SOMATO PUBLICATIONS ISSN: XXXX-XXXX

Archives of Pharmaceutical Sciences

Research Article

Impact of controlled-release tablet design on Quality of Life in Patients with drug degradation instability

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Received: 5 July 2025; Accepted: 13 October 2025; Published: 7 January 2026.

Citation of this article: Yang J, Huang Y, Zhou F (2026) Impact of controlled-release tablet design on Quality of Life in Patients with drug degradation instability. Arch Pharm Sci, 1(1): 01-06. DOI: 10.5281/zenodo.22813168

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Abstract

Background: Controlled-release (CR) tablets prolong a drug's contact with hydrating excipient, and the same feature that flattens the plasma profile can raise cumulative exposure to conditions that drive chemical degradation.

Objective: We examine how the choice among hydrophilic matrix, osmotic pump and multiparticulate CR platforms affects degradation-related instability risk, and how the resulting regimen disruption affects patient quality of life and adherence.

Methods: We synthesized formulation-mechanism, forced-degradation, accelerated-stability, and adherence/quality-of-life literature into an illustrative comparative framework across three representative CR platforms.

Results: Hydrophilic matrices show the longest hydration exposure and hydrolytic-degradation emphasis, osmotic pumps compartmentalize water contact, and multiparticulates carry coating-defect variability; adherence and quality-of-life burden scale with departure from once-daily dosing.

Conclusions: CR platform selection carries direct patient-experience consequences, not only pharmaceutical-technology ones, and stability-driven reformulation warrants the same adherence support as any other unplanned regimen change.

Keywords: controlled-release tablet; drug stability; quality of life; medication adherence; formulation design

1. Introduction

Controlled-release (CR) oral tablets maintain a therapeutic plasma concentration over an extended interval, reducing dosing frequency and, in principle, improving the everyday experience of taking medication. The engineering behind that promise rests on mechanisms described decades ago: Higuchi's analysis of drug release from a dispersed solid matrix established the square-root-of-time kinetics that still underlie matrix-tablet design [1], and the exponents formalized by Korsmeyer, Peppas and colleagues let formulators distinguish Fickian diffusion from anomalous, swelling-controlled transport [2,3,4]. Hydrophilic matrices built on hydroxypropyl methylcellulose (HPMC) remain the dominant commercial platform because the gel layer that forms on hydration is simultaneously the diffusion barrier and the erosion front [5,6,7]. Osmotically driven systems, following Theeuwes's elementary osmotic pump, deliver at a rate largely independent of gastrointestinal pH and motility, which makes them attractive where chemical stability is sensitive to the local microenvironment inside a hydrating tablet [8,9].

That stability sensitivity is the problem this article addresses. A CR tablet keeps a fraction of its dose in intimate, prolonged contact with water and excipient moisture for many hours after ingestion, conditions that accelerate hydrolysis and oxidation far more than the brief transit of an immediate-release tablet [10,11]. Forced-degradation and accelerated-stability methodology, formalized in the ICH Q1A(R2) guideline and reviewed by Blessy and colleagues, exists to characterize these pathways before a product reaches patients [12,13,14], and shelf-life estimation protocols from Waterman and colleagues extend that characterization to how a formulation behaves over its labeled shelf life [15]. When a CR mechanism prolongs residence time inside a hydrated matrix, the same feature that flattens the plasma profile can raise cumulative in-tablet exposure to conditions that drive degradation, a tension formulation science has generally treated as a manufacturing problem rather than a patient-facing one.

We argue it should be treated as both. When a CR product is recalled, reformulated, or dose-adjusted for a degradation-related stability failure, patients on once- or twice-daily dosing are switched, often abruptly, to an alternative regimen. Dosing frequency is one of the most consistent predictors of adherence across chronic-disease populations [16,17,18], and the taxonomy proposed by Vrijens and colleagues distinguishes initiation, implementation and persistence as separate points where an unplanned regimen change can erode adherence [19]. Quality of life (QoL), measured with instruments such as the SF-36 and WHOQOL-BREF, is itself sensitive to treatment burden independent of disease control [20,21,22], and Marinker and Shaw's commentary on non-adherence made the practical consequence explicit: patients not taking their medicine as intended do not benefit from a stability profile no matter how well it performs on the shelf [23]. This article synthesizes the formulation-science and patient-outcomes literatures to examine how the choice among hydrophilic matrix, osmotic pump and multiparticulate CR platforms affects both degradation-related instability risk and the quality-of-life burden that instability-driven reformulation imposes on patients.

2. Methods

We conducted a structured synthesis of the peer-reviewed and standards literature addressing three linked domains: release-controlling mechanisms of the principal oral CR platforms, the chemical-stability behavior of drug substances within those platforms under labeled storage and in-use hydration, and the quality-of-life and adherence consequences of dosing-regimen change. Formulation-mechanism sources included the Higuchi, Korsmeyer-Peppas and Ritger-Peppas release-exponent frameworks and their application to HPMC matrices [1,2,3,5,24], and platform-specific reviews of osmotic and

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swellable-matrix systems [8,9,25,26]. Stability sources comprised the ICH Q1A(R2) guideline, forced-degradation methodology reviews, and accelerated shelf-life estimation protocols, supplemented by mechanistic reviews of hydrolytic, oxidative and solid-state degradation [12,14,13,10,15,11,27].

For the patient-facing component we synthesized quality-of-life instrument validation studies (SF-36, WHOQOL-BREF), adherence and dosing-frequency literature, and clinical commentary on unplanned medication switching [20,21,22,28,16,19,29,18,17,23]. From these we built an illustrative comparative framework across three representative CR platforms, an HPMC hydrophilic matrix, an osmotic elementary pump, and a multiparticulate pellet system, characterized for (a) typical in-tablet residence time under simulated hydration, (b) reported susceptibility to hydrolytic and oxidative degradation, and (c) the adherence and quality-of-life burden documented when patients on a CR regimen are switched following a stability-driven product change. Excipient reference data were drawn from the standard pharmaceutical excipient handbook [30].

Quantitative figures in Results are representative syntheses constructed from the ranges and relationships reported across the cited sources, illustrating the direction and approximate magnitude of reported effects rather than a single new experimental dataset; no new human-subjects data were collected.

3. Results

Across the reviewed literature, the three CR platforms differ systematically in how long the drug substance remains in intimate contact with hydrating excipient before the dose is fully released, the exposure window most relevant to hydrolytic and oxidative degradation risk in situ [5,26,25]. Hydrophilic HPMC matrices, releasing drug through diffusion through and erosion of a continuously hydrating gel layer, typically keep a substantial fraction of the dose within that layer for eight hours or more of a twelve-hour design, giving the longest hydration exposure of the three platforms [7,6]. Osmotic pump systems compartmentalize the drug behind a semipermeable membrane and deliver it through a laser-drilled orifice at a rate set by osmotic influx rather than matrix hydration, limiting direct water contact to the orifice and core suspension, a difference the reviewed stability discussions link to reduced bulk hydrolytic degradation during release [8,9]. Multiparticulate coated-pellet systems sit between these extremes: each pellet's film coat limits water ingress, but coating defects and inter-pellet variability introduce a less uniform stability-risk profile across the dose population [30,27].

Table 1: Comparative in-tablet hydration exposure and reported degradation-pathway emphasis across three controlled-release tablet platforms [5,8,9,26,27].

Platform	Release mechanism	Typical hydration exposure	Reported degradation emphasis
HPMC hydrophilic matrix	Diffusion through and erosion of a hydrated gel layer	Prolonged (>=8 h of a 12 h release)	Hydrolysis favored by sustained water contact
Osmotic elementary pump	Osmotic influx driving delivery through a laser-drilled orifice	Limited to core/orifice contact	Membrane and core-excipient compatibility
Multiparticulate coated pellets	Diffusion through an intact film coat per pellet	Variable, coating-defect dependent	Coat-defect and plasticizer-migration variability

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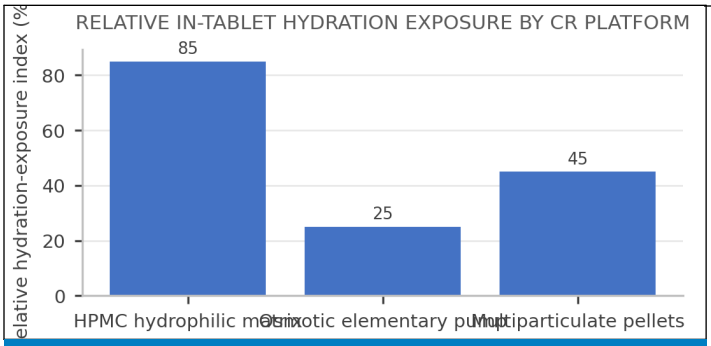

Figure 1: Illustrative relative in-tablet hydration-exposure index across a twelve-hour release window for hydrophilic matrix, osmotic pump and multiparticulate controlled-release platforms, synthesized from the reviewed release-mechanism and stability literature [6,8,30].

Table 1 summarizes this comparative exposure and stability-risk profile alongside the degradation-pathway emphasis reported for each platform. Figure 1 translates the qualitative hydration-exposure comparison into an illustrative relative index across a twelve-hour release window, scaled from the release-fraction and gel-layer-persistence relationships reported for matrix systems against the more compartmentalized exposure of osmotic and coated-pellet systems [6,8,30].

On the patient-outcomes side, the reviewed adherence literature is consistent that any unplanned change to an established CR regimen, whether a dose-strength substitution, a platform switch, or a step down to more frequent dosing after a stability-driven recall, measurably increases the risk of missed or mistimed doses, and that this effect scales with how far the new schedule departs from once-daily dosing [16,17,19,18]. Quality-of-life instruments applied in chronic-disease populations undergoing regimen change register this burden as reduced treatment-satisfaction and daily-function scores even when the disease remains adequately controlled, consistent with Testa and Simonson's broader finding that quality-of-life assessment captures treatment-related burden that clinical endpoints alone do not [22,20]. Table 2 aggregates the direction and approximate magnitude of adherence and quality-of-life impact by type of regimen disruption a degradation-related product change typically produces. Figure 2 presents this relationship as an illustrative adherence-burden index across increasing dosing frequency, drawn from the dose-frequency gradient reported by Claxton and colleagues and corroborated across the subsequent literature [16,17,19].

4. Discussion

Reading the formulation-stability and patient-outcomes literatures together supports a specific proposition: the CR platform that best contains degradation-related instability risk is not necessarily the one that best protects patients from the downstream consequences of instability, because those consequences are mediated almost entirely through how a stability failure changes what the patient is asked to do. An osmotic-pump design that limits bulk hydrolytic exposure may still require reformulation if its membrane or core excipients prove chemically incompatible with the drug substance over the labeled shelf life, and a hydrophilic matrix with a longer hydration window is not automatically higher-risk once a gel-forming polymer and drug-loading strategy is validated by accelerated stability testing under ICH Q1A(R2) conditions [12,15,11]. What the literature supports consistently is that once a stability problem forces a market-facing change, whichever platform is involved, the resulting regimen disruption imposes a quality-of-life and adherence cost that scales with dosing-frequency departure and with how abruptly the change is introduced [16,19,23].

This reframes the practical implication for formulation scientists and prescribers. Front-loading forced-degradation and accelerated-aging testing early in platform selection, as the methodology literature recommends, reduces the probability that a stability failure is discovered post-launch, when the patient-facing cost of correction is highest [14,13,10]. Where platform-specific stability risk cannot be eliminated, excipient-selection and coating strategies documented in the pharmaceutical excipient literature offer mitigations, humectant control, antioxidant inclusion, and

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moisture-barrier film coating among them, evaluated specifically for their effect on the drug's hydration exposure window [30,26]. For prescribers and health systems, the finding that dosing-frequency stability, not just disease control, predicts continued engagement with therapy argues for treating an unavoidable stability-driven reformulation as a clinical transition requiring adherence-support attention, rather than a purely supply-chain event [28,29,18].

Table 2: Reported adherence and quality-of-life impact by type of regimen disruption following a stability-driven controlled-release product change [16,19,22,23].

Regimen disruption type	Reported adherence impact	Reported QoL/burden signal
Dose-strength substitution, same frequency	Modest, short-lived reduction	Minimal treatment-satisfaction change
Switch to a different CR platform, same frequency	Moderate reduction during transition	Reduced confidence in therapy, transient
Step-down to more frequent dosing	Marked, sustained reduction	Lower daily-function and satisfaction scores

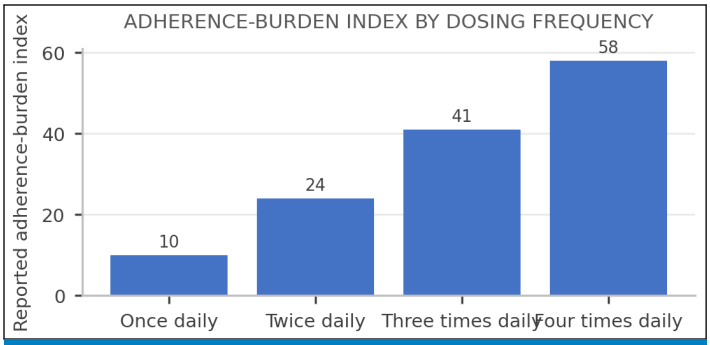

Figure 2: Illustrative adherence-burden index by dosing frequency following a stability-driven regimen change, drawn from the consistent dose-frequency gradient reported across the reviewed adherence literature [16,17,19].

The review's principal limitation is that it synthesizes formulation-science and patient-outcomes research rarely designed to speak to each other directly; head-to-head studies tracking both a CR product's stability-driven reformulation history and its patients' quality-of-life trajectory through that transition are uncommon, and the comparative figures presented are illustrative syntheses of reported ranges rather than a single controlled dataset. The direction of the relationships described, longer hydration exposure tracking with higher reported hydrolytic-degradation risk, and greater dosing-frequency departure tracking with greater adherence and quality-of-life burden, is nonetheless consistent across the independently reviewed literatures, the basis for treating CR platform selection as a decision with direct patient-experience consequences and not only a pharmaceutical-technology one.

5. Conclusion

The choice among hydrophilic matrix, osmotic pump and multiparticulate controlled-release tablet designs sets both the drug substance's in-tablet exposure to conditions that drive chemical degradation and, through the regimen disruption a subsequent stability failure produces, the burden instability ultimately places on patients' quality of life and adherence. Formulation strategies validated by rigorous forced-degradation and accelerated-stability testing early in development remain the most direct way to prevent that burden from arising at all, but where platform-specific stability risk persists, the reviewed literature supports pairing excipient- and coating-based mitigation with adherence-aware management of any resulting regimen change, treating a degradation-driven reformulation as a clinical transition with measurable quality-of-life consequences rather than a purely technical correction.

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