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Improving Safety and Reliability of Corticosteroid Production Processes

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Corticosteroid synthesis involves multiple highly exothermic reaction steps and the handling of sensitive intermediates, which pose significant process safety and operational risks. This work presents an extensive calorimetric and explosibility study of a three-step corticosteroid synthesis, aiming to optimize process safety while maintaining product quality. Differential Scanning Calorimetry (DSC), Adiabatic Calorimetry (ARC), and reaction calorimetry (RC1) were used to quantify thermal stability, reaction enthalpies, and maximum temperature of the synthesis reaction (MTSR) for each step. In parallel, dust explosibility properties of isolated intermediates were evaluated, including Minimum Ignition Energy (MIE) and K_{st} values. The study identified the first synthesis step as particularly critical due to its high exothermicity and the hazardous properties of the intermediate product when dried. A process redesign was proposed, eliminating the drying and isolation of the intermediate, resulting in improved safety, sustainability, and reduced operational costs. This comprehensive hazard evaluation demonstrates the importance of integrating calorimetric tools and dust explosion testing to systematically identify hazards, refine operating parameters, and design inherently safer corticosteroid production processes.

1. Introduction

Corticosteroids are widely used pharmaceutical compounds with potent anti-inflammatory and immunosuppressive properties. Industrial synthesis typically relies on complex multistep processes involving steroidal precursors, derived either from plant-based raw materials or microbial fermentation (Gupta and Saxena, 2020).

The synthesis of corticosteroids presents substantial safety challenges due to the combination of highly exothermic reactions (Stoessel, 2020), hazardous solvents, and the complexity of multi-step synthetic routes, which often require cryogenic temperatures and precise thermal control to avoid runaway reactions (Copelli et al., 2016). Even minor deviations, such as inadequate mixing, incorrect reagent dosing, or cooling failures, can trigger rapid, uncontrolled temperature increases, leading to decomposition reactions and the release of hazardous gases, which may form flammable or explosive atmospheres within reactors (Jensen Hughes, 2023). In addition, many corticosteroid intermediates are handled in dry, powdered form, posing a risk of combustible dust explosions (Vignesh et al., 2025), as these powders frequently exhibit low Minimum Ignition Energies (MIE) (Eckhoff, 2016) and high explosion severity indices (K_{st}) (Scotton et al., 2020). Ignition sources may include electrostatic discharge, mechanical friction, or hot surfaces during transfer, drying and packaging. Catastrophic pharmaceutical industry incidents, such as the West Pharmaceutical Services explosion, illustrate how dust accumulation and inadequate hazard communication can lead to devastating losses (CSB, 2003). Beyond physical hazards, corticosteroids pose toxicological risks; even low-dose exposure can lead to systemic effects such as immunosuppression or endocrine disruption, while chronic inhalation of fine powders increases occupational health risks (PMC, 2024). Regulatory frameworks such as NFPA 652 for combustible dust, NFPA 30 for flammable liquids, and OSHA's Process Safety Management emphasize the need for systematic hazard identification, process hazard analysis, and engineered safety solutions, including explosion-proof equipment,

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interlocked alarms, dust collection systems, and rigorous Standard Operating Procedures (SOPs) (Jensen Hughes, 2023).
In this context, corticosteroid process development must prioritize “safety by design” (Wen et al., 2025), reducing opportunities for powder handling, optimizing reaction steps (Copelli et al., 2017), and leveraging calorimetric analysis to quantify exothermicity, decomposition behaviour, and ignition risks.
This study addresses these challenges through a full calorimetric and explosibility characterization of a corticosteroid synthesis route, focusing on identifying hazards and proposing safer, more sustainable manufacturing practices.

2. Materials and Methods

2.1 Chemicals and Process Overview

The corticosteroid synthesis under investigation consisted of three main steps, each performed in a single batch reactor. Step 1 involved the reaction of a steroidal precursor, called Axplora 1, in a solvent mixture of tetrahydrofuran (THF), acetone, and water to obtain a product called Axplora 2. The reaction was carried out at -3 °C under stirring and Axplora 2 product, in the original process, was separated and dried for further processing. Step 2 included a base-catalyzed transformation using aqueous sodium hydroxide; particularly, product called Axplora 3 was salified to produce Axplora 4 intermediate starting from 45 °C (to 100 °C).
Finally, Step 3 finalized the corticosteroid structure by reacting Axplora 2 (previously purified and dried) and Axplora 4 intermediates (not isolated during Step 2), using N,N-dimethylformamide (DMF) and demi water, at 100 °C.
All the previously described steps are reported in Figure 1.

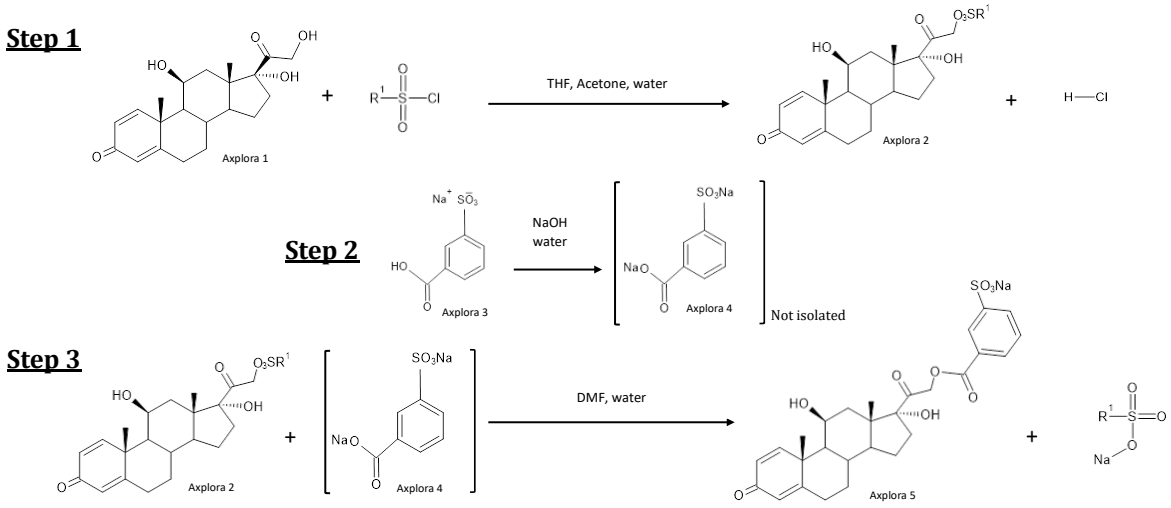

Figure 1: Steps for the synthesis of Axplora 5 final product.

The most critical expected step is Step 1 because of: 1) the addition of the sulfonyl (chloride) group (which is expected to be exothermic) and, 2) the drying process of Axplora 2 intermediate (which can imply dust explosion risk during either handling and the successive storing phase before carrying out Step 2 synthesis).

2.2 Thermal Stability Testing

Differential Scanning Calorimetry (DSC) was employed to determine both the onset temperature of an eventual decomposition of the dried powders and the enthalpy of reaction for all key intermediates. Experiments were carried out under both air and nitrogen atmospheres (closed crucible), at heating rates of 5 °C/min, in a temperature range of 30 – 280 °C, using stainless steel, medium pressure crucibles.
Moreover, an Accelerating Rate Calorimetry (ARC) test was conducted to assess adiabatic self-heating rates, Time to Maximum Rate (TMR), and pressure build-up during the different expected decomposition events of the final reacting mixtures (all steps).
Several intermediates (labeled Axplora 1 to Axplora 5) were tested both as wet and dry solids; in this work only the most conservative (from the safety point of view) results are reported.

2.3 Reaction Calorimetry

Reaction calorimetry (RC1) experiments quantified the heat release rate, reaction enthalpy, and maximum temperature of the synthesis reaction (MTSR) for each step. These data were used to calculate process safety parameters, including thermal accumulation potential.

2.4 Dust Explosion Testing

The explosibility of dried intermediates was studied using a 20-L sphere apparatus, measuring maximum explosion pressure (P_{max}), maximum rate of pressure rise $(dP/dt)_{max}$, and calculating the explosion (or deflagration) index (K_{st}). Minimum Ignition Energy (MIE) was also determined using inductance-modulated spark discharge testing in a MIKE 3 apparatus.

3. Results and Discussion

3.1 Thermal Stability of Intermediates

The results of the most relevant DSC tests carried out, under both nitrogen and air atmosphere, were reported in Figure 2.

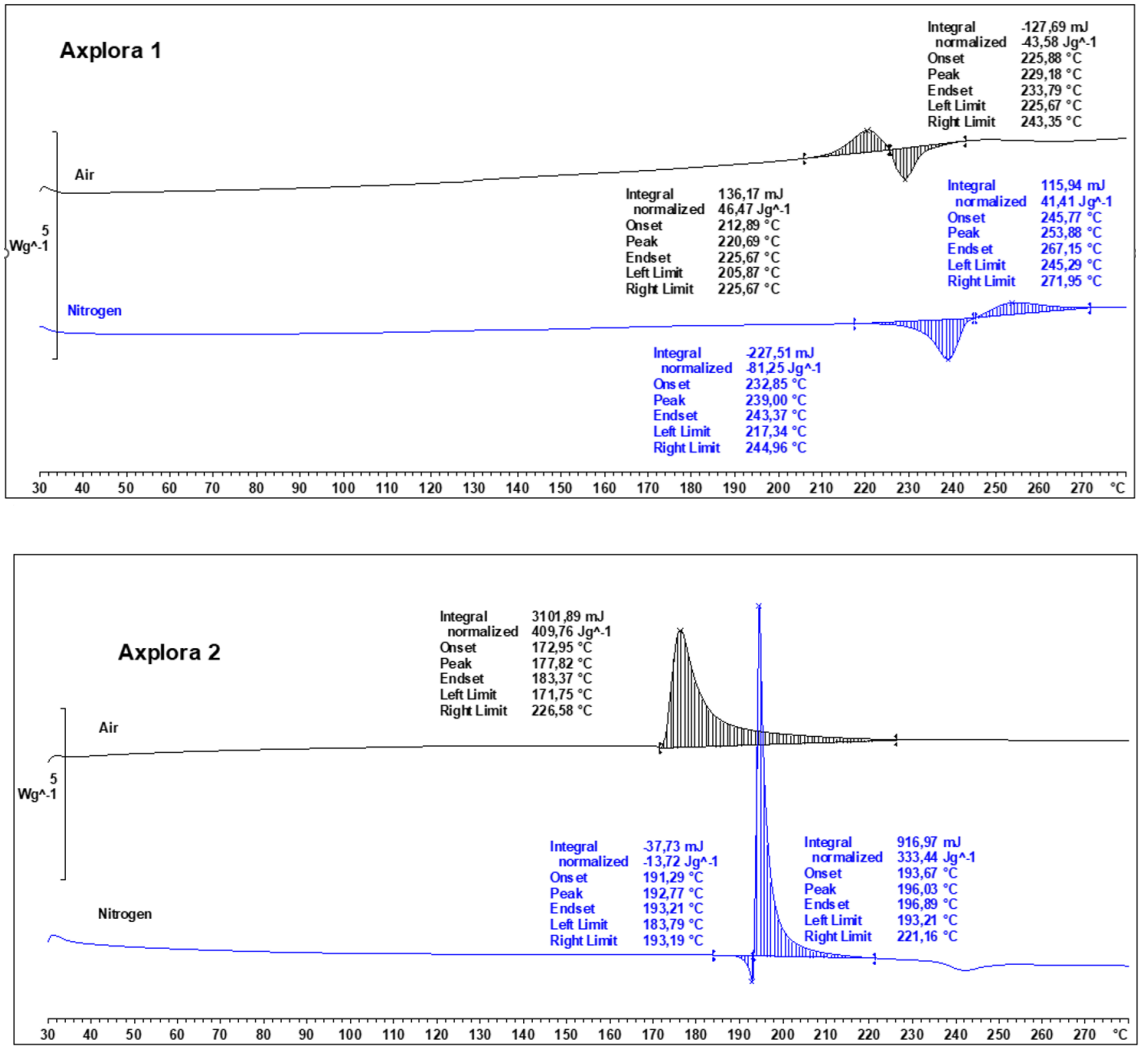

Figure 2: DSC tests traces (both nitrogen and air) for a) Axplora 1, b) Axplora 2 and c) Axplora 5 (crude) products.

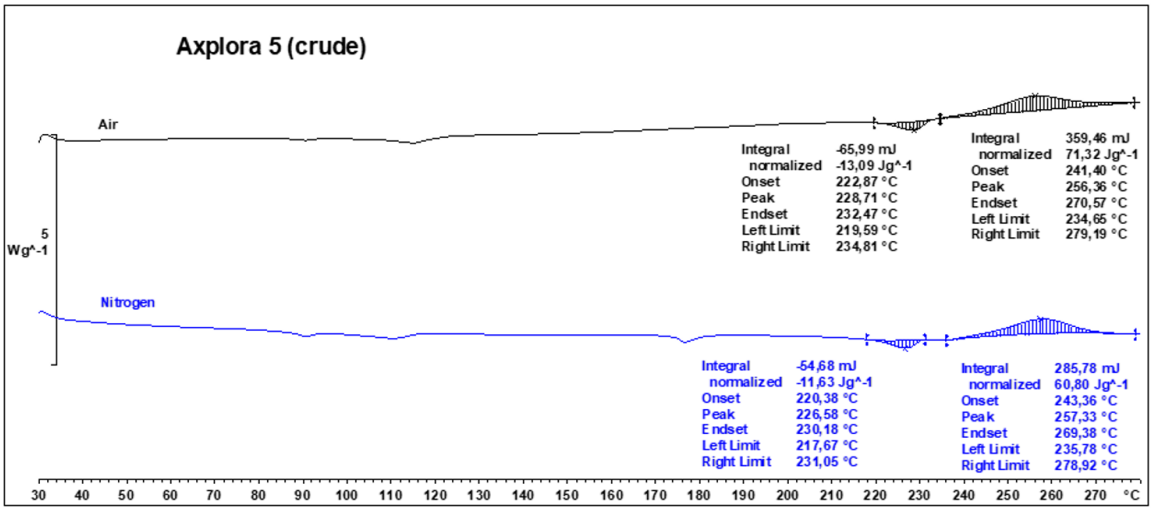

Figure 2: DSC tests traces (both nitrogen and air) for a) Axplora 1, b) Axplora 2 and c) Axplora 5 (crude) products.

DSC testing revealed significant differences in the stability of the different intermediates. Particularly, Axplora 1 exhibited a different behaviour depending on the atmosphere of the closed crucible. In air it was possible to observe a first oxidation reaction immediately followed by a melting of the product. On the contrary, in nitrogen, the first effect detected was a melting, followed by a weak product decomposition. Anyway, the onset temperature at which such phenomena started to be detectable were quite high (more than 200 °C), therefore Axplora 1 can be considered a quite safe product to be handled (at least in the first screening process).
The compound labelled Axplora 2 demonstrated a notably low onset of decomposition at 173 °C with an enthalpy of −410 J/g (in air) and -333 J/g (in nitrogen); this means that such a product can be considered as critical for safety viewpoint. Axplora 3 and Axplora 4 intermediates did not show any exothermic relevant effects (both in air and nitrogen atmosphere) in the investigated temperature range (which was always between 30 and 280 °C). Axplora 5 product was tested as either crude or pure compound, showing minor differences in the thermal behaviour; particularly, crude product exhibited a melting phenomenon just before an exothermic decomposition occurring at 241 °C (both nitrogen and air with negligible differences).
Finally, the final reacting mixtures coming from all the previously described steps syntheses were tested in an ARC apparatus. Results, for Step 1 final reacting mixture, are summarized in Figure 3.

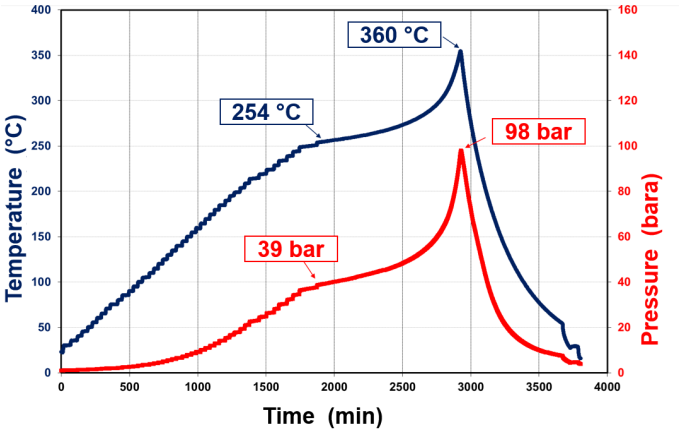

Figure 3: ARC test on the final reacting mixture coming from Step 1 synthesis.

ARC test revealed a strong thermal decomposition of the reacting mixture occurring after 254 °C, even if the final pressure after cooling was not so high to evidence huge amounts of permanent gases evolved during the unwanted event (see Figure 3). All the parameters both measured and calculated from the ARC test are reported in Table 1.

Table 1: ARC test parameters

Parameter	Value	Unit	Parameter	Value	Unit
Exothermic Onset Temperature	254	°C	Final Pressure at maximum temperature	98	bara
Final Temperature	355	°C	Residual Pressure	7	bara
Initial Pressure at onset	39	bara	TMR24	227	°C

Anyway, the high thermal sensitivity of Step 1 was confirmed, showing a corrected adiabatic temperature rise of 280 °C and a TMR of 24 hours at 227 °C.

3.2 Reaction Calorimetry and Process Chemical Safety Assessment

Reaction calorimetry measurements for Step 1 confirmed a total reaction enthalpy of −52.5 kJ/kg and an MTSR of 28 °C above the process temperature (which was -3 °C). This indicates good safety margins for synthesis temperature control. Moreover, as no decomposition phenomenon seems to occur before 254 °C (see the results of the ARC test), the process, basing on a risk matrix integrating decomposition temperatures, boiling points, and MTSR, can be classified as of Stoessel Class I. Step 2 is a little bit critical because it exhibited a higher reaction enthalpy (-67.5 kJ/kg), even if the criticality class remains I. Finally, Step 3 (whose temperature and heat fluxes profiles are not reported) exhibited an intermediate reaction enthalpy (−24.6 kJ/kg) and a Class I.

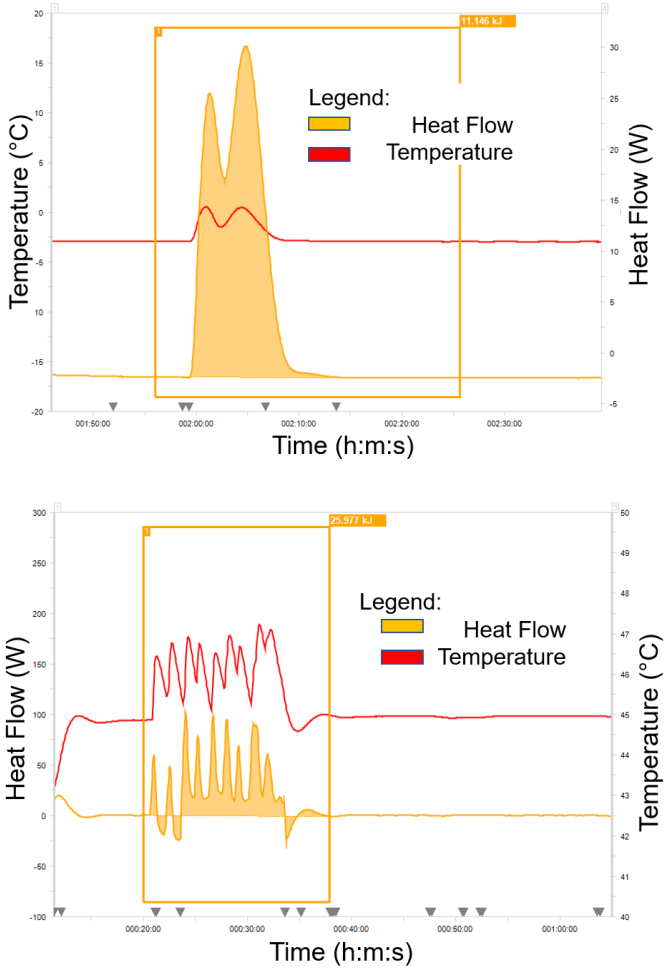

Figure 4: RC1 registered temperature and heat flux during: a) Step 1 and, b) Step 2 (global heat released is also highlighted).

3.3 Dust Explosion and MIE Characterization

Dust explosion testing demonstrated the severe explosibility of dried Axplora 2, with a maximum explosion pressure of 7.4 bar, a $(dP/dt)_{max}$ of 405 bar/s, and a K_{st} of 110 m·bar/s. Each test was carried according to the reference technical standard: EN ISO/IEC 80079-20-2 for MIE, EN 14034-1,2:2004 for the explosion severity.
MIE measurements showed ignition at energies below 30 mJ, indicating susceptibility to electrostatic ignition. Comparison with ARC data confirmed that drying this intermediate significantly increases process risk. Axplora 5 and other downstream intermediates did not exhibit such sensitivity. Particularly, Axplora 3 and Axplora 4 were not explosible because salts.

3.4 Process Optimization and Risk Reduction

Based on all these findings, which evidenced that the most critical synthesis step was Step 1 (because it provided a slurry mixture that must be purified and dried to obtain the pure intermediate Axplora 2, which was explosive and easily flammable), a modified synthesis approach was proposed: eliminating the isolation and drying of Axplora 2, instead using it as a wet slurry in subsequent steps. This modification drastically reduces dust handling risks, minimizes energy consumption by removing a drying step, and streamlines production.
A new synthesis of Step 3 in an RC1 equipment was carried out using directly the crude mixture coming from Step 1, instead of Axplora 2 product, showing a good conversion to Axplora 5. Purification operations after Axplora 5 were not affected by the excess of other solvents within the mixture to be treated, demonstrating the feasibility of such a modification for the complete reaction sequence.
Additionally, solvent use and reactor cooling requirements were reassessed, demonstrating potential energy and cost savings.

4. Conclusions

This study demonstrates the importance of integrating calorimetric methods and dust explosion testing in pharmaceutical process development. The corticosteroid synthesis examined here features a highly hazardous first step, where both reaction exothermicity and powder explosibility of the isolated intermediate pose significant risks. By eliminating the drying step and optimizing process parameters, a safer, more sustainable synthesis route was developed. These findings emphasize the need for early hazard identification and holistic process safety evaluations in the pharmaceutical industry.

Acknowledgments

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