RESEARCH PAPER

Comparative Evaluation of Hydrophobic Matrix Incorporation and Polymeric Film Coating for Stabilization of Potassium Clavulanate Under Open Exposure Conditions

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Received: 25th May, 2026; **Revised:** 6th June, 2026; **Accepted:** 8th June, 2026; **Available Online:** 09th June, 2026

ABSTRACT

Potassium clavulanate is a moisture- and temperature-sensitive β-lactamase inhibitor prone to hydrolytic degradation, discoloration, and packaging instability under humid and thermal conditions. The present study comparatively evaluated two stabilization strategies—hydrophobic matrix incorporation using stearic acid and polymeric film coating using HPMC–ethylcellulose applied to potassium clavulanate diluted with Sylloid (1:1). Stearic acid was incorporated at 10% and 20% w/w levels via physical blending, while film coating was applied to achieve 5% weight gain using a top-spray fluidized bed system. Samples were assessed under open exposure at 25°C/60% RH and under refrigerated conditions (2–8°C). Additional evaluation included solution stability of 1% (w/v) aqueous preparations and thermal stress testing (80°C, 1 h) in Alu–Alu blisters. Stearic acid incorporation delayed initial discoloration but did not fully prevent degradation under prolonged humidity exposure. Film coating provided improved resistance to moisture ingress and reduced blister bulging under thermal stress, although strict temperature control during processing was essential. The findings support a diffusion-controlled degradation mechanism and highlight the relative advantages of internal hydrophobic modification and external barrier coating strategies for stabilizing moisture-sensitive clavulanate systems.

Keywords: Potassium clavulanate; Moisture-induced degradation; Stearic acid; Film coating; Hydrophobic matrix; Blister bulging; Stability study; Thermal stress; β-lactam degradation; Solid-state stability.

How to cite this article: MahePatil, Veena Khandade, MahviKhan, Suankit Harane, Milind Umekar, Vinita Kale. Comparative Evaluation of Hydrophobic Matrix Incorporation and Polymeric Film Coating for Stabilization of Potassium Clavulanate Under Open Exposure Conditions. Int J Drug Deliv Technol. 2026;16(79s):638-648. DOI: 10.25258/ijddt.16.79s.119.

Source of support: Nil.

Conflict of interest: Nil.

INTRODUCTION

Amoxicillin–potassium clavulanate remains one of the most widely prescribed antibacterial combinations due to clavulanic acid's irreversible inhibition of β-lactamase enzymes, thereby restoring amoxicillin activity against resistant organisms [1]. Pharmacokinetic compatibility between the two agents enables effective clinical use in respiratory, urinary, and paediatric infections[2]. Despite its therapeutic importance, potassium clavulanate is chemically labile and represents the primary stability-limiting component in the combination[3].

The instability of clavulanic acid has been extensively characterized in aqueous systems. Early kinetic investigations demonstrated pseudo first-order degradation behavior across a broad pH range, with maximal stability near neutral pH and accelerated decomposition under acidic and alkaline conditions[4,5]. Mechanistic studies confirmed hydroxide-ion catalyzed β-lactam ring opening as a dominant degradation pathway [6]. Arrhenius modeling further established the strong temperature dependence of degradation kinetics [7].

Importantly, clavulanate degradation exhibits autocatalytic characteristics, wherein degradation products further accelerate decomposition once initiated[8]. This self-propagating behavior becomes particularly critical in partially hydrated solid systems, where localized moisture ingress may initiate and amplify degradation within the matrix.

Recent stability investigations continue to confirm the vulnerability of clavulanate under elevated temperature conditions [9]demonstrated rapid potency decline of amoxicillin–clavulanate in aqueous systems under stress temperatures, reinforcing earlier kinetic findings. Studies evaluating refrigerated and room-temperature storage consistently report faster degradation of clavulanate relative to amoxicillin[10]. Clinical observations in hot climates further highlight the impact of improper

storage on therapeutic effectiveness [11].

Market surveillance and tropical storage evaluations indicate high variability and frequent substandard clavulanate content under high humidity and heat conditions[12]. Real-world warehouse monitoring data further demonstrate the influence of seasonal temperature and humidity variations on pharmaceutical stability [13].Collectively, these findings underscore the moisture sensitivity of clavulanate under practical storage conditions.

Beyond aqueous systems, solid-state instability has also been reported[14] demonstrated potential moisture-mediated interactions between amoxicillin trihydrate and potassium clavulanate. Film-coating strategies have been explored to mitigate humidity effects [15], and recent formulation optimization studies continue to investigate polymer selection for moisture-sensitive drug stabilization [16].

Despite extensive understanding of aqueous degradation kinetics, comparatively limited literature addresses short-term solid-state stabilization strategies focused on controlling moisture diffusion under open exposure conditions[17].Given the moisture-driven and autocatalytic nature of clavulanate degradation, restricting water ingress into the solid matrix represents a rational and mechanistically justified stabilization approach[18].

Hydrophobic excipients such as stearic acid have been employed to modify moisture interaction and reduce water accessibility within solid systems [19]. In parallel, polymer coating technologies, particularly hydroxypropyl methylcellulose (HPMC) and ethylcellulose, provide external diffusion barriers capable of limiting water vapor transmission and enhancing the stability of moisture-sensitive drugs[15,20].

However, a direct comparative evaluation of stearic acid blending as a hydrophobic stabilization approach versus external polymeric film coating under controlled humidity exposure remains insufficiently explored.

Therefore, the present study aims to:

- Evaluate stearic acid incorporation as a hydrophobic matrix modifier.
- Assess HPMC and ethylcellulose coating as external moisture diffusion barriers.
- Compare physical appearance and stability behavior under controlled humidity and thermal stress.
- Interpret degradation behavior in relation to established kinetic and mechanistic literature.

1. MATERIALS

Potassium clavulanate (diluted with Sylloid®, 1:1) was obtained from Fermic, s.a. de c.v, Mexico. Stearic acid (BP grade) was supplied by Signet India. Hydroxypropyl methylcellulose (HPMC E15), Triacetin and Ethylcellulose N10 were gifted by colorcon India. Isopropyl alcohol (IPA) and methylene dichloride (MDC) used for coating were of pharmaceutical grade and procured from Avantor India.

2. METHODS

2.1 Preparation of Stearic Acid–Based Stabilized Blends (Physical Blending Approach)

To evaluate the influence of hydrophobic matrix incorporation on the stability of potassium clavulanate diluted with Sylloid (1:1), stearic acid was incorporated at different concentrations using a physical blending approach. Blends were prepared under controlled environmental conditions to minimize premature moisture-induced degradation.

Three experimental blends were prepared as described below:

Blend	Composition
Blend 1	Potassium clavulanate diluted with Sylloid (1:1)
Blend 2	Blend 1 + 10% w/w stearic acid
Blend 3	Blend 1 + 20% w/w stearic acid

All materials were passed through a 60-mesh sieve prior to blending. The components were mixed for 30 minutes under controlled environmental conditions (temperature < 20°C and relative humidity < 20%) to minimize premature moisture-induced degradation. Blending was conducted in a closed system to ensure uniform distribution of stearic acid and maintain environmental control.

Following preparation, samples were subjected to open exposure conditions at 25°C / 60% RH for 7 days. Refrigerated controls were maintained at 2–8°C for comparative assessment of stability behavior.

2.2 Preparation of Polymeric Film-Coated Samples and Exposure Conditions

Uncoated cores were used as control samples. Coated samples were prepared to achieve a target weight gain of 5%.

The coating formulation consisted of HPMC E15 (30.0 g), Ethylcellulose N10 (8.0 g), and triacetin (2.0 g), yielding a total solid content of 40.0 g. The solvent system comprised isopropyl alcohol (400 g) and methylene dichloride (400 g), resulting in a total solution weight of approximately 840 g.

Coating was performed using a laboratory-scale Glatt fluidized bed processor operating in top-spray mode and equipped with a 1.0 mm spray nozzle.

The coating solution was prepared by dispersing HPMC E15 in methylene dichloride under continuous stirring. Ethylcellulose N10 was dissolved in isopropyl alcohol and gradually incorporated into the HPMC dispersion. Triacetin was added as plasticizer and mixed until a homogeneous solution was obtained. The solution

was filtered prior to spraying and used immediately after preparation.

A batch of 760 g potassium Clavulanate-Sylloid (1:1) cores was fluidized under controlled airflow. Process parameters were maintained as follows: inlet temperature 35–40°C; product temperature 30–35°C (maintained below 35°C to prevent thermal degradation); atomizing air pressure 0.8–1.5 bar; and nozzle diameter 1.0 mm.

Spraying was initiated at a low rate and continued until a 5% weight gain was achieved. Intermittent drying phases were applied as necessary to prevent tackiness. Following completion of spraying, post-coating drying was performed for 5–10 minutes until product temperature stabilized and residual solvent levels were within acceptable limits.

Following coating 1% w/v aqueous solution was prepared from both coated and uncoated samples to assess solution stability behavior. The freshly prepared solutions were stored at 25°C and 2–8°C and monitored for stability trends.

3. RESULTS AND DISCUSSION

4.1 Influence of Relative Humidity on Solid-State Stability

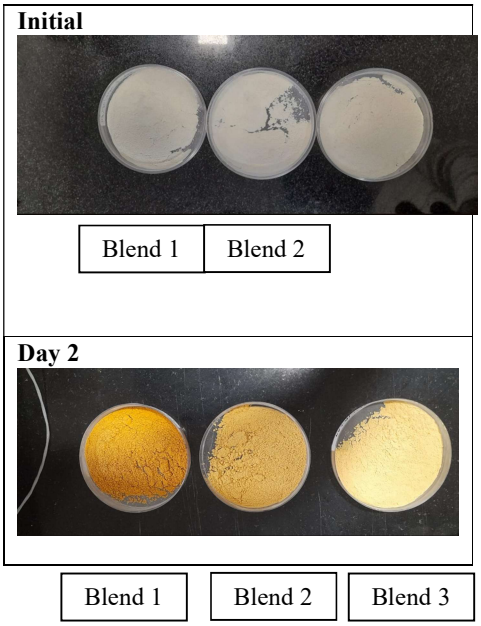
Exposure of potassium clavulanate blends to 25°C/60% RH under open conditions resulted in progressive discoloration across all samples, consistent with moisture-mediated degradation (Table 1; Figure 1). The untreated API exhibited visible yellowing within 24 h, transitioning to dark yellow by Day 3, with no further significant chromatic change observed by Day 7. The rapid onset of discoloration suggests early initiation of hydrolytic degradation under humid conditions.

Table 1: Visual appearance of potassium clavulanate powder blends under open exposure at 25°C/60% RH

Condition:25°C/60% RH				
Sample ID	**Appearance Initial**	**Appearance Day 1**	**Appearance Day 3**	**Appearance Day 7**
Blend 1 (As such)	White to off white	Yellow	Dark yellow	Dark yellow
Blend 2 (10 % Stearic acid)	White to off white	slight yellow	Dark yellow	Dark yellow
Blend 3 (20 % stearic acid)	White to off white	Off white to slight yellow	Dark yellow	Dark yellow

Incorporation of stearic acid delayed the onset of visible degradation. The 10% stearic acid blend demonstrated only slight yellowing at Day 1, whereas the 20% stearic acid blend remained predominantly off-white with minimal colour shift at the same time point. However, by Day 3, both lipid-containing blends exhibited dark yellow coloration comparable to the untreated API (Table 1), indicating that while stearic acid incorporation retards moisture-driven degradation, it does not completely prevent it under sustained humidity exposure.

The observed transition from white/off-white to yellow and subsequently dark yellow is consistent with β-lactam ring opening followed by the formation of conjugated degradation species. Moisture ingress likely facilitates nucleophilic attack on the β-lactam carbonyl, producing ring-opened intermediates that may further undergo decarboxylation and secondary reactions, including oxidative processes, leading to chromophore formation. The delayed discoloration in stearic acid–containing blends supports a diffusion-limited degradation mechanism, wherein hydrophobic excipient incorporation reduces the rate of moisture penetration and lowers effective water activity within the powder bed.



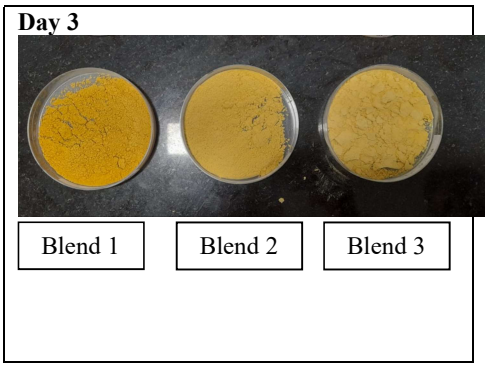


Fig. 1. Progressive discoloration of stearic acid–containing potassium clavulanate blends under open exposure (25°C/60% RH)

4.2 Temperature Dependence of Degradation Behaviour

Samples stored under refrigerated conditions (2–8°C) demonstrated markedly reduced discoloration compared to those stored at 25°C. Minimal visual change was observed through Day 3 under refrigeration, whereas samples maintained at room temperature exhibited rapid yellowing within 24 h and progressive darkening thereafter (Figures 2 and 3). These observations confirm the pronounced temperature dependence of clavulanate degradation. This behavior is consistent with Arrhenius kinetics, wherein increasing temperature enhances molecular mobility and accelerates hydrolytic and oxidative degradation pathways. Even in the absence of bulk aqueous medium, residual or adsorbed moisture within the solid material appears sufficient to facilitate temperature-dependent degradation reactions. Upon dissolution (1% w/v aqueous solutions), the temperature effect became more evident, with rapid chromatic changes observed at 25°C compared to refrigerated conditions.

Figure 2 illustrates the visual stability of aqueous solutions prepared from stearic acid–containing blends. Solutions stored at 2–8°C exhibited comparatively slower discoloration through Day 3, whereas samples maintained at 25°C showed accelerated yellowing. Although stearic acid incorporation delayed solid-state discoloration, its protective influence was not sustained following dissolution, indicating that the stabilization mechanism is primarily related to moisture diffusion control in the solid state rather than intrinsic chemical stabilization in solution.

Similarly, Figure 3 demonstrates the temperature-dependent behavior of aqueous solutions prepared from uncoated and polymer-coated potassium clavulanate cores. Under refrigerated storage, both samples showed relatively slower visual degradation through Day 7. In contrast, room temperature storage resulted in pronounced discoloration, particularly in the uncoated API solution. The polymer-coated API exhibited comparatively delayed chromatic transition, suggesting partial mitigation of pre-dissolution moisture exposure prior to solution preparation. The slight yellowing observed at the initial time point may indicate that partial degradation occurred during the coating process, potentially due to elevated processing temperatures and mechanical agitation.

Collectively, these findings reinforce the critical role of temperature in governing clavulanate degradation kinetics and underscore the necessity of low-temperature storage for moisture-sensitive β-lactamase inhibitors.

Photographs represent aqueous solutions of Blend 1 (control), Blend 2 (10% w/w stearic acid), and Blend 3 (20% w/w stearic acid), arranged from left to right. Samples were evaluated at Time 0 (initial), after storage at 2–8°C for 3 days, and at 25°C for 1 and 3 days.

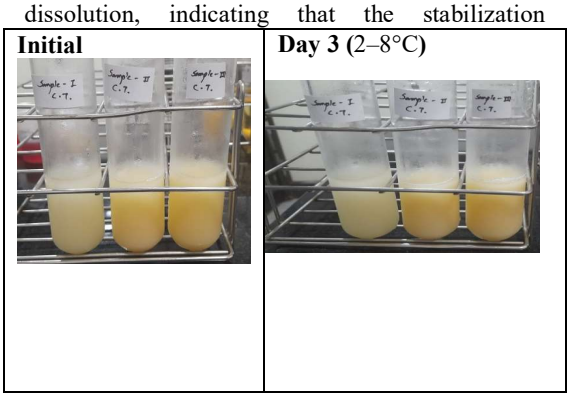
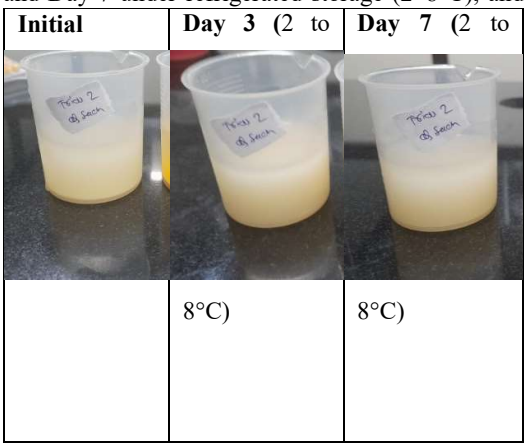


Fig. 2. Appearance of 1% (w/v) aqueous solutions

prepared from stearic acid–containing potassium clavulanate blends under refrigerated and room Photographs show aqueous solutions of uncoated API (left) and 5% weight-gain polymer-coated API (right). Images correspond to Time 0 (initial), Day 3 and Day 7 under refrigerated storage (2–8°C), and



temperature conditions

Day 1, Day 3, and Day 7 under room temperature storage (25°C), demonstrating temperature-dependent degradation behavior.

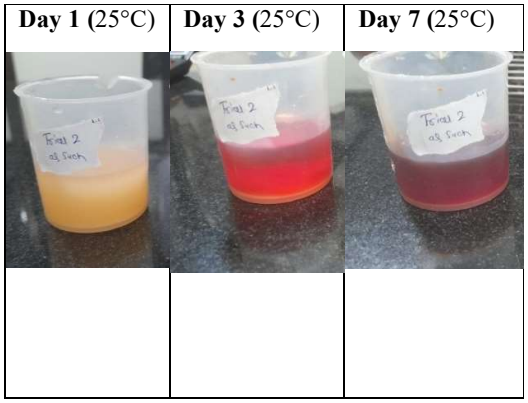


Fig. 3. Visual stability of 1% (w/v) aqueous solutions prepared from uncoated and polymer-coated potassium clavulanate cores under refrigerated and room temperature conditions

4.3 Comparative Performance under Thermal Stress (80°C, 1 h)

Exposure of Alu–Alu blister-packed samples to thermal stress at 80°C for 1 h revealed pronounced differences in physical integrity and discoloration patterns (Figure 4).

The untreated API exhibited significant blister bulging accompanied by marked yellowing, indicating thermally accelerated degradation and internal pressure buildup. Elevated temperature likely enhanced degradation kinetics, consistent with Arrhenius behavior, resulting in rapid decomposition and generation of volatile byproducts.

Blister deformation is plausibly attributed to gas evolution associated with decarboxylative degradation pathways and expansion of residual moisture vapor. Potassium clavulanate degradation is known to involve decarboxylation reactions, which may contribute to internal pressure accumulation within sealed blister cavities under thermal stress.

The polymer-coated API demonstrated reduced blister bulging relative to the untreated control, confirming the barrier properties of the coating layer in limiting rapid moisture exchange and possibly moderating heat-induced moisture redistribution. However, visible discoloration remained evident, suggesting that although the external polymeric barrier mitigates environmental ingress, it does not fully prevent internally initiated degradation processes.

In contrast, stearic acid blends (10% and 20%) exhibited minimal blister bulging and comparatively limited color change following heat exposure. Because blending does not subject the API to additional thermal processing, degradation initiation prior to stress exposure is minimized. The hydrophobic lipid phase likely reduces internal moisture mobility and oxygen permeability within the powder bed, thereby attenuating thermally accelerated oxidative and decarboxylative reactions. The 20% stearic acid blend demonstrated the most pronounced resistance to physical deformation, supporting a diffusion-limited stabilization mechanism.

Overall, under acute thermal stress conditions, hydrophobic excipient incorporation via blending provided superior resistance to blister deformation compared to external polymer coating, suggesting that internal moisture mobility control plays a critical role in limiting heat-induced degradation.

Blister-packed samples are shown from left to right: Blend 1 (as such API), Blend 2 (10% w/w stearic acid), Blend 3 (20% w/w stearic acid), uncoated API, and 5% weight-gain coated API. Images represent initial condition (prior to heat exposure) and after exposure to thermal stress at 80°C for 1 hour. Blister deformation and discoloration illustrate heat-induced degradation and internal pressure buildup.

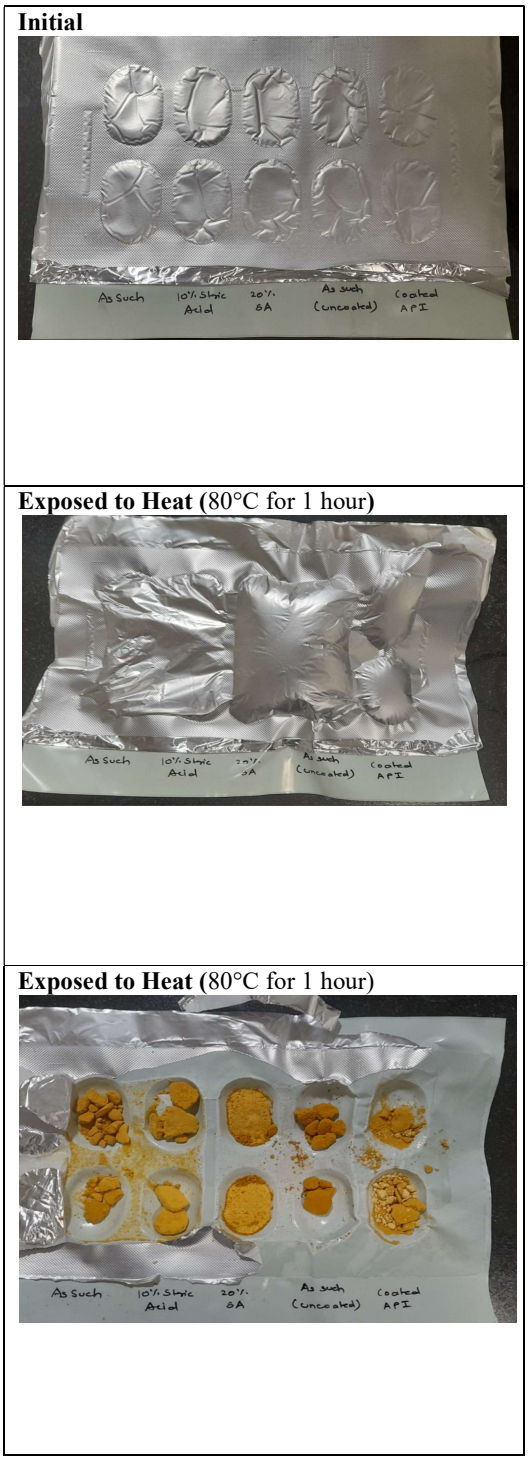


Fig. 4. Effect of thermal stress (80°C, 1 h) on Alu–Alu blister-packed potassium clavulanate blends and coated samples

4.4 Solid-State Characterization by Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD)

To complement the appearance-based stability assessment described above, preliminary solid-state characterization by DSC and XRD was performed on the control blend (Blend 1) and the 20% w/w stearic acid blend (Blend 3) to evaluate the thermal behavior and crystallinity changes associated with stearic acid incorporation. This analysis was undertaken to test whether the delayed discoloration observed in stearic acid-containing blends (Section 4.1) corresponds to a physically distinct, hydrophobic solid-state environment rather than a simple physical admixture.

Differential Scanning Calorimetry (DSC)

DSC analysis of Blend 1 (control) showed a single, weak thermal event with onset at 169.27°C, peak at 172.35°C, and endset at 175.97°C, corresponding to a normalized enthalpy of only −0.45 J/g (Table 2). The absence of a sharp, well-defined melting endotherm is consistent with the predominantly amorphous character of the API–Sylloid system confirmed by XRD (below), and is compatible with a weak decomposition-associated thermal event rather than a true crystalline melting transition, in line with the known tendency of potassium clavulanate to decompose rather than melt cleanly on heating.

In contrast, Blend 3 (20% w/w stearic acid) exhibited three distinguishable thermal events: two weak endothermic transitions at 57.78°C (ΔH = −0.21 J/g) and 89.60°C (ΔH = −0.26 J/g), and a higher-temperature event at 184.39°C (ΔH = +0.15 J/g) that was notably opposite in sign to the corresponding control event and shifted approximately 12°C higher than the control peak at 172.35°C (Table 2). Pure stearic acid is reported to melt at approximately 71°C with an enthalpy of fusion of ≈210.8 J/g [21]; for a 20% w/w blend, bulk crystalline stearic acid present in its ordinary polymorphic form would therefore be expected to contribute a melting endotherm of approximately 40 J/g. The markedly smaller enthalpies observed here (≤0.3 J/g), together with peak temperatures offset from the expected melting point, indicate that the automated peak-integration routine did not fully capture the underlying thermal event(s) associated with stearic acid melting — a recognized limitation when scanning small sample masses (2 mg) across the multiple, closely spaced polymorphic transitions that fatty acids such as stearic acid commonly display before final melting. Re-examination of the raw thermal curve, ideally using a larger sample mass and/or a slower heating rate, is recommended to fully resolve and quantify this transition; this is noted as a methodological limitation of the present preliminary dataset (Section 6.1).

Table 2: DSC thermal transition data for Blend 1 (control) and Blend 3 (20% w/w stearic acid)

Sample	Onset (°C)	Peak (°C)	Endset (°C)	ΔH (J/g)	Tentative assignment

Blend 1 (control)	169.27	172.35	175.97	−0.45	API/excipient thermal event (decomposition-associated)
Blend 3 (20% SA)	55.30	57.78	59.29	−0.21	Stearic acid–related transition (low-temperature)
Blend 3	85.11	89.60	93.81	−0.26	Stearic acid–related transition
Blend 3 (20% SA)	178.41	184.39	186.04	+0.15	API-related event (shifted, sign-inverted vs. control)

X-ray Diffraction (XRD)

XRD analysis of Blend 1 (control) showed no discrete diffraction peaks, only a broad amorphous halo centered around 24–26° 2θ (Figure 5), consistent with the amorphous nature of Sylloid (colloidal silicon dioxide) and indicating that potassium clavulanate, at the diluted 1:1 ratio, does not contribute significant long-range crystalline order detectable by this technique.

Blend 3 (20% w/w stearic acid) showed clear, sharp diffraction peaks superimposed on a similar amorphous background, most prominently at 2θ = 20.95° and 22.00°, with additional reflections at 22.97°, 24.24°, 29.67°, and 41.36° (Table 3; Figure 5). These positions correspond closely to literature values reported for crystalline stearic acid, including characteristic reflections near 21.6° and 24.3° 2θ assigned to its (118) and (200) crystallographic planes (Guo et al., 2025), confirming that stearic acid is retained in a crystalline form within the blend.

Table 3: XRD peak positions observed for Blend 3 (20% w/w stearic acid) and comparison with literature stearic acid reflections

Observed 2θ (°)	**d-spacing (Å)**	**Literature stearic acid 2θ (°)**
20.95	4.24	≈21.6 (118 plane)
22.00	4.04	—
22.97	3.87	—
24.24	3.67	≈24.3 (200 plane)
29.67	3.01	—
41.36	2.18	—

Fig. 5. DSC overlay thermograms of Blend 1 (control) and Blend 3 (20% w/w stearic acid), showing the thermal transitions observed at 172.35°C for Blend 1 and at 57.78°C, 89.60°C, and 184.39°C for Blend 3

Fig. 6. XRD overlay of Blend 1 (control) and Blend 3 (20% w/w stearic acid), showing the amorphous halo in the control and characteristic crystalline stearic acid reflections (~21–24° 2θ) in the stearic acid–containing blend

Combined interpretation of DSC and XRD

Taken together, the DSC and XRD results demonstrate that incorporation of 20% w/w stearic acid produced a measurable change in the solid-state characteristics of the formulation. DSC showed additional low-temperature thermal events and a modified higher-temperature thermal response in Blend 3, while XRD demonstrated the presence of distinct crystalline diffraction peaks that were absent from the control blend.

The apparent discrepancy between the relatively small DSC enthalpy values and the clear crystalline reflections observed by XRD should be interpreted cautiously. XRD demonstrates the presence of crystalline order but does not quantify the amount of crystalline material, whereas the DSC response may be affected by sample mass, peak overlap, baseline selection, heating rate, and the thermal behavior of the multicomponent formulation. Therefore, the present results should be regarded as preliminary solid-state evidence rather than definitive proof of a particular molecular interaction or phase transformation.

From a formulation perspective, the retention of crystalline stearic acid in Blend 3 is consistent with the proposed hydrophobic barrier mechanism described in Section 4.5. The crystalline stearic acid phase may contribute to reducing moisture penetration into the API–excipient matrix and thereby reduce exposure of potassium clavulanate to moisture, potentially contributing to the delayed discoloration observed during stability evaluation (Section 4.1). However, the present DSC/XRD data do not directly demonstrate that stearic acid is localized at the surface of API–Sylloid particles; this aspect remains a mechanistic hypothesis requiring further investigation.

Overall, the solid-state characterization supports the conclusion that stearic acid incorporation produces a physically distinguishable formulation environment, while avoiding the stronger claim of a demonstrated molecular interaction or formation of a new crystalline phase. The characterization was limited to Blend 1 and Blend 3; evaluation of the 10% w/w stearic acid blend and comparison with uncoated and polymer-coated cores would provide additional evidence for establishing the relationship between

stearic acid concentration, solid-state properties, and stabilization performance.

4.5 Mechanistic Considerations

The degradation of potassium clavulanate under humidity and thermal stress conditions appears to follow a moisture-initiated, diffusion-controlled pathway. Based on the experimental observations and prior literature on clavulanate instability, the degradation sequence may be summarized as follows:

1. Diffusion of environmental moisture into the powder bed
2. Nucleophilic attack on the β-lactam carbonyl
3. β-Lactam ring opening and formation of hydrolyzed intermediates
4. Decarboxylation reactions with potential gas evolution
5. Secondary oxidative and condensation-type transformations
6. Formation of conjugated chromophoric species responsible for yellow to dark-yellow discoloration

Moisture ingress acts as the primary triggering event. Even limited adsorbed water may initiate β-lactam hydrolysis in the solid state. The resulting ring-opened intermediates are unstable and may undergo decarboxylation, generating volatile byproducts that contribute to internal pressure buildup under thermal stress conditions, consistent with the blister bulging observed at 80°C. Subsequent oxidative transformations likely lead to formation of conjugated degradation species responsible for progressive discoloration.

The degradation process may exhibit autocatalytic characteristics, as acidic degradation products can lower the local microenvironmental pH, thereby accelerating further hydrolysis. In partially hydrated solids, localized moisture domains may act as reaction centers, resulting in heterogeneous propagation of degradation throughout the particle bed.

Hydrophobic excipient incorporation via stearic acid blending likely reduces effective water activity and limits internal moisture mobility, thereby delaying hydrolytic initiation. In contrast, polymer coating primarily functions as an external diffusion barrier, reducing environmental moisture ingress post-processing but exerting limited control over internally retained moisture or degradation initiated during coating. A schematic representation of the proposed degradation pathway under combined heat and humidity stress is presented in Figure 6.

Schematic illustration depicting moisture diffusion, β-lactam ring opening, formation of hydrolyzed intermediates, decarboxylation with potential gas evolution, oxidative transformations, and generation of conjugated chromophoric degradation products responsible for discoloration and blister deformation.

conditions

Fig. 6. Proposed degradation pathway of potassium clavulanate under heat and moisture stress

4.6 Overall Stability Assessment

Across evaluated conditions, stearic acid blending demonstrated a favorable balance between moisture protection and process-induced stability. While polymer coating effectively reduced blister deformation under heat stress, its susceptibility to processing-related degradation suggests that optimization of coating parameters is essential.

From a mechanistic standpoint, internal hydrophobic matrix modification appears to offer more robust stabilization against combined humidity and thermal stress compared to external diffusion barrier approaches alone.

4.7 Implications for Formulation Development

These findings highlight the critical interplay between moisture diffusion, processing stress, and solid-state degradation kinetics in moisture-sensitive β-lactamase inhibitors. Strategies that minimize thermal exposure during manufacturing while reducing internal water activity may provide superior stability outcomes.

Further quantitative kinetic analysis and moisture sorption profiling would enable deeper understanding of diffusion-controlled degradation mechanisms and facilitate rational formulation optimization.

5. CONCLUSION

The present study systematically evaluated internal hydrophobic matrix modification and external polymer coating as stabilization strategies for moisture-sensitive potassium clavulanate under humidity and thermal stress conditions.

Exposure to 25°C/60% RH confirmed that degradation is strongly moisture-driven and temperature-dependent, with rapid onset of discoloration observed in untreated API. Refrigerated storage significantly mitigated degradation, reinforcing the thermally activated nature of the hydrolytic pathway.

Polymer coating demonstrated partial effectiveness by reducing blister bulging under thermal stress, indicating a functional external moisture barrier. However, initial yellowing observed in coated samples suggests that processing-induced stress, particularly thermal exposure during coating, may contribute to early degradation. This highlights the critical need for careful optimization of coating parameters when applied to labile β-lactamase inhibitors.

In contrast, stearic acid blending provided consistent stabilization without introducing additional thermal stress. The hydrophobic lipid matrix likely reduced effective water activity, oxygen diffusion, and internal moisture mobility, thereby delaying degradation initiation. Stearic acid blends exhibited

reduced bulging and improved visual stability under heat stress, suggesting enhanced resistance to decarboxylative and oxidative pathways.

Mechanistically, the findings support a diffusion-controlled degradation model involving moisture ingress, β-lactam ring opening, decarboxylation, and chromophore formation. Internal matrix modification appears to more effectively mitigate these pathways compared to external coating alone.

Overall, hydrophobic matrix incorporation represents a promising and industrially feasible stabilization strategy for potassium clavulanate and other moisture-sensitive APIs. Future work should focus on quantitative kinetic modeling, moisture sorption analysis, and optimization of processing conditions to further enhance stability and scalability.

6. LIMITATIONS AND FUTURE PERSPECTIVES

6.1 Limitations

While the present investigation provides valuable insights into moisture- and heat-induced degradation behavior of potassium clavulanate, certain limitations should be acknowledged.

First, the study primarily relied on visual appearance and physical observations (color change and blister deformation) as the main indicators of degradation. Preliminary DSC and XRD characterization (Section 4.4) was performed only for the control (Blend 1) and the 20% w/w stearic acid blend (Blend 3); quantitative analytical data for the remaining samples (Blend 2, uncoated core, coated core), as well as assay loss, impurity profiling, and degradation kinetics, were not incorporated into the current evaluation. The DSC melting enthalpies recorded for the stearic acid-related transitions were also substantially smaller than expected from the confirmed XRD crystallinity, indicating that the automated DSC peak integration likely under-captured the true transition and that manual re-integration of the raw thermograms is needed. Integration of chromatographic and spectroscopic characterization would allow deeper mechanistic validation.

Second, moisture sorption behavior and water activity within the solid matrix were not directly measured. Given that degradation appears diffusion-controlled and strongly humidity-dependent, dynamic vapor sorption (DVS) analysis would provide quantitative understanding of moisture uptake kinetics and threshold water activity for degradation initiation.

Third, the influence of particle size distribution, surface area, and microstructural characteristics of blends was not evaluated. These factors may significantly affect moisture diffusion pathways and internal microenvironmental stability.

Additionally, while heat stress at 80°C for 1 h provided accelerated insights into thermal sensitivity, real-time long-term stability studies under ICH-recommended conditions would be necessary to confirm practical shelf-life benefits of stearic acid incorporation.

Finally, scalability considerations—including blending homogeneity, impact on compressibility, and compatibility with downstream processing—were not addressed in this preliminary investigation.

6.2 Future Perspectives

Future studies should focus on quantitative and mechanistic expansion of the present findings.

1. **Comprehensive Analytical Profiling**
   High-performance liquid chromatography (HPLC), LC–MS, and impurity mapping should be performed to identify and quantify specific degradation products, enabling correlation between chromophore formation and molecular transformation pathways.
2. **Moisture Sorption and Water Activity Modeling**
   Dynamic vapor sorption studies and sorption–desorption isotherms would clarify the critical relative humidity threshold for degradation initiation. Coupling these data with Arrhenius-based kinetic modeling could facilitate predictive shelf-life estimation.
3. **Microenvironmental pH and Autocatalysis Investigation**
   Given the potential for autocatalytic degradation via acidic intermediates, evaluation of microenvironmental pH modifiers or buffering excipients may further enhance stabilization.
4. **Comparative Lipid Screening**
   Evaluation of alternative hydrophobic excipients (e.g., glyceryl behenate, hydrogenated castor oil, wax matrices) may identify superior diffusion barriers or synergistic combinations.
5. **Process Optimization Studies**
   For polymer-coated systems, systematic evaluation of inlet air temperature, atomization rate, and drying kinetics could minimize processing-induced degradation.
6. **Solid-State Characterization**
   Preliminary DSC and XRD analysis (Section 4.4) confirmed that crystalline stearic acid is retained within the 20% w/w blend, supporting a surface-associated hydrophobic barrier mechanism. Extending this characterization to the 10% w/w stearic acid blend and to the uncoated and polymer-coated cores, together with manual re-integration of the DSC thermograms and complementary FTIR mapping, would further elucidate solid-state interactions between potassium clavulanate and stearic acid, including any polymorphic changes or surface adsorption phenomena.
7. **Scale-Up and Dosage Form Integration**
   Translation of the optimized stabilization strategy into tablet or combination

formulations should be explored to confirm manufacturability and long-term performance under ICH stability conditions.

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