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Nanoparticle and Hydrogel Drug Delivery Vehicles for Stimuli-Responsive and Sustained Controlled Release of Active Pharmaceutical Ingredients: A Systematic Review Protocol

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 March 2026 and was last updated on 27 March 2026.

INTRODUCTION

Review question / Objective The aim of this systematic review is to comprehensively synthesise and critically compare the in vitro and in vivo controlled release performance of five major drug delivery vehicle classes — polymeric nanoparticles (PLGA, chitosan), lipid nanoparticles (ionisable LNPs, SLNs, NLCs), inorganic nanoparticles (MSNs, AuNPs, IONPs), hydrogels (natural and synthetic), and injectable in situ-forming depot systems for stimuli-responsive and sustained release of active pharmaceutical ingredients (APIs).

Specific questions addressed:
(1) What quantitative release performance (cumulative % release, stimuli-response ratio, release duration) is achieved by each vehicle class across stimuli-responsive and sustained release modalities?
(2) Which mathematical release kinetic models (zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Weibull) best characterise drug release from each vehicle class, and what Korsmeyer-Peppas n values are reported?
(3) What in vivo pharmacokinetic parameters (AUC, Cmax, t½, bioavailability vs free API) are achieved in preclinical and clinical studies?
(4) What are the principal in vitro-in vivo correlation (IVIVC), safety, and translational barriers limiting clinical adoption of each platform?

Rationale Despite the clinical validation of several nanoparticulate and hydrogel platforms i.e., ionisable LNP-based mRNA vaccines (BNT162b2, mRNA-1273), PLGA long-acting injectable antiretroviral regimens (Cabenuva®), and emerging NP-hydrogel composite systems, no systematic review has comprehensively synthesised and cross-compared the quantitative release performance and kinetic modelling data of all five

major vehicle classes within a unified analytical framework. Release kinetics data are inconsistently reported across the literature, with fewer than 40% of studies providing AIC/BIC goodness-of-fit statistics alongside R^2 values, and the mechanistic interpretation of Korsmeyer-Peppas n values is frequently omitted or incorrect. This review will address these specific evidence gaps, provide a cross-platform comparative kinetic analysis, and identify the most critical translational barriers for each vehicle class.

Condition being studied This review addresses the physicochemical and biopharmaceutical performance of drug delivery vehicle systems for controlled and stimuli-responsive API release, with therapeutic applications spanning oncology, infectious diseases (HIV/AIDS, mRNA vaccines), neurological disorders, cardiovascular disease, and inflammatory conditions. The review is not restricted to a single disease; it examines vehicle platform performance across all API classes (small molecules, peptides/proteins, nucleic acids) and therapeutic contexts.

METHODS

Search strategy Five electronic databases will be searched from January 2015 to March 2026: MEDLINE (PubMed), Embase, Web of Science Core Collection, Scopus, and Cochrane CENTRAL, supplemented by ClinicalTrials.gov, WHO ICTRP, and EU CTR.

Vehicle: nanoparticles, PLGA, chitosan nanoparticles, lipid nanoparticles, ionisable lipid nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, mesoporous silica nanoparticles, gold nanoparticles, iron oxide nanoparticles, hydrogel, injectable depot, in situ forming implant, long-acting injectable, respectively.
Release mechanism: controlled release, sustained release, stimuli-responsive, pH-responsive, thermo-responsive, thermosensitive, redox-responsive, photoresponsive, light-triggered, enzyme-responsive, magnetically triggered, respectively.
API/outcome: drug release kinetics, in vitro release, drug delivery, release profile, bioavailability, pharmacokinetics, respectively.

Participant or population Drug delivery vehicle systems: polymeric NPs (PLGA, PLA, chitosan, PAMAM dendrimers), lipid NPs (ionisable LNPs, SLNs, NLCs), inorganic NPs (MSNs, AuNPs, IONPs), hydrogels (natural: alginate, hyaluronic acid, gelatin, chitosan; synthetic: PNIPAM, PEG-based, polyacrylamide-based), and injectable in situ-forming depot systems (PLGA-NMP, PLA-NMP, PLGA-DMSO, ISFIs) loaded with any small-molecule, peptide/protein, or nucleic acid API.

Ineligible: liposomes as sole vehicle; polymeric micelles without NP/hydrogel component; macroscale surgical implants without nanoscale components; purely cosmetic or nutraceutical applications.

Intervention Stimuli-responsive controlled release / sustained (≥24 h) drug release from eligible vehicle classes.
Eligible stimuli types:
Endogenous: pH gradient (tumour/endosomal acidification); redox potential (elevated GSH); enzyme activity (MMPs, lipases, NQO1); glucose; H2O2
Physical/exogenous: temperature (LCST-responsive; mild hyperthermia); near-infrared or visible light; magnetic field; ultrasound
Sustained/passive: any release lasting ≥ 24 hours without a specific external trigger
Multi-stimuli: dual- or triple-stimuli responsive systems.

Comparator Free drug (unencapsulated API) at the same dose — for in vivo pharmacokinetic comparison
Alternative vehicle formulation of the same API
Absence of triggering stimulus (% release with vs without stimulus at the same time point)
Placebo vehicle in cytotoxicity studies
Studies without explicit comparator (single-group in vitro release characterisation) are eligible if quantified release profiles and kinetic model parameters are reported.

Study designs to be included In vitro release studies: quantified release profiles using validated apparatus (USP paddle, basket, Franz cell, flow-through, or equivalent), with reported release medium, temperature, and ≥3 time points. In vivo preclinical PK studies: animal studies reporting AUC, Cmax, t½ for encapsulated vs free drug. Phase I, II, and III clinical trials reporting PK or PD endpoints. Case series and observational studies reporting real-world PK data for approved controlled-release formulations. Exclusion: purely in silico studies; patents without experimental data; conference abstracts.

Eligibility criteria Inclusion Criteria:
1. Vehicle type: any eligible system from Item 12
2. Release mechanism: stimuli-responsive (any from Item 13) OR sustained (≥24 h)

3. API: any small molecule, peptide/protein, or nucleic acid
4. Outcomes: cumulative % release at ≥3 time points OR in vivo PK parameters
5. Language: English
6. Dates: January 2015 – March 2026
7. Study design: per Item 15

Exclusion Criteria:
1. Liposomes as sole vehicle
2. Purely in silico/computational studies without experimental data
3. Cosmetic or nutraceutical applications without pharmaceutical/therapeutic context
4. Encapsulation efficiency reported without any release profile
5. Conference abstracts without peer-reviewed full publication
6. Non-English language publications
7. Publications before January 2015
8. Macroscale surgical implants without nanoscale components.

Information sources Electronic databases:
• MEDLINE (via PubMed)
• Embase (via Elsevier)
• Web of Science Core Collection (Clarivate)
• Scopus (Elsevier)
• Cochrane CENTRAL

Clinical trial registries:
• ClinicalTrials.gov
• WHO ICTRP
• EU Clinical Trials Register

Additional sources:
• Hand-searching of reference lists of included studies and relevant systematic reviews
• Hand-searching of Journal of Controlled Release, Biomaterials, Advanced Drug Delivery Reviews, ACS Nano, and Nanomedicine (2023–2026)
• FDA Guidance Documents database (nanomaterial drug products)
• FDA Orange Book (approved LAI formulations).

Main outcome(s) 1. Cumulative percentage drug release (%): quantified in vitro release at pre-specified time points (24 h, 48 h, 72 h, 7 d, 14 d, 30 d, and the final reported time point)
2. Korsmeyer-Peppas release exponent n: mechanistic discriminator (n0.85 super Case II)
3. Stimuli-response ratio: (% release under trigger) / (% release without trigger) at the same time point
4. In vivo pharmacokinetic parameters (where reported): AUC (ng·h/mL), Cmax (ng/mL), t½ (h), and relative bioavailability vs free API (%).

Additional outcome(s) 1. Encapsulation efficiency (%)
2. Particle size (nm) and polydispersity index (PDI)
3. Zeta potential (mV)
4. In vitro cytotoxicity: IC50 or % cell viability at specified concentrations
5. Goodness-of-fit statistics: R^2, AIC, BIC where reported
6. Stimuli trigger threshold (pH value, temperature, GSH concentration) at which >50% release is achieved
7. Duration of sustained release: total time to 80% cumulative release (t80%).

Data management Screening: Two independent reviewers will use Rayyan QCRI (www.rayyan.ai) for title/abstract screening followed by full-text assessment. Discrepancies resolved by discussion; adjudication by third reviewer if needed. Cohen's kappa (κ) will be calculated; κ≥0.80 considered satisfactory.

Data extraction: Standardised electronic extraction form (Microsoft Excel or Covidence), pilot-tested on five randomly selected studies. Extraction performed independently in duplicate. Variables extracted: vehicle type; fabrication method; API identity, MW, BCS class; particle size, PDI, zeta potential; encapsulation efficiency; release medium, apparatus, temperature; cumulative % release data; kinetic model type and parameters (n, kKP, R^2, AIC, BIC); stimuli type, magnitude, and response ratio; in vivo PK parameters; quality assessment ratings.

Software: Rayyan (screening); Microsoft Excel or Covidence (extraction); R v≥4.3.0 with meta package (statistical analysis).

Quality assessment / Risk of bias analysis Risk of bias tools matched to study design:
1. In vitro physicochemical studies --> Custom 8-item quality checklist: (i) analytical method validation; (ii) release medium physiological relevance; (iii) apparatus standardisation; (iv) replicate number (≥3); (v) statistical reporting (mean±SD); (vi) mass balance reporting; (vii) sink condition stability; (viii) kinetic model reporting (R^2 minimum; AIC/BIC preferred)
2. Preclinical in vivo studies --> SYRCLE Risk of Bias Tool (Hooijmans et al., BMC Med Res Methodol. 2014;14:43): sequence generation; baseline characteristics; allocation concealment; random housing; blinding; random outcome assessment; incomplete data; selective reporting
3. Clinical trials --> Cochrane Risk of Bias 2 (RoB 2; Sterne et al., BMJ. 2019;366:l4898): randomisation; deviations from intervention;

missing outcome data; measurement of outcomes; selection of reported results
4. Kinetic modelling studies --> Custom 6-item checklist: model selection rationale; goodness-of-fit metric (R^2, AIC, BIC); confidence intervals; mechanistic interpretation of n; ≥3 models compared; n boundary reporting (0.43, 0.85, 1.0)
Overall certainty: GRADE approach where ≥3 comparable studies available for a given outcome.

Strategy of data synthesis Primary synthesis: Narrative synthesis structured by vehicle class, then by release mechanism (stimuli-responsive vs sustained), given anticipated high heterogeneity.
Quantitative synthesis: Korsmeyer-Peppas n values tabulated by vehicle class (median, IQR, range). Stimuli-response ratios calculated as a standardised comparability measure. Descriptive pooling (median, range) of comparable outcome metrics within vehicle class subgroups.
Meta-analysis: Where more than 3 studies report the same outcome metric using comparable methods, random-effects meta-analysis will be performed (DerSimonian-Laird estimator). Heterogeneity assessed by I^2 (substantial: I^2 is over 50%). Publication bias assessed by funnel plot asymmetry (Egger's test) where more than 10 comparable studies pooled.
Deviations from this pre-specified strategy will be reported as 'differences between protocol and review' in the published paper.

Subgroup analysis Pre-specified subgroup analyses (minimum 5 studies per subgroup required):
1. Vehicle class: polymeric NPs vs lipid NPs vs inorganic NPs vs hydrogel vs injectable depot
2. Stimuli type: pH vs temperature vs redox vs light vs enzyme vs magnetic
3. API class: small molecule vs peptide/protein vs nucleic acid
4. Release medium: simulated physiological vs cell culture vs in vivo (preclinical) vs in vivo (clinical)
5. Fabrication method: emulsion-solvent evaporation vs nanoprecipitation vs microfluidics vs self-assembly.

Sensitivity analysis Pre-specified sensitivity analyses:
1. Exclusion of studies rated high risk of bias by SYRCLE or RoB 2
2. Restriction to studies using phosphate-buffered saline (PBS, pH 7.4) as release medium
3. Restriction to studies providing AIC/BIC statistics alongside R^2 for kinetic model selection
4. Inclusion/exclusion of studies published before 2020 (temporal trend analysis).

Language restriction Only studies published in English will be included. Non-English records identified during searching will be noted and listed as excluded studies in the PRISMA 2020 flow diagram.

Country(ies) involved România.

Keywords drug delivery; nanoparticles; hydrogel; controlled release; stimuli-responsive; PLGA; lipid nanoparticles; mesoporous silica; injectable depot; release kinetics; Korsmeyer-Peppas; NP-hydrogel composite; systematic.

Dissemination plans The completed systematic review will be submitted for publication in the Journal of Controlled Release (Elsevier; SCIE, IF ~10.5; ISSN 0168-3659). The INPLASY registration number and DOI will be cited in the Methods section. Findings will be disseminated through oral/poster presentations at AAPS Annual Meeting and CRS Annual Meeting, and through the corresponding author's institutional research communications.

Contributions of each author
Author 1 - Paul Albu - Contribution: Conceiving the review; designing the review; coordinating the review; data collection; data management; analysis of data; interpretation of data; writing the protocol.
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