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Opinion

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Controlled release of clarithromycin: In situ polymorphic transformation

Abstract

Conventional oral controlled-release formulations depend heavily on functional excipients to modulate drug release through mechanisms like swelling, erosion, and diffusion barriers. However, these approaches often increase tablet size, complicate manufacturing, and reduce patient compliance. This study presents a novel formulation strategy that leverages the intrinsic solid-state properties of the active pharmaceutical ingredient (API), specifically crystal polymorphism, to control drug release without the need for added excipients. Using clarithromycin (CAM) as a model, the research highlights a unique phenomenon wherein the metastable anhydrous form (Form I), despite its high solubility and rapid dissolution rate, suppresses drug release when incorporated into tablets. This unexpected behavior is attributed to a spontaneous hydration-induced transition from Form I to Form IV, a hydrated polymorph with lower solubility, upon contact with aqueous media. The transformation generates a dense layer of fine, needle-shaped crystals on the tablet surface, impeding water ingress and delaying disintegration, effectively creating a self-coating, controlled-release system. This excipient-free approach has significant implications for high-dose drugs, improving patient compliance, and simplifying manufacturing. The findings suggest that harnessing polymorphic transitions can revolutionize sustained-release formulation strategies, reducing reliance on excipients and advancing patient-centered drug delivery systems.

Keywords: crystal polymorphism, drug release modulation, solid-state transitions, clarithromycin polymorphs, oral dosage forms, pharmaceutical formulation design

Volume 14 Issue 2 - 2026

Renan Marcel Bonilha Dezena[1,2]
[1]Pontifical Catholic University of Campinas (PUC-Campinas), Brazil
[2]Preformulation Specialist, Pharmaceutical Company, Brazil

Correspondence: Renan Marcel Bonilha Dezena, Pontifical Catholic University of Campinas (PUC-Campinas), Brazil, Tel 5519991361228

Received: April 15, 2026 | **Published:** May 29, 2026

Introduction

Oral controlled-release formulations have traditionally depended on the inclusion of functional excipients—such as hydrophilic polymers (e.g., hydroxypropyl methylcellulose), disintegrants, and coating agents—to modulate drug release behavior.[1,2] These excipients facilitate mechanisms like swelling, erosion, or diffusion barriers to achieve sustained or delayed drug delivery.[3] While these technologies are well established and effective, they frequently require high excipient loadings, leading to increased tablet size, complex manufacturing steps, and ultimately reduced patient compliance—especially among elderly or pediatric populations.[4–8]

To address these limitations, recent research has focused on formulation strategies that minimize or eliminate functional excipients by leveraging the inherent physicochemical properties of the active pharmaceutical ingredient (API).[9–11] Among these properties, crystal polymorphism has emerged as a particularly promising mechanism for controlling drug release without relying on conventional polymeric matrices or coatings.[12–16]

Polymorphism refers to the ability of a compound to exist in multiple crystalline forms, each characterized by distinct arrangements of molecules in the crystal lattice.[17] These different forms—stable or metastable—can exhibit markedly different melting points, hygroscopicity, mechanical behavior, solubility, and dissolution rates, all of which can significantly impact the performance of solid oral dosage forms.[18] This makes polymorphism a powerful and versatile tool in formulation design, allowing for the manipulation of bioavailability and release kinetics without additional excipient systems.[19]

Metastable polymorphs, for instance, often possess higher apparent solubility and faster dissolution rates compared to their stable counterparts.[20,21] However, under certain conditions, these metastable forms can undergo phase transitions to more stable forms, sometimes accompanied by significant morphological changes that influence water penetration, tablet disintegration, and drug release.[22]

An illustrative case is the metastable Form I of clarithromycin, which, despite exhibiting superior solubility and intrinsic dissolution rate, shows suppressed release when incorporated into tablets. This is due to its rapid transformation into Form IV (a hydrate) upon exposure to aqueous media. This phase transition results in the in situ formation of needle-shaped crystals on the tablet surface, creating a dense layer that impedes fluid ingress and delays tablet disintegration—ultimately serving as a self-forming sustained-release system.[23,24]

Case study

Clarithromycin and its polymorphic behavior

Clarithromycin (CAM) is a broad-spectrum 14-membered macrolide antibiotic widely used in the treatment of respiratory tract infections and *Helicobacter pylori* eradication regimens. From a solid-state chemistry perspective, clarithromycin is known to exist in multiple polymorphic and pseudopolymorphic forms, including:

1. Form I: Metastable anhydrous form
2. Form II: Thermodynamically stable anhydrous form
3. Form IV: Hydrate (monohydrate) form

Among these, Form I exhibits significantly higher solubility and intrinsic dissolution rate. However, tablets prepared using Form I unexpectedly show suppressed drug release, which has been attributed to a hydration-induced transition to Form IV at the tablet surface, forming a dense crystalline barrier (Table 1).[23]

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Table 1 Comparison of Clarithromycin Polymorphs: Physical properties and In-Tablet Behavior[23]

Property	Form I	Form II	Form IV
Polymorph Type	Metastable	Stable	Hydrate (Pseudopolymorph)
Surface morphology after solution exposure	Needle-shaped Form IV microcrystals form and cover surface	Minimal changes	No major transformation
Impact on cam release	Highly suppressed due to form IV crystal coating	Normal (rapid disintegration)	Normal (rapid disintegration)
Potential application	Controlled/sustained-release formulation	Immediate release	Immediate release

Polymorphic influence on drug release behavior

The influence of polymorphic forms on the performance of oral solid dosage forms is a key factor in determining therapeutic efficacy and drug release profiles. In this study, three crystalline forms of clarithromycin were evaluated: Form I (metastable anhydrous), Form II (thermodynamically stable anhydrous), and Form IV (monohydrate). The comparison revealed distinct behaviors in terms of solubility, disintegration, and dissolution performance, each with direct implications for controlled-release formulation strategies.[23]

Form I exhibited the highest apparent solubility and the fastest intrinsic dissolution rate when assessed as a pure solid.[23] However, tablets composed exclusively of this form showed significantly reduced drug release, even after prolonged exposure to aqueous media. Surface analysis after hydration revealed the spontaneous formation of a dense layer of needle-shaped crystals, characteristic of Form IV, indicating a moisture-induced polymorphic transformation. This crystalline layer acts as a physical barrier, limiting fluid ingress and effectively preventing matrix disintegration—even in the absence of functional excipients.[23]

In contrast, tablets prepared with Form II, the most thermodynamically stable polymorph, demonstrated predictable behavior: rapid disintegration and complete drug release.[23] Although Form II has lower solubility and a slower dissolution rate compared to Form I, its release performance is more consistent and unaffected by significant surface transformations.[23] This stability contributes to its widespread use in commercial clarithromycin formulations, where consistent pharmacokinetic profiles are required.[23]

Form IV, the monohydrated pseudopolymorph, exhibited intermediate behavior. Despite being a hydrate, its solubility is slightly higher than that of Form II, and its dissolution rate is comparable. Tablets made from Form IV showed fast disintegration and complete drug release, with no significant changes to surface morphology during testing. This supports the view that dynamic polymorphic transitions, rather than intrinsic properties alone, are the primary drivers of release modulation in this system.[23]

Therefore, the release suppression observed in Form I tablets cannot be explained solely by its high solubility or fast intrinsic dissolution rate. Instead, it is governed by a solid-to-solid transformation at the tablet–medium interface, leading to the in situ formation of a low-permeability crystalline layer composed of Form IV. This barrier is formed spontaneously and progressively, impeding medium penetration and delaying disintegration, despite the favorable solubility of the initial form.[23]

The comparison across the three forms clearly demonstrates that the evolving surface architecture upon hydration, rather than the inherent solubility of the API alone, is the critical factor determining drug release behavior. Understanding this phenomenon enables the intentional use of polymorphic transitions as a functional tool for controlled-release systems, making it possible to design excipient-free formulations with modified drug release profiles (Figure 1).[23]

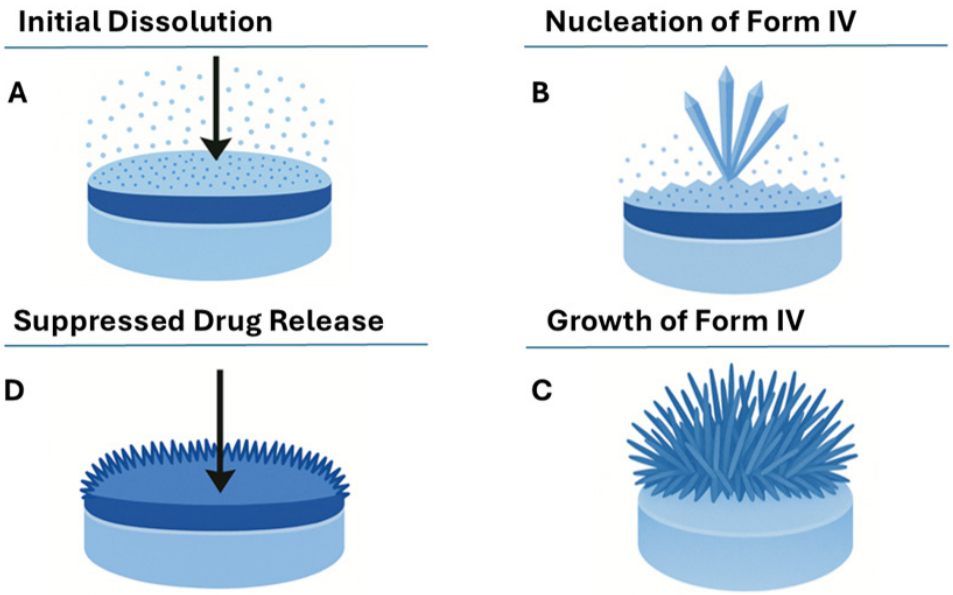

Figure 1 A: Form I rapidly dissolve saturating the local solution at the tablet surface. **B:** The resulting supersaturated microenvironment promotes the nucleation of form IV, a hydrated and thermodynamically more stable polymorph with significantly lower solubility. **C:** Crystals of form IV grow on the tablet surface in the form of fine needle-shaped microcrystals. These structures gradually cover the tablet exterior forming a dense microcrystalline layer. **D:** With water ingress tablet disintegration is delayed or completely inhibited leading to suppression of drug release despite the high solubility of initial polymorphic form.[23]

Citation: Dezena RMB. Controlled release of clarithromycin: In situ polymorphic transformation. *Pharm Pharmacol Int J.* 2026;14(2):43–46.
DOI: 10.15406/ppij.2026.14.00493

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Formulation composition

Disintegration was dramatically delayed in Form I tablets, even with the inclusion of the disintegrant L-HPC. The cause was attributed to auto-crystallization of Form IV at the tablet surface, blocking fluid entry and preventing L-HPC from swelling and functioning.

Clinical relevance of the polymorphic transition to Form IV

Despite the absence of pharmacological or clinical studies directly comparing the therapeutic profiles of different clarithromycin polymorphs, current evidence suggests that the final transition from Form I to Form IV is unlikely to negatively impact the drug's pharmacodynamic performance. Form IV, which emerges as the terminal product of the hydration-induced transformation at the tablet surface, exhibits solubility and intrinsic dissolution rate values that are very similar to those of Form II the thermodynamically stable polymorph widely used in commercial formulations.[23]

Given that Form II is well established in terms of bioavailability and clinical efficacy, it is reasonable to infer that the transition to Form IV would not result in significant deviations in pharmacodynamic behavior. The comparable dissolution performance between Form II and Form IV supports the assumption that the transformation involved in the self-coating mechanism does not compromise systemic drug availability or therapeutic outcomes.[23]

Nonetheless, it is important to acknowledge that this hypothesis requires experimental validation. Future studies involving in vivo pharmacokinetic assessment or bioequivalence testing are necessary to fully confirm the clinical applicability of polymorph-driven release modulation strategies. Such validation would strengthen the scientific foundation for utilizing solid-state transitions as a functional design tool in excipient-free sustained-release formulations.[23]

Disintegration suppression and release kinetics

Tablets composed of Form I exhibited pronounced resistance to disintegration, remaining physically intact for over 480 minutes in aqueous media under USP testing conditions at 37 °C.[23] This observation stands in stark contrast to the rapid disintegration recorded for tablets containing Form II and Form IV, which disintegrated completely in a few minutes. The extended integrity of Form I tablets is attributed to the formation of a dense, low-porosity barrier composed of fine, needle-shaped Form IV crystals, which emerge from a spontaneous hydration-induced polymorphic transformation at the tablet surface.[23]

This crystal layer likely impedes matrix erosion, limits water ingress, and effectively stabilizes the external structure, functioning as a physical barrier to both disintegration and drug diffusion. As a result, the release profile of clarithromycin from Form I tablets is significantly delayed, consistent with a sustained-release behavior achieved without conventional polymeric matrices or functional excipients.[23]

These findings highlight that disintegration behavior cannot be inferred solely from intrinsic solubility or dissolution rate. While Form I demonstrates the highest solubility among the three polymorphs, its transition to a hydrated phase fundamentally alters the dosage form's wetting and diffusion characteristics. This underscores the importance of considering solid-state transitions and dynamic interfacial phenomena in the rational design and performance prediction of oral dosage forms.[23]

Implications of the clarithromycin case

This case highlights the transformative potential of polymorphism in formulation science. By enabling the API to serve as both the therapeutic and the release-modulating agent, it is possible to develop simplified, high-load, sustained-release tablets.

Such designs are especially useful for:

I. High-dose drugs, where excipient volume must be minimized

II. Pediatric and geriatric applications, where swallowability is key

III. Lean manufacturing environments, where fewer processing steps and excipients are preferred.

This paradigm suggests that solid-state engineering, not just excipient selection, should play a central role in the design of next-generation oral formulations.[23]

Future perspectives

Advanced controlled release systems

The self-coating phenomenon of form IV crystals on form I tablets presents an opportunity to develop controlled or sustained-release formulations without relying heavily on excipients.[23]

Future research could explore scaling up production of such tablets for clinical use and evaluating their bioavailability and therapeutic efficacy.

Application to other APIs with similar properties

This crystalline transition mechanism might be applicable to other APIs with multiple polymorphic forms.

An analogous case is the transformation of anhydrous theophylline to its hydrate during processing of dissolution, which generates a hydrate layer on the tablet surface and decreases the dissolution rate.[25]

Studies could investigate whether similar phase transitions can be exploited to control drug release in other systems.

Patient compliance and dosage form optimization

The approach could help develop smaller tablets with high drug load and prolonged release, improving patient compliance, particularly for those with swallowing difficulties.[23,25]

Mechanistic and kinetic studies

Deeper understanding of the kinetics of polymorphic transitions, including environmental factors like humidity and temperature, is crucial.

Advanced imaging techniques (e.g., in situ SEM, AFM) could provide insights into crystal growth dynamics on tablet surfaces.[26]

Industrial feasibility and stability studies

Studies on long-term stability of form I in tablet formulations under various storage conditions are necessary.

Investigating scalability and manufacturing challenges for consistent tablet quality is essential for commercial application.

Regulatory considerations

Establishing regulatory pathways and guidelines for polymorph-based sustained release formulations will be key for market acceptance.

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Conclusion

The findings from this study open new avenues for the rational design of advanced controlled-release drug delivery systems. The observed crystalline phase transition from metastable form I to the hydrated form IV of clarithromycin presents an innovative mechanism to modulate drug release kinetics directly through the active pharmaceutical ingredient's polymorphic properties.

This paradigm shift—from relying primarily on excipients to utilizing intrinsic solid-state transformations—holds immense potential for formulating compact, high-dose tablets with sustained-release profiles, thereby enhancing patient compliance. Extending this approach to other APIs with similar polymorphic behavior could revolutionize sustained-release formulation strategies across the pharmaceutical industry. Further research is warranted to elucidate the underlying transition kinetics, optimize manufacturing processes, and assess long-term stability under various storage conditions. Regulatory frameworks must also evolve to accommodate these novel formulation strategies, paving the way for next-generation, patient-centered pharmaceutical products.

Acknowledgments

None.

Conflicts of interest

The author declares that they have no conflicts of interest.

Funding

None.

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