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SOLFORD COMPATIBILY STUDIES

SOLFORD is a mechanochemistry based technology mainly used for degradation studies, it offers a powerful and efficient alternative for stress testing, but this is not the only use for this technology. The application of this technology includes 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.

For any new drug, the development of stability indicating methods is imperative for being able to detect any degradation that may develop during the manufacturing process or during its shelf life. One of the parameters that are needed for a stability indicating method is mass balance, in this case meaning that every product present in the sample is reflected in the chromatogram (API + degradation products) we quantify mass balance by subtracting the sum of impurities to the API

During formulation development, a significant decrease in API content was observed under accelerated stability conditions, which was not fully explained by the increase in known degradation products. In addition, it was necessary to rapidly assess whether the impurity method was stability-indicating and to better understand the contribution of formulation components to product degradation. Therefore, a mechanochemical stress study and an excipient compatibility study were performed using SOLFORD technology as a rapid alternative to conventional forced degradation studies. This approach enabled accelerated generation of degradation products, supporting the investigation of degradation pathways, the identification of potential drug–excipient interactions, and the evaluation of the suitability of the analytical method for monitoring stability-related changes.

The forced degradation using SOLFORD technology study was done to API (active pharmaceutical ingredient), DP (drug product) and placebo in 3 conditions: acidic (H_2SO_4), alkaline (KOH) and oxidative ($KMnO_4$) and were degraded using a ball mill (Restch MM301) for 10 minutes at 20 Hz. Samples were analyzed by high-performance liquid chromatography (HPLC) to quantify degradation levels and identify impurity profiles.

For the excipient compatibility study, a modified SOLFORD approach was employed. Considering that the manufacturing process includes a wet granulation step, the API was incorporated in solution form to better mimic manufacturing conditions and evaluate their potential impact on degradation pathways and product stability.

To obtain a comprehensive understanding of formulation-related degradation, two complementary experimental designs were implemented. Binary API:excipient mixtures were prepared by combining the API individually with each excipient (Table 1) to assess direct drug-excipient interactions. In parallel, a component omission approach was applied, whereby formulations containing all excipients except one were prepared (Table 2), allowing the contribution of each component to the overall degradation profile to be evaluated.

Table 1: Binary mixture

Ingredients	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
API	X	X	X	X	X
Mannitol	X	-	-	-	-
Crospovidone	-	X	-	-	-
Povidone	-	-	X	-	-
Magnessium stearate	-	-	-	X	-
Capsule	-	-	-	-	X

Table 2: Eliminating one component at a time

Ingredients	Sample 6	Sample 7	Sample 8	Sample 9	Sample 10	Sample 11
API	-	X	X	X	X	X
Mannitol	X	-	X	X	X	X
Crospovidone	X	X	-	X	X	X
Povidone	X	X	X	-	X	X
Magnessium stearate	X	X	X	X	-	X
Capsule	X	X	X	X	X	-

Once the samples were prepared, they were mill using a ball mil for 10 minutes at 20Hz, then were prepared and analyzed by the impurity HPLC method.

Results:

After completion of the forced degradation and drug–excipient compatibility studies, the results demonstrated satisfactory mass balance, confirming the suitability of the analytical method as stability-indicating. Oxidation was identified as the main degradation pathway of the API, while acidic and alkaline conditions showed limited impact. The studies also enabled the identification of the major degradation products and the differentiation between API-related and excipient-related peaks, providing a better understanding of the origin of the degradation products observed during stability studies. In addition, the compatibility assessment helped to identify formulation components potentially contributing to product instability.

Table 3: forced degradation using SOLFORD

Sample	API (%)	Main degradation products (%)	Mass balance (%)
API Control	95.5	No significant degradation	-
API KOH	90.8	No significant degradation	6.44
API $KMnO_4$	52.2	Impurity 1 (30.67), impurity 5(10.55), impurity 6(1.41)	0.90
API H_2SO_4	92.5	No significant degradation	4.63
DP KOH	97.2	Impurity 1 (0.30), impurity 2 (0.26), known impurity A (0.02),	2.97
DP $KMnO_4$	89.1	Impurity 1 (0.25), impurity 2 (0.32), known impurity A (0.25), impurity 3 (0.851), impurity 4 (0.7)	3.97
DP H_2SO_4	98.7	Impurity 1 (0.30), impurity 2 (0.26), a known impurity A (0.02), impurity 3 (0.687)	4.48
PCB KOH	–	Placebo Peak 1, Placebo Peak 2, Placebo Peak 3	–
PCB $KMnO_4$	–	Placebo Peak 1, Placebo Peak 2, Placebo Peak 3	–
PCB H_2SO_4	–	Placebo Peak 1, Placebo Peak 2, Placebo Peak 3	–

Mass balance being defined by the API assay degradation minus the sum of the impurities. To achieve mass balance this number must be below 10%

Table 4: compatibility study: binary mixtures

Sample	Total impurities (%)	Main degradation products (%)
API + Mannitol	1.25	Impurity 2 (1.25)
API + Crospovidone	0.00	Povidone/crospovidone peak.
API + Povidone	0.00	Povidone/crospovidone peak.
API + Mg Stearate	0.00	No significant degradation
API + Capsule	2.89	Capsule peak, impurity 1 (2.61), impurity 7 (0.28)

Table 5: compatibility study: component omission

Sample	Total impurities (%)	Main degradation products (%)
All components – API	○ 0.00	Povidone/crospovidone peak, Capsule peak
All components – Mannitol	○ 0.00	Povidone/crospovidone peak (2.02), Capsule peak, Placebo Peak
All components – Crospovidone	● 0.34	Capsule peak, IMPURITY 2 (0,34)
All components – Povidone	● 0.47	Capsule peak; IMPURITY 2 (0,47)
All components – Mg Stearate	● 0,66	Povidone/crospovidone peak, Capsule peak, impurity 2 (0,66)
All components – Capsule	● 0,92	Povidone/crospovidone peak, impurity 2 (0,92)

The results from both the binary mixtures and the formulation-minus-one-component studies suggest that impurity formation is primarily associated with the presence of mannitol. In the binary compatibility study, the highest impurity levels were observed for the **AP:Mannitol** and **API:Capsule** mixtures, indicating that these components have the greatest impact on the stability of the API. This observation is further supported by the formulation studies, where no impurities were detected when mannitol was excluded from the formulation, while impurities were present in all mixtures containing mannitol. Overall, the data indicates that mannitol is likely a key contributor to impurity formation, with the capsule material also showing a significant influence on API stability.

SOLFORD-enabled forced degradation and compatibility studies rapidly identified oxidation as the main degradation pathway, characterized the major degradation products, and provided insight into the impact of formulation components on product stability. The satisfactory mass balance obtained confirmed the analytical method as stability-indicating, while the compatibility assessment supported formulation development by identifying excipients and interactions potentially involved in the observed degradation profile.

Compared with conventional approaches, the mechanochemical ball-milling technology significantly reduced study timelines and experimental effort, enabling the generation of relevant stability data within days rather than weeks. This accelerated understanding of degradation pathways and formulation risks supports faster development of robust analytical methods and optimized formulations, ultimately streamlining pharmaceutical development.