ARDENA

Application Note

Mechanochemistry-Enabled Solid-State Stress Testing

A Rapid, Resource-Efficient Approach for Forced Degradation in Drug Development

INTRODUCTION

As regulatory agencies demand ever more robust stability data, drug developers face mounting pressure to generate degradation profiles earlier in development, using less material and in shorter timeframes. Traditional stress testing—rooted in solution-phase approaches—can be both time-consuming and poorly predictive of real-world solid-state degradation, particularly for formulated drug products.

At Ardena, we have evaluated the Solford solid-state degradation technology developed and patented by RD&C, which has been validated in several use cases with drug substances and drug products. This approach is based on mechanochemistry, offering a powerful and efficient alternative for stress testing. This technique enables stress simulation in the solid phase, providing rapid insight into degradation pathways under realistic conditions without solvents.

THE REGULATORY CONTEXT

Stability testing is a cornerstone of regulatory submissions, used to establish shelf-life, packaging strategy, and formulation robustness. As outlined in ICH Q1A(R2), both drug substances (DS) and drug products (DP) must be subjected to environmental stress conditions—temperature, humidity, and light exposure—to determine degradation behavior.

Accelerated conditions (e.g., 40 °C/75% RH for six months) are standard in development. While these long-term studies are necessary, they require significant time and resources. Stress testing offers a faster route to identifying degradation products and validating analytical methods. However, traditional stress testing often involves solution-based conditions, which can generate degradation pathways that do not reflect solid-state product behavior.

LIMITATIONS OF CONVENTIONAL STRESS TESTING

In standard forced degradation studies, APIs and DPs are typically exposed to:

- Thermal stress (e.g., 40–70 °C)
- Humidity (e.g., 40 °C/75% RH)
- Acidic and basic hydrolysis
- Oxidative conditions (e.g., 3–6% H_2O_2)
- Photolysis

Testing durations commonly exceed 14 days. In the case of ibuprofen, these conventional methods produced minimal degradation (<5%), limiting their value for impurity profiling and stability prediction.

A SOLID-STATE APPROACH TO DEGRADATION TESTING

To address these limitations, Ardena assessed a solid-state degradation platform driven by mechanochemistry. This technology simulates stress environments (acidic, basic, oxidative, neutral) by ball milling drug substances or formulations with dry-phase catalysts—without solvents. Key features include:

- Rapid degradation within 30–120 minutes
- Low material requirements
- Applicability across APIs, excipient mixtures, and finished dosage forms
- Simulation of real-world solid-state degradation
- Compatibility with QbD and DoE strategies

This approach not only accelerates stress testing timelines but also yields more representative impurity profiles, supporting earlier formulation decisions.

APPLICATION AREAS

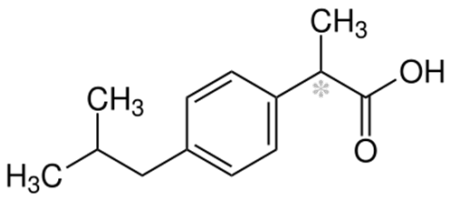
This solid-state platform offers versatile utility across various pharmaceutical development needs, including drug–excipient compatibility screening, support for formulation design within Quality by Design (QbD) frameworks, identification of degradation-prone combinations, assessment of packaging and storage conditions, and evaluation of polymorphic transformations. Additionally, it enables the creation of a degradation knowledge base to support early-stage formulation strategy.

Case Study: Ibuprofen

INTRODUCTION

To evaluate the performance of the solid-state degradation platform, Ardena conducted a comparative study using ibuprofen as a model compound. Ibuprofen is a widely used non-steroidal anti-inflammatory drug (NSAID) with a well-characterized structure and high chemical stability. Its consistent and predictable behavior under stress makes it a suitable reference for benchmarking novel degradation approaches.

Figure 1: Ibuprofen molecular structure



The study focused on comparing conventional ICH-recommended stress testing with mechanochemistry-enabled solid-state degradation, applied to both the active pharmaceutical ingredient (API) and the drug product (DP) formulation.

TRADITIONAL STRESS TESTING APPROACH

In the conventional setup, ibuprofen samples (API and DP) were subjected to a range of stress conditions as outlined in ICH Q1A(R2):

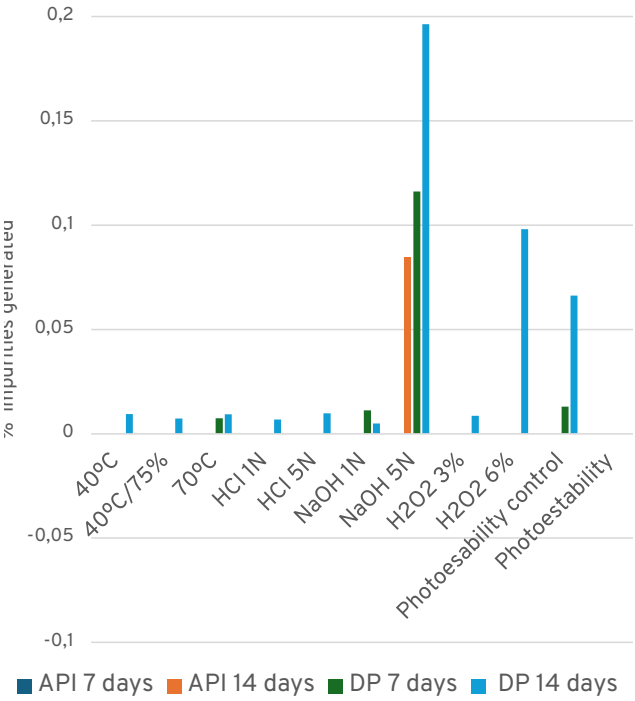
- Thermal stress at 40 °C and 70 °C
- Humidity stress at 40 °C/75% RH–Acid and base hydrolysis using HCl and NaOH at 1N and 5N concentrations
- Oxidative stress with 3% and 6% hydrogen peroxide
- Photolytic stress via light exposure

Each condition was maintained for 14 days, with intermediate sampling performed on day 7. Samples were analyzed by high-performance liquid chromatography (HPLC) to quantify degradation levels and identify impurity profiles.

However, despite the prolonged exposure, degradation levels across all tested conditions remained below the required 5–20% range—a threshold typically necessary to assess impurity formation and degradation pathways meaningfully.

Figure 2: Total impurities after traditional stress testing. Low degradation levels were observed, limiting the ability to identify relevant impurities.

Increased impurities versus control:



MECHANOCHEMICAL SOLID-STATE STRESS TESTING PROTOCOL

Based on previous screening data indicating that ibuprofen is prone to oxidative degradation in the solid state, among other factors, Ardena designed a focused Design of Experiments (DoE) to assess oxidative stress conditions using the solid-state platform. The experimental matrix included the following variables:

- Catalysts: Oxone® and potassium permanganate
- Milling times: 10 and 30 minutes
- Sample types: API and DP
- Central point settings: 20-minute milling with a 50:50 mixture of both catalysts

Ball milling was performed under solvent-free conditions, simulating oxidative stress within a solid-state environment. Following treatment, all samples were subjected to HPLC analysis.

Figure 3: Compendial oxidative impurities (J, E, and total) using mechanochemical stress fell within the desired 5-15% range.

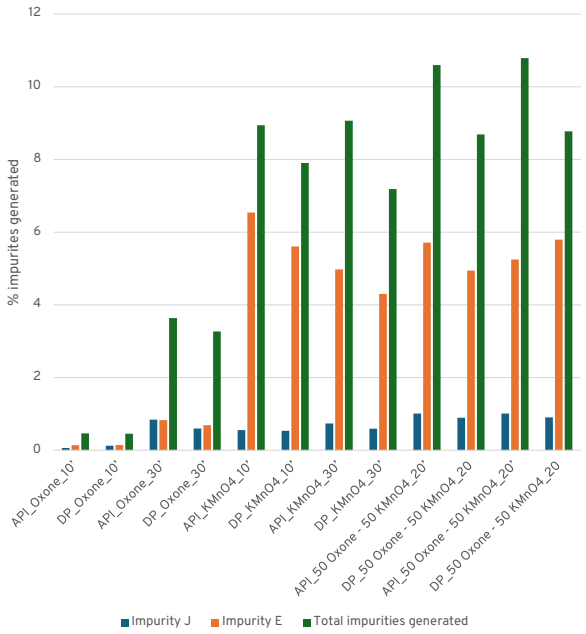
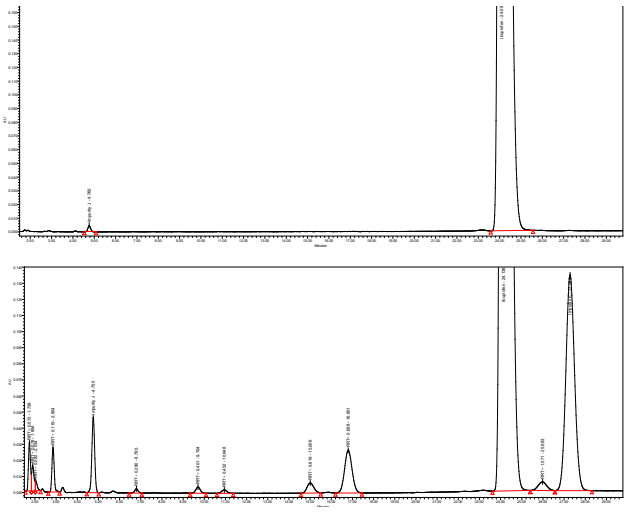


Figure 4: HPLC comparison between traditional oxidative environment (top) vs. 50:50 mixture mechanochemical solid-state testing (bottom) in drug product revealed additional impurity peaks, highlighting degradation pathways not observed with conventional methods.



COMPARATIVE RESULTS

Literature shows that ibuprofen requires harsh conditions or long reaction times to achieve relevant degradation. The Solford approach avoids this, as it uses solid-state mechanochemical stress without aqueous stressors, eliminating solubility issues and preventing solvent-driven reactions from altering the degradation profile. The Ardena study confirmed RD&C's results for ibuprofen, consistent with literature data for both drug substance and drug product, providing comprehensive insights and revealing relevant additional impurity peaks not seen with conventional testing.

	TRADITIONAL STRESS TESTING	MECHANOCHEMICAL SOLID-STATE TESTING
TIME TO RESULTS	~14 days	30–120 minutes
MATERIAL NEEDED	High	Low
STRESS ENVIRONMENT	Solution-based	Solid-state
RELEVANCE TO DP	Limited	High
SCALABILITY FOR DOE	Low	High
QBD COMPATIBILITY	Partial	Strong alignment

CONCLUSIONS

The mechanochemistry-based solid-state stress testing platform developed by RD&C represents a major advancement in degradation testing. It enables fast, solvent-free, and highly relevant conditions, giving developers deeper insights into drug stability. Its flexible setup allows processing a wide range of drug substances and products for various applications.

The ibuprofen study showed that this approach achieves ICH-recommended degradation in minutes and reveals impurity pathways not seen with conventional testing. Ardena continues to integrate such innovative tools to enhance agility and informed decision-making across drug development.