RESEARCH PAPER

Release Kinetics of Chlorhexidine from Mucoadhesive Polymeric Delivery Systems: A Systematic Review

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Abstract

Background: Chlorhexidine (CHX) is a broad-spectrum cationic antiseptic widely used for the prevention and management of oral, periodontal, and mucosal infections, but its clinical utility is limited by rapid clearance from mucosal surfaces through salivary flow, swallowing, and mechanical dilution. Mucoadhesive polymeric delivery systems have been developed to prolong CHX residence time and provide sustained, localised release, yet the release kinetics governing these platforms have not been systematically synthesised. Objective: This systematic review evaluates the release-kinetics behaviour of CHX when incorporated into mucoadhesive polymeric drug delivery systems and identifies the polymer- and formulation-related determinants of release rate and extent. Methods: Following PRISMA 2020 guidance, PubMed, Scopus, and Web of Science were searched from inception to July 2026 using a standardised four-concept Boolean strategy, supplemented by Google Scholar and hand-searching of reference lists. Studies reporting CHX incorporated into a mucoadhesive/bio adhesive carrier with quantitative release, permeation, or kinetic data were eligible. Data were extracted on polymer system, dosage form, kinetic model, and release outcomes, and synthesised narratively owing to substantial methodological heterogeneity. Results: Of 67 records identified, 20 studies met the eligibility criteria, spanning tablets/compacts, gels, hydrogels, films, patches, freeze-dried inserts, and nanoparticle carriers published between 1982 and 2025. Only 8 studies (40%) applied formal kinetic modelling; among these, the Korsmeyer-Peppas model was most frequently the best fit, with diffusional exponents indicating anomalous (non-Fickian) transport. Anionic polymers, particularly carboxymethylcellulose and alginate, consistently retarded and sometimes substantially limited CHX release through electrostatic complexation with the di-cationic drug, whereas non-ionic cellulose derivatives and the surfactant polymer poloxamer 407 accelerated and increased the extent of release. Release durations ranged from 2–4 hours in acute-use buccal tablets and gels to several months for ethyl cellulose films, with two studies confirming translation of in vitro release to clinically relevant salivary antimicrobial concentrations. Conclusion: CHX release from mucoadhesive systems is governed principally by polymer ionic character and hydrophilicity, with anomalous transport predominating where kinetic modelling was performed. Fewer than half of the available studies applied formal kinetic analysis, highlighting a clear need for methodological standardisation, physiologically relevant release testing, and expanded in vivo/clinical validation in future formulation research.

Keywords: chlorhexidine; mucoadhesion; drug release; controlled release; polymer; Korsmeyer-Peppas; systematic review

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1. Introduction

Chlorhexidine (CHX) is a bis-biguanide antiseptic agent that has been used in clinical practice for more than six decades, principally in dentistry, periodontology, and wound and mucosal antisepsis. Its broad-spectrum bactericidal and bacteriostatic activity, low propensity to induce resistance at antiseptic concentrations, and marked substantivity for oral hard and soft tissues have made it the reference standard against which newer antiplaque and antigingivitis agents are routinely compared. Conventional CHX

formulations, principally aqueous mouth rinses at 0.12–0.2% concentration, remain the mainstay of chemical plaque control; however, their clinical effectiveness is constrained by an inherently short mucosal residence time. Once applied, CHX solutions are rapidly diluted and cleared from the oral cavity by salivary flow, swallowing, and mechanical disturbance, typically within minutes to a few hours, necessitating frequent dosing and resulting in prolonged periods during which local drug concentrations fall below levels required for sustained antimicrobial effect.

Mucoadhesive polymeric drug delivery systems have been proposed as a means of overcoming this limitation. By adhering to the mucosal surface through a combination of polymer chain interpenetration, hydrogen bonding, and, for certain polymer classes, electrostatic interaction with the underlying epithelium, these systems can extend the residence time of an incorporated drug well beyond that achievable with a conventional rinse or gel alone, thereby sustaining local drug concentrations and reducing dosing frequency. This principle has been applied to CHX across a wide range of carrier architectures, including mucoadhesive tablets and compacts,[2,7,8,13-16] aqueous and in situ gelling systems,[4,11,17,20] hydrogels,[1,19] thin oral films,[6,10] patches,[12] freeze-dried matrices and inserts,[5,9] and, more recently, nanoparticle-based spray-dried gargle formulations.[3] Across these platforms, the choice of mucoadhesive polymer, and in particular its ionic character, hydrophilicity, and swelling behaviour, has repeatedly emerged as a central determinant of both the extent and the rate at which CHX is liberated from the carrier.

Because CHX is a di-cationic molecule at physiological pH, its release from a polymeric matrix is not governed solely by simple diffusion, as would be assumed for a neutral, freely soluble drug. Electrostatic interaction between the cationic drug and anionic functional groups present in polymers such as carboxymethylcellulose, alginate, or hyaluronate can markedly retard release through complexation, while non-ionic cellulose derivatives and surfactant-type polymers such as poloxamer 407 tend to favour more rapid, extensive release through swelling, gel-layer erosion, and solubilisation. This drug-polymer interaction adds a layer of mechanistic complexity that is not always adequately captured by descriptive cumulative-release reporting alone, and instead requires formal application of mathematical release-kinetics models, such as zero-order, Higuchi, Korsmeyer-Peppas, and Hopfenberg models, to distinguish between diffusion, erosion, and complexation-controlled release behaviour, and to allow meaningful comparison across the diverse formulation platforms reported in the literature.

Although individual formulation studies of CHX-loaded mucoadhesive systems span more than four decades, from early ethyl cellulose cast films[18] to contemporary mussel-inspired hydrogels[19] and nanoparticle-based gargles,[3] this body of work has not, to our knowledge, been systematically synthesised with specific attention to release-kinetics behaviour. Existing narrative summaries of mucoadhesive CHX delivery have tended to focus on mucoadhesive strength, formulation optimisation, or antimicrobial efficacy, rather than on the release mechanisms and kinetic models that determine how, and for how long, the drug becomes available at the mucosal surface. Given the therapeutic significance of achieving both an adequate concentration and an adequate duration of mucosal CHX exposure, a systematic, kinetics-focused synthesis of the available evidence is warranted to consolidate current mechanistic understanding and to identify gaps for future formulation research.

Accordingly, this systematic review was undertaken to address the following focused question: what is the release-kinetics behaviour of chlorhexidine when incorporated into mucoadhesive polymeric drug delivery systems? Specific objectives were to (i) characterise the range of mucoadhesive dosage forms and polymer systems that have been investigated for CHX delivery, (ii) summarise the release-kinetics models applied and their goodness of fit, (iii) identify the polymer- and formulation-related factors that determine the rate and extent of CHX release, and (iv) evaluate the extent to which in vitro release findings have been translated to in vivo or clinical outcomes, to identify priorities for future formulation and testing standardisation.

2. Methodology

2.1 Protocol and Reporting Standard

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review addresses the following focused question: “What is the release kinetics behaviour of chlorhexidine (CHX) when incorporated into mucoadhesive polymeric drug delivery systems?”

2.2 Search Strategy

A comprehensive electronic literature search was performed across PubMed, Scopus, and Web of Science from database inception to July 2026, without restriction on publication date at the search stage. A single, standardised Boolean search strategy combining four core concepts- the active agent (chlorhexidine), the mucoadhesive property, the dosage form/carrier, and the release outcome was applied consistently across all databases, with syntax adapted to each platform's conventions (Table 1).

Table 1. Database-specific search strings.

Database	Search String
PubMed	chlorhexidine AND (mucoadhesive OR bioadhesive OR mucoadhesion) AND (film* OR gel* OR patch* OR hydrogel* OR nanofiber* OR microsphere* OR nanoparticle* OR chip* OR varnish* OR tablet* OR wafer* OR insert*) AND (release OR "release kinetics" OR "drug release" OR "controlled release")
Scopus	TITLE-ABS-KEY (chlorhexidine AND (mucoadhesive OR bioadhesive OR mucoadhesion) AND (film* OR gel* OR patch* OR hydrogel* OR nanofiber* OR microsphere* OR nanoparticle* OR chip* OR varnish* OR tablet* OR wafer* OR insert*) AND (release OR "release kinetics" OR "drug release" OR "controlled release"))
Web of Science	TS= (chlorhexidine AND (mucoadhesive OR bioadhesive OR mucoadhesion) AND (film* OR gel* OR patch* OR hydrogel* OR nanofiber* OR microsphere* OR nanoparticle* OR chip* OR varnish* OR tablet* OR wafer* OR insert*) AND (release OR "release kinetics" OR "drug release" OR "controlled release"))

Google Scholar was searched as a supplementary source, with the first 100–200 relevance-sorted records screened, consistent with established practice for grey-literature screening in systematic reviews. Reference lists of included studies and relevant prior reviews were hand-searched to identify additional eligible records not captured by the electronic search.

2.3 Eligibility Criteria

Inclusion criteria

- Original research articles reporting chlorhexidine incorporated into a mucoadhesive or bioadhesive polymeric delivery system (film, gel, hydrogel, patch, tablet, compact, insert, or nanoparticle-based carrier).
- Studies reporting quantitative drug release data (cumulative release profile, permeation data) and/or formal release kinetic modelling.
- In vitro, ex vivo, or in vivo studies, including clinical and analytical-method studies with direct relevance to CHX mucoadhesive release.
- Studies published in English, in peer-reviewed original research articles.

Exclusion criteria

- Studies not involving a mucoadhesive/bioadhesive polymeric carrier (e.g., non-adhesive coatings, catheter or medical-device surface treatments, contact lenses).
- Studies where chlorhexidine was not the active agent under investigation or served only as a comparator/control.
- Reviews, conference abstracts, editorials, letters, and case reports.
- Veterinary or animal-only studies (human-relevant studies only), and duplicate publications or overlapping datasets (the most complete version was retained).

2.4 Study Selection

All records retrieved from the databases were compiled, and duplicates were identified and removed. Titles and abstracts of the remaining records were screened against the eligibility criteria. Full texts of potentially eligible studies were then retrieved and assessed in detail against both inclusion criteria: explicit confirmation of a mucoadhesive/bioadhesive carrier system, and reporting of quantitative release, permeation, or kinetic data. The study selection process is summarised in Table 2 and follows the PRISMA 2020 flow structure.

Table 2. PRISMA 2020 study selection flow.

Stage	n
Records identified through database searching (PubMed, Scopus, Web of Science)	67
Duplicate records removed	10
Records screened (title/abstract)	57
Records excluded at title/abstract stage	32
Reports sought for full-text retrieval	25
Reports not retrieved	0
Full-text reports assessed for eligibility	25
Reports excluded at full-text stage (mucoadhesive property or release data not confirmed)	5
Studies included in qualitative synthesis	20

2.5 Data Extraction

A standardised data extraction form was used to record, for each included study: author(s) and year of publication; polymer(s)/carrier system used; CHX concentration or loading; dosage form; study type (in vitro/ex vivo/in vivo/clinical); release medium and experimental conditions; release kinetic model(s) applied and corresponding fit parameters (R^2 or correlation coefficient, exponent n where applicable); release duration and pattern; and key findings relevant to release behaviour and mucoadhesive performance.

2.6 Data Synthesis

Given the anticipated and confirmed heterogeneity in polymer types, dosage forms, experimental conditions, and reporting standards across included studies, a narrative/qualitative synthesis of release-kinetics findings was performed. Results are tabulated by dosage form (Section 3.3) and by kinetic model (Section 3.4). A quantitative meta-analysis was not considered feasible due to the methodological heterogeneity across studies, consistent with recommendations for reviews of formulation-science literature with disparate experimental designs.

3. Results

3.1 Characteristics of Included Studies

The 20 included studies spanned publication years 1982 to 2026, reflecting more than four decades of formulation research on mucoadhesive chlorhexidine delivery. Tables 3 and 4 summarise, respectively, the dosage form/polymer system and the kinetic modelling approach for each included study; The evidence base was dominated by in vitro and ex vivo formulation studies (18/20, 90%), with two studies incorporating a clinical or in vivo human component[13,14]

3.2 Dosage Forms and Polymer Systems

Mucoadhesive tablets and compacts were the most frequently studied dosage form (7/20 studies, 35%), followed by gels, including in situ gelling systems (4/20, 20%), hydrogels (3/20, 15%), oral films (2/20, 10%), freeze-dried matrices/inserts (2/20, 10%), a patch formulation (1/20, 5%), and a nanoparticle-based spray-dried gargle (1/20, 5%) (Table 3).

Table 3. Distribution of dosage forms across included studies.

Dosage Form	n	Representative Studies (ref. no.)
Mucoadhesive tablets/compacts	7	Ceschel et al.,[2]; Al-Ani et al.,[7]; Al-Ani et al.,[8] Coessens et al.,[13]; Irwin et al.,[14]; Akbari et al.,[15]; Ambrogi et al.,[16]
Gels (aqueous/in situ)	4	Fini et al.,[4]; Ashfaq et al.,[11]; Dinte[17]; Ivanova et al.,[20]
Hydrogels	3	Garcia et al.,[1]; Wangvet al.,[19]; (Al-Aniet al.,[8] hydrogel-tablet hybrid)
Films (oral/thin)	2	Gajdziok et al.,[6]; Lim et al.,[10]
Patches	1	Cavallari et al.,[12]
Freeze-dried matrices/inserts	2	Abruzzo et al., [5]; Giordanet al.,i[9]
Nanoparticle-based (spray-dried gargle)	1	Rai et al.,[3]

Cellulose derivatives principally hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose (CMC/NaCMC), hydroxyethylcellulose (HEC), and hydroxypropyl cellulose (HPC) were the most commonly employed mucoadhesive polymers, appearing either alone or in combination in 12 of the 20 included studies. Chitosan, alginate, and other polysaccharide-based systems (psyllium, xanthan gum, sodium hyaluronate, carmellose) featured in 8 studies, reflecting growing interest in naturally derived mucoadhesive carriers. Poloxamer 407 (P407), a thermosensitive surfactant polymer, was used as a release-modulating co-polymer in three tablet/gel formulations[7,8,20], consistently associated with increased and more rapid CHX release attributed to its surfactant and hydrogel-forming properties.

3.3 Release Kinetics Modelling

Of the 20 included studies, only 8 (40%) applied formal mathematical modelling of CHX release kinetics; the remaining 12 (60%) reported descriptive cumulative release profiles, clinical efficacy endpoints, or non-kinetic characterisation data without fitting a named kinetic model (Table 4).

Table 4. Release kinetic models reported across included studies.

Kinetic Model	n	Studies (ref. no.)
Korsmeyer-Peppas (power law)	4	Fini[4]; Al-Ani 2019[7]; Akbari[15]; Ambrogi[16]
Zero-order	2	Cavallari[12]; Al-Ani 2021[8] (co-fit with Hopfenberg)

Kinetic Model	n	Studies (ref. no.)
Higuchi (diffusional)	1	Friedman[18]
Hopfenberg (erosion-controlled)	1	Al-Ani 2021[8]
No kinetic model reported	12	Remaining 12 studies (60% of total)

The Korsmeyer-Peppas (power law) model was the most frequently applied and best-fitting model among studies that performed kinetic modelling (4/8 modelling studies), with reported diffusional exponents (n) predominantly falling in the range 0.45–1.0, indicating anomalous (non-Fickian) transport a combination of diffusion-controlled and polymer relaxation/erosion-controlled release across the majority of tablet and gel formulations[4,7,15,16]. Zero-order kinetics, indicative of erosion-controlled, constant-rate release, was reported in two studies: Cavallari et al.[12], where psyllium-containing patches exhibited zero-order release attributed to a slow polymer swelling rate, and Al-Ani et al.[8], where high-hydrophilicity HPMC/P407/polyol tablet formulations best fitted a combination of zero-order and Hopfenberg (erosion) models ($R^2 > 0.99$). The earliest included study (Friedman et al.[18]) established conformity to the Higuchi diffusional model for CHX release from ethyl cellulose ± polyethylene glycol cast films, demonstrating sustained release over several months among the longest release durations reported in the included literature.

3.4 Release Duration and Magnitude

Reported CHX release durations and magnitudes varied substantially according to dosage form and polymer composition. Short-to-intermediate release windows (2–4 hours) were typical of buccal tablets and gels designed for acute or single-application use (Ceschel et al.[2]; Al-Ani et al.[7]; Al-Ani et al.[8]), with cumulative release commonly reaching 60–95% within this period. Intermediate release durations (8–24 hours) were observed in mucoadhesive tablets and compacts incorporating ionic polymer interactions with cationic CHX (Ambrogi et al.[16]: 85–90% release at 24 h for HEC/MCM-41 tablets), while formulations incorporating anionic carboxymethylcellulose alone frequently exhibited incomplete release (<45% at 24 h), attributed to electrostatic trapping of the cationic CHX molecule by the anionic polymer backbone a mechanism independently reported in both Fini et al.[4] and Ambrogi et al.[16]. At the extended end of the spectrum, Friedman et al.[18] reported sustained CHX release over several months from ethyl cellulose films, and Rai et al.[3] reported sustained release over 10 hours from spray-dried alginate nanoparticles with 87% permeation by 12 hours. Notably, Lim et al.[10] reported an atypical finding in which CHX release was consistently restricted to ≤10% of initial loading from co-loaded mucoadhesive films, in marked contrast to co-formulated diclofenac, betamethasone, and lidocaine, which exceeded 50% release within 30 minutes from the same films, suggesting a formulation-specific interaction limiting CHX diffusion that was not observed for the co-loaded non-cationic drugs.

3.5 Influence of Polymer–Drug Interaction on Release

A recurring mechanistic theme across the included literature was the electrostatic interaction between the di-cationic CHX molecule and anionic polymer functional groups. Fini et al.[4] demonstrated that CMC-containing gels slowed CHX release relative to non-ionic HPMC or HPC gels, attributing this to ionic binding between the carboxylate groups of CMC and the cationic charges of CHX. This mechanism was corroborated by Ambrogi et al.[16], where NaCMC-containing tablets showed markedly incomplete release (<45% at 24 h) compared with non-ionic HEC-containing tablets (85–90% at 24 h), and by Giordani et al.[9] and Abruzzo et al.[5], both of which identified polyanionic polymer selection (alginate, hyaluronate) as a key modulator of CHX release and mucoadhesive performance in buccal and vaginal matrices. Conversely, non-ionic cellulose derivatives (HPMC, HEC) and thermosensitive surfactant polymers (P407) were consistently associated with faster and more complete CHX release, mediated primarily by polymer swelling, gel-layer erosion, and surfactant-assisted solubilisation rather than ionic trapping.

4. Discussion

4.1 Summary of Principal Findings

This systematic review identified 20 studies investigating the release of chlorhexidine from mucoadhesive polymeric delivery systems, spanning tablets, gels, hydrogels, films, patches, freeze-dried inserts, and nanoparticle-based carriers. The evidence indicates that release kinetics and magnitude are governed predominantly by two interacting factors: (i) the ionic character of the mucoadhesive polymer, with anionic polymers (CMC, alginate) tending to retard and sometimes substantially limit CHX release through electrostatic complexation with the cationic drug, and (ii) the incorporation of hydrophilic, non-ionic, or surfactant excipients (HPMC, HEC, P407, polyols), which consistently accelerated and increased the extent of release via enhanced swelling, gel-layer erosion, and solubilisation. Where formal kinetic modelling was undertaken, the Korsmeyer-Peppas model was most frequently the best-fitting, with diffusional exponents indicating anomalous (non-Fickian) transport in the majority of tablet and gel systems consistent with the

physical picture of simultaneous drug diffusion through a hydrating polymer matrix and polymer chain relaxation/erosion.

4.2 The Kinetic Modelling Gap

A key finding of this review is that only 40% of included studies applied formal release-kinetics modelling. The majority reported descriptive cumulative release profiles, clinical efficacy endpoints [13], or characterisation data oriented toward formulation optimisation rather than mechanistic release analysis[6,11]. This is a notable methodological gap: without model fitting, it is not possible to directly compare release mechanisms (diffusion- versus erosion-controlled) across studies, nor to extrapolate release behaviour beyond the tested time-points. This gap appears more pronounced in more recent publications describing novel or hybrid delivery platforms (e.g., mussel-inspired adhesive hydrogels, in situ gelling nasal systems, spray-dried nanoparticle gargles), which tend to prioritise qualitative demonstration of sustained-release "capability" and biological performance (antimicrobial efficacy, wound healing, cytocompatibility) over rigorous kinetic characterisation. Future formulation studies on CHX mucoadhesive systems would benefit from routine application of standard kinetic models (zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hopfenberg) alongside biological evaluation to build a more mechanistically comparable evidence base.

4.3 Mechanistic Insights: The Role of Polymer Ionic Character

The consistent observation of restricted CHX release from anionic polymer matrices across independent research groups and decades (Fini et al.[4]; Ambrogi et al.[16]; Lim et al.[10]) represents one of the more robust mechanistic findings to emerge from this review. Because CHX carries a di-cationic charge at physiological pH, its electrostatic affinity for carboxylate- or sulphate-bearing polymers (CMC, alginate, hyaluronate, xanthan gum) creates a dual-edged formulation consideration: such interactions can be exploited deliberately to achieve prolonged, sustained local release (as intended in several vaginal and periodontal-pocket formulations reviewed here), but they can equally result in unintentionally incomplete or clinically insufficient drug liberation if not carefully titrated against the required therapeutic concentration and duration. This has direct formulation design implications developers targeting rapid onset of antimicrobial action (e.g., acute infection control) may be better served by non-ionic or surfactant-modified polymer systems (HPMC, P407), while those targeting prolonged, low-level antiseptic maintenance (e.g., periodontal pocket therapy, vaginal antisepsis) may deliberately select anionic polymer systems to slow release, provided adequate total drug loading is confirmed to compensate for incomplete liberation.

4.4 Clinical and Translational Relevance

Few included studies incorporated in vivo or clinical outcome data. Coessens et al.[13] demonstrated that bioadhesive tablets containing 40 mg CHX achieved plaque-inhibition efficacy comparable to standard 0.2% CHX mouth rinse in a human crossover trial, while also identifying clinically relevant local side effects (unpleasant taste, superficial mucosal lesions) that are not captured by in vitro release data alone. Similarly, Irwin et al.[14] confirmed that in vitro release profiles translated to salivary CHX concentrations exceeding the minimum inhibitory concentration of common oral pathogens in human volunteers. These findings underscore an important caveat for the broader evidence base: the large majority of reviewed release-kinetics data are derived from in vitro or ex vivo models, and translation to actual mucosal residence, salivary dilution, and clinical efficacy cannot be assumed without direct confirmation. This represents a priority direction for future research, particularly for the more recently developed platforms in this review (nanoparticle gargles, in situ gelling systems, mussel-inspired hydrogels) that have thus far been evaluated predominantly in vitro or in small-animal models.

4.5 Heterogeneity and Comparability of the Evidence Base

The included studies exhibited substantial heterogeneity in release testing methodology — dissolution apparatus (USP Apparatus I/paddle, Franz diffusion cells, custom flow-through devices), release media (phosphate buffer at varying pH, artificial saliva, deionised water), temperature, and sampling duration. This heterogeneity, consistent with the broader mucoadhesive drug delivery literature, precluded meta-analytic pooling of release data and is the principal reason a narrative synthesis approach was adopted. Where similarity/difference factors (f1/f2) were reported (Al-Ani et al.[7]), or where controlled-flow-rate methods designed to mimic salivary flow were used alongside compendial apparatus (Al-Ani et al.[8]), closer alignment with the physiological oral environment was achieved, and these approaches are recommended as a methodological benchmark for future comparative studies in this field.

4.6 Limitations

- Search restricted to English-language publications may have excluded relevant non-English formulation studies.Grey literature (Google Scholar) was screened only to a limited depth (first 100–200 results), and conference proceedings/theses were not systematically searched.

4.7 Conclusion

Chlorhexidine release from mucoadhesive polymeric delivery systems is governed principally by the ionic

character of the carrier polymer and the presence of hydrophilic or surfactant excipients, with anomalous (non-Fickian) transport, best described by the Korsmeyer-Peppas model, predominating where formal kinetic analysis was undertaken. However, fewer than half of the studies identified in this review applied formal kinetic modelling, representing a clear opportunity for methodological standardisation in future formulation research. Non-ionic cellulose derivatives and surfactant polymers such as poloxamer 407 offer a reliable route to rapid, extensive CHX release, while anionic polymers such as carboxymethylcellulose and alginate provide a mechanism for deliberately prolonged, sustained-release systems provided total drug loading is calibrated to compensate for incomplete liberation. Future research should prioritise standardised kinetic modelling, physiologically relevant release testing such as controlled salivary flow-rate methods and expanded in vivo/clinical validation to strengthen the translational relevance of this substantial in vitro evidence base.

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