µg/mL, confirming that sink conditions were properly maintained. Additionally, using this receptor medium produced reproducible drug release profiles and consistent $R^2$ values across all trials.

***Selection of Synthetic Membrane***

Among the membranes tested, Supor 200 and Tuffryn HT200 showed significant LCZ binding at 3.81% and 2.68%, respectively. In contrast, the Ultipor N66 membrane demonstrated minimal drug binding of 1.58%, resulting in a higher recovery rate of 98.42%. Due to its lower drug retention and cost-effectiveness, Ultipor N66 was selected as the most suitable membrane for conducting IVRT experiments.

***Sensitivity, Specificity, and Recovery***

The developed IVRT method demonstrated sensitivity by effectively distinguishing among the three concentrations, with average release rates increasing proportionally with LCZ strength: 30.3829, 63.5267, and 103.1695 µg/cm$^2$/$h^{1/2}$ for the 0.5%, 1.0%, and 1.5% formulations, respectively (Fig. 1).

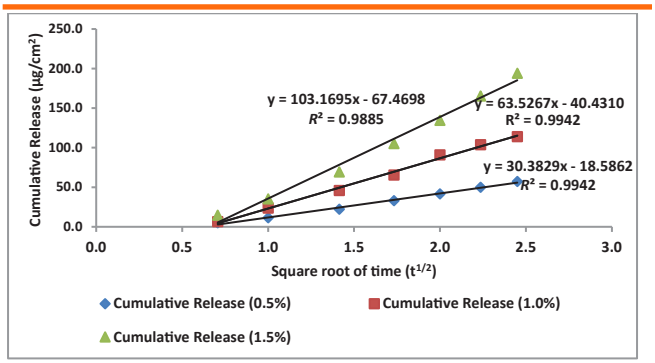



*Figure 1. Cumulative release of different strengths of luliconazole formulations (0.5%, 1.0%, and 1.5%), showing sensitivity of the method.*

Specificity was assessed through linear regression analysis, using release rate as the dependent variable and LCZ concentration as the independent variable. The analysis showed a strong linear correlation, with an $R^2$ value of 0.9918 (Fig. 2).

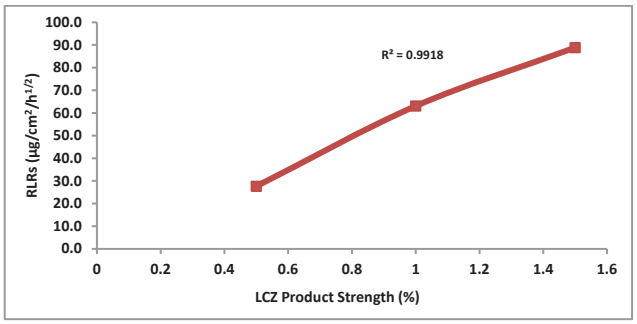



*Figure 2. $R^2$ between different strengths of luliconazole (LCZ) formulations (0.5%, 1.0%, and 1.5%), showing specificity of the method (n = 6). RLR: release rate.*

To evaluate selectivity, pairwise comparisons were conducted between the 1.0% LCZ cream and both the 0.5% and 1.5% formulations (Tables 3 and 4). The method's ability to detect performance differences fell outside the acceptance range of 75–133.33%, indicating non-equivalence between the products.

Recovery studies were performed over three separate IVRT runs, each utilizing six FDCs with the reference formulation applied. The recovery values obtained were 6.62%, 6.48%, and 6.13%, respectively. Because all recovery values remained below 30.00% and the LCZ release rates exhibited consistent linearity over time, the extent of drug depletion was considered acceptable.

**Comparison of Release Rates**

Release rates were calculated for both products; the $R^2$ exceeded 0.90, indicating consistent drug release over the 6-h period. The intra-day variation in release rate, expressed as the %CV between cells, was below 15%, demonstrating minimal variability and confirming the reproducibility of the method. Collectively, these results support that the developed IVRT method conforms to the principles of the Higuchi release model (*10*).

***Case 1: Reference Versus Test Formulation***

The 90% CI was calculated based on the release data of the reference and test formulations. As shown in Table 5, the 90% CI bounds (8$^{th}$ and 29$^{th}$ ranked values) are 123.95% and 151.45%, respectively. This indicates that the 90% CI falls outside the acceptable limits of 75–133.33%, as specified by the SUPAC-SS guidance (*9*). Therefore, the reference and test formulations are considered non-equivalent.

*Table 3. Calculated T/R Ratios for Release Rates (Slope) of Luliconazole (LCZ) 1% (Reference [R]) Versus LCZ 0.5% (Test [T]).*

| Test Release Rate, µg/cm²/h$^{1/2}$ | Reference Release Rate, µg/cm²/h$^{1/2}$ | | | | | |
|---|---|---|---|---|---|---|
| - | **63.5267** | **67.5495** | **60.8094** | **63.2525** | **62.8280** | **60.3677** |
| **30.3829** | 0.4783 | 0.4498 | 0.4996 | 0.4803 | 0.4836 | 0.5033 |
| **23.8143** | 0.3749 | 0.3525 | 0.3916 | 0.3765 | 0.3790 | 0.3945 |
| **27.8709** | 0.4387 | 0.4126 | 0.4583 | 0.4406 | 0.4436 | 0.4617 |
| **25.6603** | 0.4039 (8$^{th}$)[a] | 0.3799 | 0.4220 | 0.4057 | 0.4084 | 0.4251 |
| **29.2862** | 0.4610 | 0.4336 | 0.4816 | 0.4630 | 0.4661 | 0.4851 |
| **28.8480** | 0.4541 | 0.4271 | 0.4744 | 0.4561 | 0.4592 | 0.4779 (29$^{th}$)[a] |

*Bold values are mean release rates (slope) over time obtained from six Franz diffusion cells.*
*[a]Rank order is given in parentheses for the lower (8$^{th}$) and upper (29$^{th}$) bounds of the 90% CI.*

*Table 4. Calculated T/R Ratios for Release Rates (Slope) of Luliconazole (LCZ) 1% (Reference [R]) Versus LCZ 1.5% (Test [T]).*

| Test Release Rate, µg/cm²/h$^{1/2}$ | Reference Release Rate, µg/cm²/h$^{1/2}$ | | | | | |
|---|---|---|---|---|---|---|
| - | **63.5267** | **67.5495** | **60.8094** | **63.2525** | **62.8280** | **60.3677** |
| **97.1062** | 1.5286 | 1.4376 | 1.5969 | 1.5352 | 1.5456 | 1.6086 |
| **70.4472** | 1.1089 | 1.0429 | 1.1585 | 1.1137 | 1.1213 | 1.1670 |
| **78.9356** | 1.2426 (8$^{th}$)[a] | 1.1686 | 1.2981 | 1.2479 | 1.2564 | 1.3076 |
| **103.1695** | 1.6240 | 1.5273 | 1.6966 | 1.6311 | 1.6421 | 1.7090 |
| **86.1924** | 1.3568 | 1.2760 | 1.4174 | 1.3627 | 1.3719 | 1.4278 |
| **97.1584** | 1.5294 | 1.4383 | 1.5978 (29$^{th}$)[a] | 1.5360 | 1.5464 | 1.6094 |

*Bold values are mean release rates (slope) over time obtained from six Franz diffusion cells.*
*[a]Rank order is given in parentheses for the lower (8th) and upper (29th) bounds of the 90% CI.*

***Case 2: Reference Versus Reference Formulation***

Conversely, the 90% CI was calculated using release data from the reference formulation obtained on 2 different days. As shown in Table 6, the 90% CI bounds (8$^{th}$ and 29$^{th}$ ranked values) are 91.58% and 112.14%, respectively. This indicates that the 90% CI falls within the acceptable limits of 75–133.33%, in accordance with the SUPAC-SS guidance (*9*).

Thus, when comparing inter-day data of the reference formulation, the method is discriminatory between reference vs. test formulations, as well as consistent between reference vs. reference formulations.

## DISCUSSION

To ensure the reproducibility and reliability of an IVRT method, comprehensive validation is essential prior to its application in product evaluation. During the qualification of the IVRT apparatus, all critical parameters of the FDC system were rigorously assessed, including receptor chamber volume, cell diameter, membrane surface temperature, temperature control, stirring speed, and sampling volume. Each parameter was tested in triplicate, with all results falling within predefined acceptable limits. Laboratory qualification further confirmed system compliance, as intra-run %CV values for two IVRT runs remained below 15%, and the 90% CI for release rate comparisons across 2 days fell within the established acceptance range, confirming reproducibility of the method.

Quantification of LCZ in IVRT samples was performed using a validated HPLC method. Key validation parameters such as sensitivity, specificity, and selectivity were also evaluated, demonstrating the method's capability to effectively differentiate formulations based on drug concentration.

The IVRT method showed suitability through consistent drug release profiles throughout the study, indicated by an $R^2$ exceeding 0.99. Additionally, the coefficient of variation among diffusion cells (intra-cell variability) remained below 15%, confirming excellent reproducibility. After 6 hours, cumulative drug release from each FDC was below 30% of the applied dose, confirming maintenance of sink conditions during the experiment.

Comparison of release rates revealed a significant difference between the test and reference formulations, with the test formulation exhibiting approximately 35%

*Table 5. Calculated T/R Ratios for Release Rates (Slope) of Lulifin 1% (Reference [R]) Versus Luliconazole 1% (Test [T])*

| Test Release Rate, µg/cm²/h$^{1/2}$ | Reference Release Rate, µg/cm²/h$^{1/2}$ | | | | | |
|---|---|---|---|---|---|---|
| - | **40.3060** | **46.5885** | **41.4833** | **51.6100** | **48.7019** | **49.3251** |
| **63.5267** | 1.5761 | 1.3636 | 1.5314 | 1.2309 | 1.3044 | 1.2879 |
| **67.5495** | 1.6759 | 1.4499 | 1.6284 | 1.3088 | 1.3870 | 1.3695 |
| **60.8094** | 1.5087 | 1.3052 | 1.4659 | 1.1782 | 1.2486 | 1.2328 |
| **63.2525** | 1.5693 | 1.3577 | 1.5248 | 1.2256 | 1.2988 | 1.2824 |
| **62.8280** | 1.5588 | 1.3486 | 1.5145 (29$^{th}$)[a] | 1.2174 | 1.2901 | 1.2738 |
| **60.3677** | 1.4977 | 1.2958 | 1.4552 | 1.1697 | 1.2395 (8$^{th}$)[a] | 1.2239 |

*Bold values are mean release rates (slope) over time obtained from six Franz diffusion cells.*
*[a]Rank order for is given in parentheses lower (8th) and upper (29th) bounds of the 90% CI.*

*Table 6. Calculated T/R Ratios for Release Rates (Slope) of Lulifin 1% (Reference [R]) Versus Lulifin 1% (Test [T]) performed on 2 different days.*

| Test Release Rate, µg/cm²/h$^{1/2}$ | Reference Release Rate, µg/cm²/h$^{1/2}$ | | | | | |
|---|---|---|---|---|---|---|
| - | **40.3060** | **46.5885** | **41.4833** | **51.6100** | **48.7019** | **49.3251** |
| **42.6671** | 1.0586 | 0.9158 (8$^{th}$)[a] | 1.0285 | 0.8267 | 0.8761 | 0.8650 |
| **50.1927** | 1.2453 | 1.0774 | 1.2099 | 0.9725 | 1.0306 | 1.0176 |
| **49.1491** | 1.2194 | 1.0550 | 1.1848 | 0.9523 | 1.0092 | 0.9964 |
| **46.5193** | 1.1542 | 0.9985 | 1.1214 (29$^{th}$)[a] | 0.9014 | 0.9552 | 0.9431 |
| **51.5718** | 1.2795 | 1.1070 | 1.2432 | 0.9993 | 1.0589 | 1.0455 |
| **43.2849** | 1.0739 | 0.9291 | 1.0434 | 0.8387 | 0.8888 | 0.8775 |

*Bold values are mean release rates (slope) over time obtained from six different Franz diffusion cells.*
*[a]Rank order is given in parentheses for the lower (8th) and upper (29th) bounds of the 90% CI.*

higher release. Conversely, comparison of release data from the reference formulation collected on 2 separate days indicated equivalence, thereby confirming the method's ability to demonstrate the correct release profile, which is influenced by formulation excipients. Collectively, these findings support that the validated IVRT method is robust and appropriate for routine quality control testing.

## CONCLUSION

The primary objective of this study was to develop a sensitive, specific, and reproducible IVRT method for quantifying the release of LCZ from topical cream formulations. Statistical comparison of release rates between test and reference products, using the T/R ratio approach, showed that the results fell outside the 90% CI, indicating nonequivalence. However, release data for the reference formulation obtained on different days demonstrated equivalence within the 90% CI limit. The validated IVRT and HPLC methods developed in this study are suitable for routine release testing of LCZ cream formulations and can be extended to evaluate release profiles of other LCZ-based topical products.

## DISCLOSURES

The authors received no financial support for this work and have no conflicting interests

## REFERENCES

1. Drug Index: Luliconazole. Pediatric On Call Child Health Care website.www.pediatriconcall.com/drugs/luliconazole/175 (accessed Jan 28, 2024).
2. Prescribing information for LUZU™ (luliconazole) Cream, 1% for topical use. U.S. Food and Drug Administration. www.accessdata.fda.gov/drugsatfda_docs/label/2018/204153s004s005lbl.pdf (accessed Jan 28, 2024).
3. Draft Guidance on Luliconazole. U.S. Food and Drug Administration, October 2022. www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_204153.pdf (accessed Jan 28, 2024).
4. Upadhyay, Y.; Singh, A. K.; Mishra, S.; Gurule, S. J.; Khuroo, A. H.; Verma, S.; Tiwari, N.; Bedi, S. Comparison of release rates derived from cutaneous versus film-forming solution containing terbinafine: approach towards qualification and validation of in vitro parameters. *Dissolut. Technol*. **2022**, *29* (1), 28–35. DOI: 10.14227/DT290122P28.
5. Cetin, D.; Turker, T. G.; Yilmaz, N.; Karakoy, B. A. Comparative in vitro release test using Franz diffusion cell for luliconazole 1% cream with reference drug product. *International Labmate*. Sept 10, 2021. www.labmate-online.com/article/chromatography/1/bilim-pharmaceuticals/comparative-in-vitro-release-test-using-franz-diffusion-cell-for-luliconazole-1-cream-with-reference-drug-product/3019 (accessed Oct 15, 2025).
6. Maanvizhi, S.; Iyyappan, V.; Bhavishi, P. G. Evaluation of an antifungal luliconazole gel formulation using semiautomatic diffusion cell apparatus and application of mathematical models in drug release kinetics. *Eur. J. Mol. Clin. Med*. **2021**, *8* (4), 231–240.
7. Indira, S.; Devi, K.; Kalvimoorthi, V. Method development and validation of luliconazole bulk drug using reverse phase-HPLC technique. *Indian J. Sci. Technol*. **2024**, *40* (39), 4094–4100. DOI: 10.17485/IJST/v17i39.2787.
8. In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs; Draft Guidance for Industry. U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER), October 2022. www.fda.gov/media/162476/download (accessed Jan 28, 2024).
9. Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 1997.
10. Higuchi, T. Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci*. **1961**, *50* (10), 874–875. DOI: 10.1002/jps.2600501018.
11. Doshi, A.; Prabhakar, B.; Wairkar, S. Prolonged retention of luliconazole nanofibers for topical mycotic condition: development, in vitro characterization and antifungal activity against *Candida albicans*. *J. Mater. Sci. Mater. Med*. **2024**, *35* (1), 46. DOI: 10.1007/s10856-024-06815-w.
12. Kanfer, I.; Rath, S.; Purazi, P.; Mudyahoto, N. A. In Vitro Release Testing of Semi-Solid Dosage Forms. *Dissolut. Technol*. **2017**, *24* (3), 52–60. DOI: 10.14227/DT240317P52.
13. Shah, V. P.; Konecny, J. J.; Everett, R. L.; McCullough, B.; Noorizadeh, A. C.; Skelly, J. P. In vitro dissolution profile of water-insoluble drug dosage forms in the presence of surfactants. *Pharm. Res*. **1989**, *6* (7), 612–618. DOI: 10.1023/A:1015909716312.
14. Klein, R. R.; Heckart, J. L.; Thakker, K. D. In Vitro Release Testing Methodology and Variability with the Vertical Diffusion Cell (VDC). *Dissolut. Technol*. **2018**, *25* (3), 52–61. DOI: 10.14227/DT250318P52.

dx.doi.org/10.14227/DT320425P192

# Book Review: *The Handbook of Dissolution Testing*, 4th Edition

**Gregory P. Martin**
*Complectors Consulting, LLC, Pottstown, PA, USA.*

*e-mail: greg.martin@complectors.com*

The 4th edition of *The Handbook of Dissolution Testing*, revised and expanded by Bryan Crist, Vivian Gray, and Royal Hanson (ISBN: 979-8-89412-327-1), presents a comprehensive and well-structured overview of the dissolution testing process, offering critical insights for both novice and experienced analysts (*1*). Covering topics from theoretical underpinnings to routine implementation and troubleshooting, the *Handbook* serves as a valuable reference for pharmaceutical laboratories and regulatory professionals involved in oral dosage form testing.

Chapter 2 establishes a theoretical foundation that informs subsequent sections on compendial methodologies. The text effectively transitions into detailed discussions of standard practices, regulatory expectations, and special dosage forms—often a source of complexity for analysts who are unfamiliar with modified or nontraditional delivery systems.

Chapter 5 is especially useful, compiling relevant compendial and regulatory documentation references, including United States Pharmacopeia (USP) and International Council for Harmonization (ICH) guidelines. This serves as a convenient reference point for those who are engaged in compliance and method alignment activities.

The authors provide practical guidance in Chapter 6 on apparatus variability, an often-overlooked source of error in dissolution testing. Chapter 7 offers a step-by-step checklist for apparatus qualification, which is particularly beneficial for ensuring operational consistency in quality control settings.

Chapter 8 introduces dissolution method development, emphasizing the importance of defining the Analytical Target Profile and assessing the method's discriminatory power—an essential but sometimes underappreciated element of robust method design.

The section on method validation addresses the unique challenges of dissolution testing, particularly its dynamic, time-dependent nature and the mechanical complexity of test apparatus. The discussion on automation acknowledges both the potential benefits and the additional complexity it introduces, making it a relevant resource for laboratories integrating new technologies.

The final Chapter 11 focuses on the investigation of test failures and high result variability. Given the multifactorial nature of dissolution testing, this discussion is timely and well-developed, covering common root causes and offering structured approaches to root cause analysis.

In sum, *The Handbook of Dissolution Testing, 4th Edition* is a thorough, technically sound resource that balances theoretical context with practical application. It is suitable for training purposes, method development, regulatory reference, and quality troubleshooting. Its structured approach and inclusion of regulatory context make it a significant contribution to the available literature on pharmaceutical testing practices.

The 4th Edition of the *Handbook* can be purchased on the Dissolution Technologies website at dissolutiontech.com/ordering.php.

## REFERENCE

1. Crist, B.; Gray, V.; Hanson, R. *The Handbook of Dissolution Testing*, 4th ed.; Dissolution Technologies, Inc., 2024. DOI: 10.14277/DT2024DisHDBK.

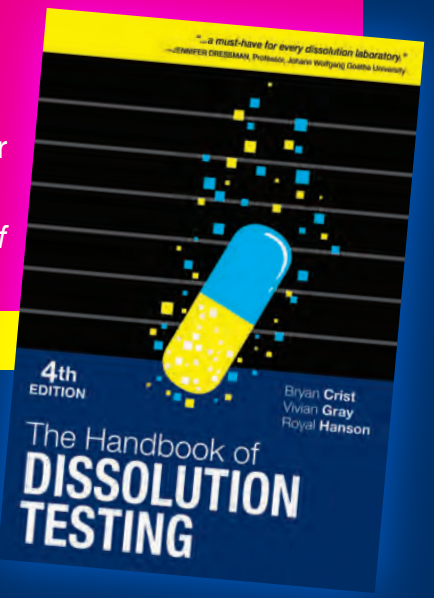
# The Handbook of DISSOLUTION TESTING

Industry experts Bryan Crist, Vivian Gray and Royal Hanson have completely updated the *Handbook of Dissolution Testing* for today's pharmaceutical executive, laboratory manager, and bench chemist.

The 4th edition builds on the teachings of the first three editions (1982, 1991, and 2004), with everything you need to know about modern dissolution testing, including:

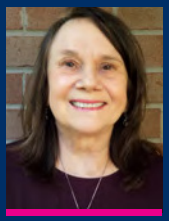
- Updates on USP, FDA, and international compendial requirements; method development and challenges; testing of special dosage forms; controlling variables and apparatus qualification; automation; treatment of aberrant data; sources of errors and failures, and more!
- Three new chapters on compendial and regulatory guidances, method validation, and Good Manufacturing Practices in the dissolution laboratory.
- Extensive reference notes on hundreds of topics for further insight.
- Handy comprehensive appendix of dissolution resources and websites.
- Foreword by Jennifer B. Dressman, PhD, preeminent researcher and teacher in the field of pharmaceutics and dissolution.
- The go-to reference for the working practitioner, the 4th edition *Handbook of Dissolution Testing* is a must-have for every dissolution lab worldwide!

**Order online at www.dissolutiontech.com**




4th EDITION

Bryan **Crist**
President of DissoAssist Consulting based in Wilmington, NC



Vivian **Gray**
President of V.A. Gray Consulting based in Hockessin, DE

Royal **Hanson**
Former Chairman, President, and CEO of Hanson Research Corp.

Dissolution Technologies, Incorporated
9 Yorkridge Trail • Hockessin, DE 19707 USA

TELEDYNE | LABS

# ARE YOU PREPARED FOR THE NEW EMA GUIDELINE ON TOPICAL PRODUCTS?

The EMA's new **Guideline on Quality and Equivalence of Locally Applied, Locally Acting Cutaneous Products** is now in force (effective April 2, 2025). This impacts nearly all topical medicine authorization requests.

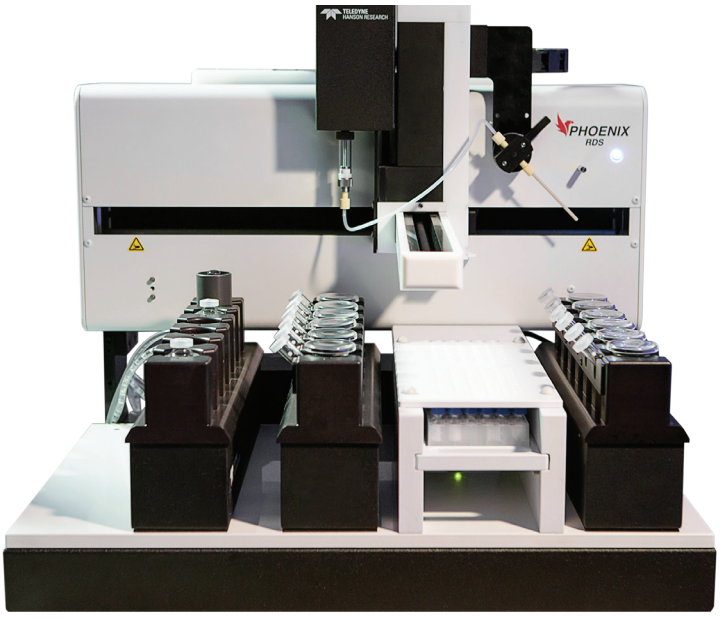
To comply, you must now demonstrate a science-based design and comprehensive product characterization—and the most effective way to do that is with **Franz Diffusion Cell testing.**

Teledyne LABS is here to help you stay compliant and ahead of the curve.

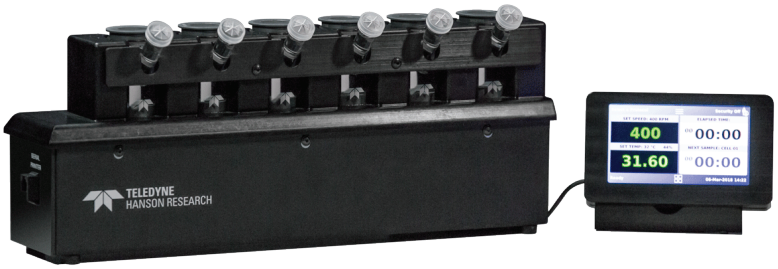
Our team is ready to support you every step of the way.

Our industry-leading **Phoenix Dry-Heat Diffusion System** was designed to:

- Make diffusion-cell testing faster, easier, and more economical
- Be compliant with Regulatory bodies
- Enhance security and compliance with 21 CFR Part 11
- Produce more accurate data and reduced variability
- Offer unattended operation during long tests
- Offer versatility – the receptor volumes, dosage volumes, and orifice diameters of the Phoenix cells are adjustable using precision modular components

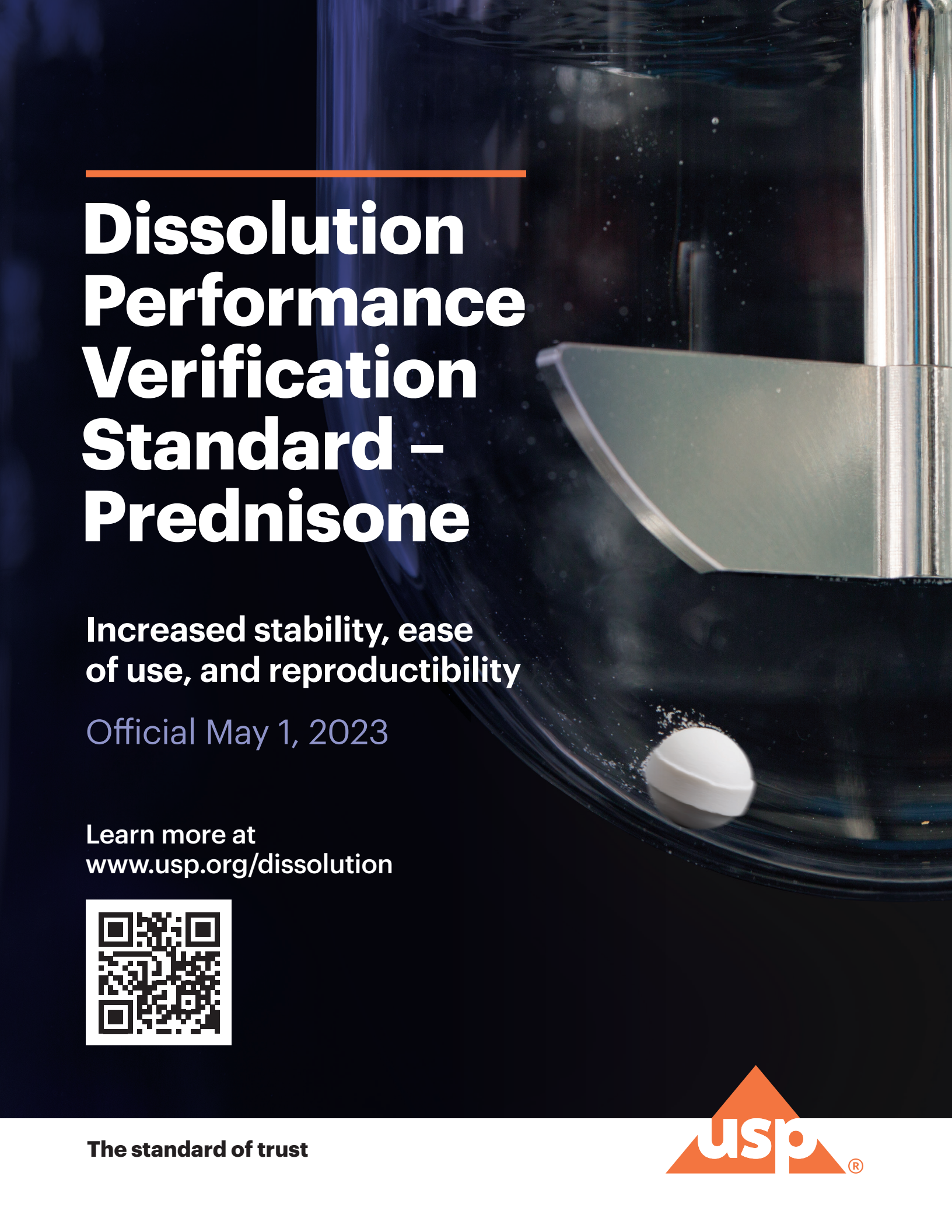



**Phoenix RDS:** Automated system for up to 24 cells




**Phoenix DB-6:** Compact, manual 6-cell system

**For more information, or to get a quote contact us today.**



# Dissolution Performance Verification Standard – Prednisone

## Increased stability, ease of use, and reproductibility

Official May 1, 2023

Learn more at
www.usp.org/dissolution

The standard of trust

usp®

dx.doi.org/10.14227/DT320425P196

# Q+A Question & Answer Section

*The following questions have been submitted by readers of Dissolution Technologies. Margareth R. Marques, Ph.D. and Mark Liddell, Ph.D., United States Pharmacopeia (USP), authored responses to each of the questions. *Note: These are opinions and interpretations of the authors and are not necessarily the official viewpoints of the USP. E-mail for correspondence: mrm@usp.org.*

**Q If the dissolution medium is water, which theoretically has a pH of 7 but can range between pH 5-8, should we use the theoretical pH of 7 and use pancreatin for dissolution using water as the medium or should we measure the pH for each dissolution and adjust the enzyme accordingly?**

**A** Yes, you should confirm the actual pH of the water used as the dissolution medium, as it may change during storage. Then use the appropriate enzyme for the measured pH.

**Q Is it mandatory to withdraw samples from dissolution vessels while the paddles are rotating, or is this considered just good practice, knowing that we only have one sampling timepoint?**

**A** The text from <711> Dissolution, under Apparatus 1 and Apparatus 2, Immediate-Release Dosage Forms states: "Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the dissolution medium and the top of the rotating basket or blade, not less than 1 cm from the vessel wall." Notice, the chapter specifies "rotating" basket or blade; meaning that the basket or paddle is in motion. It is also important to note that when sampling a suspension, the medium needs to be as homogeneous as possible.

**Q If the dissolution apparatus we are using is designed to stop by default (with no paddles rotating) when withdrawing samples, would this have any impact on the dissolution test results?**

**A** Yes. It is likely to increase the variability of the results. According to the instructions given in <711> (see previous question), the agitation should not be stopped during the sampling because you are essentially withdrawing a sample from a suspension of both dissolved and undissolved drug. The dissolution sample solution should be well-mixed. Without the mixing that results from rotation of the stirring element, the sample solution may not represent the contents of the entire vessel. We recommend that you discuss this issue with the vendor/manufacturer of the equipment.

**Q In USP general chapter <1092> The Dissolution Procedure: Development and Validation, under 5.1 Specificity/Placebo Interference, what is the composition of placebo solution? One sentence says all components except the drug substance, but the following sentence specifies that the placebo is spiked with a known amount of the drug. Furthermore, the concentration of the drug used to spike the placebo is not given in the formula. Considering a spike at 100% with drug that has the same absorbance as the standard, the result will be 100%. This is in contrast with the acceptance criteria, which states: "The interference should not exceed 2%." Can you explain the procedure for evaluation of specificity using a placebo?**

**A** The placebo solution should contain all components present in the formulation in the same proportion as in the final product, except for the drug substance. By spiking the placebo solution with a known amount of drug substance (100% of the label claim) and comparing the ratio of the spiked placebo solution absorbance/response to that of the standard solution containing the same concentration of drug substance, one can determine the degree of interference from the components in the placebo solution. Because the placebo solution does not contain any drug substance, you are correct that under ideal circumstances the ratio of the two absorbance/response values will be equal to 1, giving a result of 100% based on the formula provided. In circumstances where the placebo solution interferes with detection of the drug substance (in an additive or subtractive manner),

the deviation from 100% should be less than 2% (i.e., 98–102%). Using this method accounts for both the interference and specificity of the analytical method.

**Q Does the sampling time requirement of ± 2% include filtration as well as withdrawing the dissolution sample?**

**A** The requirement of sampling within ± 2% of the time is to start the sampling procedure. It is not the duration of the sampling; however, it is important to separate the sample solution from dissolving particles as soon as possible to stop the dissolution process. Generally, the best practice is to filter the solution immediately after withdrawing the dissolution sample. Inconsistent filtering techniques and timing can lead to inconsistent dissolution results.

**Q When sampling cannulas are introduced at the start of the dissolution test, does this have potential to impact hydrodynamics of the vessel and hence the dissolution results?**

**A** Yes, the presence of any probe in the vessel during the dissolution test could have an impact on the hydrodynamics depending on the size and shape of the sampling probe. Changes in the hydrodynamics inside the dissolution vessel may or may not have an impact on the dissolution profile depending on the release mechanism of the dosage form in question. This impact needs to be evaluated during method development. For additional information and references, see Gao Z, Smith A. The effect of sampling cannula on in vitro dissolution testing with USP paddle method. AAPS J. 2023, 25:46. https://doi.org/10.1208/s12248-023-00813-6.

**Q What is the upper and lower range of the accuracy parameter for dissolution of an extended-release tablet?**

**A** The validation of any dissolution test method and the associated analytical procedure is done considering the entire dissolution profile and not the acceptance criteria or classification of the dosage form type. You do not need to know the acceptance criteria to validate any dissolution method. For any type of finished dosage form, the accuracy should be validated at each of the expected concentration levels. Based on the validation of the method linearity, select at least three concentrations to validate accuracy. The key parameter used to determine accuracy is percentage of recovery. The placebo solution should be spiked with standard solution at a minimum of three different concentrations. For an extended-release product, it may be necessary to determine the accuracy at additional solution concentrations. Keep in mind that it is important to include the upper limit of uniformity for the product in the linearity range.

**Q If we do not use USP apparatus 1, can we skip testing of apparatus 1 during the PVT procedure for qualification of the dissolution equipment?**

**A** Yes. If a particular dissolution test assembly is dedicated for either apparatus 1 or apparatus 2 testing, the instrument qualification need only be performed for the specific apparatus in question. Keep in mind that for dissolution assemblies that can be configured for both apparatus 1 and 2, the instrument should be labelled to indicate that the instrument is qualified for "Apparatus 1 Testing Only" or "Apparatus 2 Testing Only."


Every issue of *Dissolution Technologies* features a Question and Answer section. This section is designed to address general dissolution questions submitted by our readers.

**Please send your questions to:**
**Attn: Q&A**
9 Yorkridge Trail, Hockessin, DE 19707
Email: vagray@rcn.com
Submit via our website:
www.dissolutiontech.com

# Calendar of Events

## November 4, 2025
***GastroPlus® X.2: The Deep Dive Webinar Series – Introducing Orchestrator, Automation for Complex PBPK/PBBM Modeling in GPX.2***
Location: Online
Time: 11 AM EST
Registration: https://www.simulations-plus.com/events/gastroplus-x-2-the-deep-dive-webinar-series-introducing-orchestrator/

## November 9, 2025
***The GastroPlus® 10.2 (GPX.2™) Immersive Experience at AAPS***
Location: Henry B. Gonzalez Convention Center, Rm 303AB, San Antonio, TX
Time: Noon to 4 PM CST
Registration: https://simulations-plus.learnupon.com/store/4680960-gpx107ip-the-gastroplus-10-2-gpx-2-immersive-experience-at-aaps-in-person

## November 9–12, 2025
***PharmSci 360 AAPS Meeting***
Location: Henry B. Gonzalez Convention Center, San Antonio, TX, USA
For information, visit https://www.aaps.org/pharmsci/annual-meeting

## November 11, 2025
***GastroPlus® X.2: The Deep Dive Webinar Series – How New AI-Powered Tools Can Support Your PBPK Modeling***
Location: Online
Time: 11 AM EST
Registration: https://www.simulations-plus.com/events/gastroplus-x-2-the-deep-dive-webinar-series-ai-powered-tools-for-pbpk-modeling/

## November 16–18, 2025
***Eastern Analytical Symposium and Exhibition***
Location: Crowne Plaza Princeton-Conference Center, Plainsboro, NJ, USA
For information, visit eas.org

## December 4, 2025
***GastroPlus® X.2: The Deep Dive Webinar Series – How P-PSD™ Can Be Used to Fit a Product Particle Size to Enable in vivo Dissolution Prediction for a Drug Product***
Location: Online
Time: 11 AM EST
Registration: https://www.simulations-plus.com/events/gastroplus-x-2-the-deep-dive-webinar-series-p-psd/

## May 12–13, 2026
***M-CERSI workshop "Role of In Vitro Dissolution Studies for Predictive Insight into In Vivo Performance and Biopharmaceutics Risk Mitigation"***
Location: Universities at Shady Grove (USG; Rockville, MD), Building II
Registration: www.pharmacy.umaryland.edu/centers/cersievents/2025dissolution

## On Demand Events

- ***Powder Flow Testing***
  https://www.copleyscientific.com/events/webinar-foundations-of-powder-flow-testing/
- ***dissoLab Software: Predictive Dissolution Simulated from Microscopic Images***
  https://vimeo.com/1054617734?share=copy
- ***Fiber Optic UV: Better Dissolution Testing On Demand***
  https://www.distekinc.com/watch/fiber-optic-uv-better-dissolution-testing/
- ***Advances in In Vitro Bioequivalence Assessment for Topical Products Part 2***
  https://youtu.be/iqphypToHZ0?si=mn9FJLDhm-VBoWMm
- ***Ocular Administration (OCAT™) in GastroPlus® On Demand***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-ocular-administration-ocat-virtual/

- ***Oral Cavity Administration (OCCAT™) in GastroPlus® On Demand***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-oral-cavity-administration-occat-virtual/
- ***Pulmonary Administration (PCAT™) in GastroPlus® On Demand***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-pulmonary-administration-pcat-virtual/
- ***GastroPlus® ADR – 4 Course Bundle (TCAT™ / OCAT™ / OCCAT™ / PCAT™)***
  https://www.simulations-plus.com/events/gastroplus-adr-4-course-bundle-tcat-ocat-occat-pcat/
- ***GastroPlus® ADR – 5 Course Bundle (TCAT™ / OCAT™ / OCCAT™ / PCAT™ / Injectables)***
  https://www.simulations-plus.com/events/gastroplus-adr-5-course-bundle-tcat-ocat-occat-pcat-injectables/
- ***Transdermal Administration (TCAT™) in GastroPlus®***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-transdermal-administration-tcat-virtual/
- ***Injectables (IM, SQ, IA) in GastroPlus® Including Biologics and LAIs***
  https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-injectables-incl-lai-biologics-virtual/
- ***GastroPlus® X Tutorial Series***
  https://www.simulations-plus.com/events/gastroplus-x-tutorial-series/
- ***Complimentary Introduction to GastroPlus® for up to v.9.9***
  https://www.simulations-plus.com/events/complimentary-introduction-to-gastroplus-v-9-9/
- ***Complimentary Introduction to GPX™***
  https://www.simulations-plus.com/events/complimentary-introduction-to-gpx/

# Industry News

## Pharma Test Introduces Next-Generation Tablet Dissolution Testing Instruments

*Hainburg, Germany* – Pharma Test is pleased to announce the upcoming launch of its next-generation tablet dissolution testing instruments, scheduled for release in the fourth quarter of 2025. The latest series features an enhanced user interface and a refined mechanical design.

With a modern graphical user interface, advanced user management features, and a fully integrated 21 CFR Part 11 compliant audit trail, the new systems set a new benchmark in usability and compliance. Building on decades of expertise and valuable customer feedback, Pharma Test has also introduced significant mechanical enhancements to ensure greater ease of use, improved reliability, and simplified maintenance, meeting the ever-growing needs of its customers. Made in Germany - all instruments are developed, designed, and manufactured in Germany.

"The introduction of our next-generation tablet dissolution tester marks an important milestone. Developed with user requirements in mind, these systems reflect our commitment to delivering user-oriented, robust, and sustainable solutions with long-term value for our customers," declares Pharma Test CEO Björn Fähler on the upcoming launch.

The new models scheduled to launch in Q4/2025 are PTWS 830 with 8 stations, PTWS 1230 with 12 stations, and PTWS D630 with "Dual Drive" 6 + 6 stations.

**About Pharma Test**

Since 1979 Pharma Test has been a worldwide household name for the development and production of high-value test devices and systems for the quality control in the pharmaceutical, food and cosmetics industry as well as for universities and public authorities. We offer a complete product range from manual instruments for physical testing to fully automated online dissolution testing systems to analyze the active chemical composition of a dosage form as well as its release rate. Providing well thought-out, long-lasting, user-oriented products and solutions is our driving force. Made in Germany.

# ERWEKA Launches New TBH II Tablet Hardness Tester and 21 CFR Part 11 Compliant Software for DT 950 Dissolution Series

*Langen, Germany* - ERWEKA GmbH, a global leader in high-quality test equipment for the pharmaceutical and life science industries, has introduced two major product innovations: the **TBH II manual tablet hardness tester and a new software release for the DT 950 series dissolution tester platform**, now including a 21 CFR Part 11-compliant audit trail.

"*With the TBH II, we deliver a modern, highly efficient manual hardness tester, while our DT 950 software upgrade strengthens compliance for dissolution testing," said Martin Kühn, Managing Director at ERWEKA GmbH. "Both launches underline our focus on innovation, usability, and regulatory security – giving our customers exactly what they need in today's pharmaceutical environment.*"

### TBH II: Next Generation of Manual Tablet Hardness Testing

The new TBH II offers precise measurement of five physical tablet parameters – hardness, diameter/length, thickness, width, and weight (with external balance) – in a compact, user-friendly design.


- Small footprint and compact design with modern 7" touchscreen interface for intuitive operation and fast navigation.
- **TestAssist** for testing of predefined methods to ensure reliable results.
- **Comprehensive reporting** with data export to USB, network, or LIMS integration (using ERWEKA Export Manager).
- Built to meet current pharmacopeia requirements (**USP/EP/JP**).

The TBH II provides laboratories with reliable manual testing functionality, flexible configuration, and full compliance – making it a cost-effective solution for both R&D and QC environments.

### DT 950/9510 Software v. 3.0: Full Data Integrity with 21 CFR Part 11 Compliance

The latest software release for ERWEKA's DT 950/9510 dissolution tester platform introduces a validated, 21 CFR Part 11 conform audit trail. Every action is now logged securely and tamper-proof, enabling GMP laboratories to meet the highest regulatory standards on device, without external software.

- **Audit trail** logging who, what, where, when, and why of changes.
- **User and role** management for controlled access.
- **Method management** for fast and easy testing of repeating methods.
- **Advanced filtering** for easy regulatory inspections.

This release ensures that DT 950/9510 customers can operate with complete confidence in data integrity and compliance while maintaining the platform's established precision, ease-of-use and flexibility.

The DT 950/9510 software release with audit trail functionality is available for free as an upgrade for existing DT 950/9510 customers and comes standard with all new units.

For more details, visit www.erweka.com

ERWEKA
www.erweka.com

# Simulations Plus and the Institute of Medical Biology of the Polish Academy of Sciences Announces Publication of Validation Results for ADMET Predictor® Models with Enhanced AI-Driven Drug Design

***Researchers found 70% of compounds designed in ADMET Predictor demonstrated significant activity during in vitro testing***

Simulations Plus, Inc., a leading provider of cheminformatics, biosimulation, simulation-enabled performance and intelligence solutions, and medical communications to the biopharma industry, announced that experimental results of its artificial intelligence (AI)-driven drug design (AIDD) collaboration with the Institute of Medical Biology of the Polish Academy of Sciences (IMB PAS) have been published in the American Chemical Society's *ACS Medicinal Chemistry Letters* (Bachorz, et al., 2025; DOI: 10.1021/acsmedchemlett.4c00595).

Simulations Plus and IMB PAS launched their collaboration in 2023 to use the AIDD module with ADMET Predictor® to design novel RORγ/RORγT ligands – molecules that impact gene expression related to inflammation and immune responses. Within three months, the two teams had developed models to predict RORγ/RORγT ligand potency; designed potential ligands simultaneously optimized for potency, in vivo absorption, synthesizability, and ADMET risk; synthesized compounds; and completed initial in vitro potency and toxicity testing. The recently published results show that the vast majority of compounds tested had strong potency for the target that was close to or better than the values predicted by ADMET Predictor.

"Among the 27 compounds we tested, an impressive 70% demonstrated significant inhibition of RORγT activity, with our lead compound exhibiting potent inverse agonist activity and a novel indolizine scaffold not previously reported for this target," said Rafal A. Bachorz, Senior Principal Applied Scientist at Simulations Plus and lead author of the publication. "Importantly, this compound displayed strong efficacy in cellular assays, no significant cytotoxicity, and effectively suppressed the expression of proinflammatory Th17 cytokines in human T cells. In vitro ADMET profiling of our most potent compound showed that this molecule possesses favorable drug-like properties, as predicted by ADMET Predictor, supporting its potential as a promising lead for further optimization. These findings highlight the power of AI-driven, multiparameter optimization in accelerating drug discovery and underscore the potential of our approach to deliver innovative therapies for patients across the globe."

"We are delighted to see the validation of our models and the ADMET Predictor platform," said Viera Lukacova, Chief Scientific Officer at Simulations Plus. "ADMET Predictor and the AIDD module provide our clients with a first-to-invent advantage by harnessing AI and machine learning to design and optimize compounds for specific targets. We are particularly pleased to collaborate with the scientists at IMB PAS to advance their research on RORγ/RORγT receptors and their potential role in cancer progression. We look forward to extending this partnership through further rounds of scaffold optimization based on the promising results achieved to date."

Learn more about ADMET Predictor and the AIDD module online at simulations-plus.com/software/admetpredictor/.

# ezfill+

## Dissolution Media Heating, Degassing and Dispensing SOLVED!

- Rapid, efficient media heating, vacuum deaeration, and precise dispensing
- Error-proof media dispensing with stored methods for precise control
- User-friendly touchscreen allows for users, logins, methods, and report viewing & printing
- Track media parameters and maintain data integrity with stored reports


Add **Data Integrity Compliance** to media preparation!

DISSOLUTION

FIBER OPTIC

MEDIA PREP

AUTOSAMPLER

Scan the QR Code to view the ezfill+ Product Video.

*"I highly recommend the ezfill+ to any associate involved in dissolution testing. It is a wonderful, cost and time savings device and takes up very little space."*
*- Jennifer, Sr. Scientist*

DISTEK

distekinc.com • info@distekinc.com

Agilent OpenLab

# Unlock the Future of Laboratory Compliance

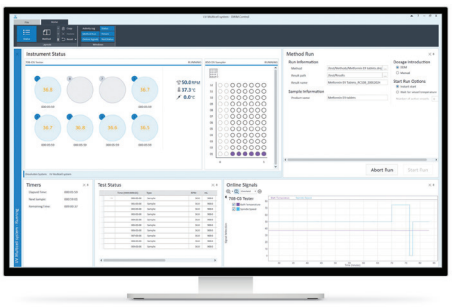
## Dissolution is now on OpenLab

Introducing the Agilent Dissolution Workflow Manager for OpenLab CDS. Whether you're using Agilent OpenLab CDS, another dissolution software, or managing testing manually, Agilent has a solution for you. This software add-on for OpenLab CDS ensures superior data integrity and consolidates all your test results in one place.

Benefits at a glance:

- Secure data storage
- Enhanced compliance
- Improved user-friendly interface
- Minimized validation effort

Learn more at: www.agilent.com/dissolution/workflow-manager



Agilent
Trusted Answers

DE-008230