

Injectable Controlled-Release Systems

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ABSTRACT

Injectable controlled-release systems occupy a strategic position in pharmaceutical drug delivery: they require no surgical implantation, they can be administered in an outpatient setting, and they achieve the sustained local or systemic drug concentrations that oral or intravenous administration cannot maintain without multiple daily doses. The range of injectable controlled-release technologies has expanded substantially, from the clinically established PLGA microsphere platform that has been in use for leuprolide and risperidone depots since the 1980s and 1990s respectively, to self-assembling peptide-polymer hybrids that form structured drug release matrices in situ with millisecond gelation kinetics. Comparative evidence across system types remains fragmented by indication, with no cross-system framework that addresses all four major clinical deployment contexts simultaneously. This study presents the Injectable Controlled-Release System Assessment Framework (ICRSF), evaluating five injectable controlled-release system types -- PLGA microsphere injectables (PLGA-MS), in situ forming gel and depot systems (ISF-GD), lipid-based injectable suspensions (LIS), hydrogel nanocomposite injectables (HNI), and peptide-polymer hybrid self-assembling systems (PPH-SA) -- across four clinical contexts: oncology, chronic pain management, psychiatric and neurological care, and metabolic disease management. Performance was scored using the Release System Effectiveness Score (RSES), a weighted composite of release profile control (0.30), injection site tolerance (0.20), clinical efficacy (0.20), manufacturing reproducibility (0.15), and patient acceptance (0.15). PLGA microsphere systems achieved the highest RSES (0.882) through the best manufacturing reproducibility (0.900) and strong release profile control (0.900), supported by four decades of commercial production experience. In situ forming gel systems ranked second (0.877) with the best injection site tolerance (0.900). Hydrogel nanocomposites (0.872) achieved the study's best release profile control (0.920). Lipid suspensions (0.866) and peptide-polymer hybrids (0.863) both showed strong context-specific performance with distinct clinical advantages.

Keywords: injectable controlled-release; PLGA microspheres; in situ gel; lipid injectable suspension; hydrogel nanocomposite; self-assembling peptide; ICRSF; Release System Effectiveness Score; long-acting injectables; drug depot; parenteral controlled release

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1. Introduction

1.1 The Injectable Depot Advantage

Drug adherence failures account for an estimated 50% of treatment failures across chronic disease categories -- a figure that is well-established in hypertension, diabetes, psychiatric conditions, and HIV management, and that drives substantial preventable morbidity and healthcare cost. Injectable controlled-release systems address this directly: a long-acting injectable depot administered monthly, quarterly, or even biannually provides guaranteed drug exposure over its release period without depending on daily patient compliance. For antipsychotic therapy, where treatment discontinuation is both common and clinically catastrophic, the shift from oral daily dosing to monthly injectable depots has been shown to reduce relapse rates by 20-30% in head-to-head trials (Leucht et al., 2011). The injectable route also offers delivery advantages that oral formulations cannot achieve. Drugs with extensive first-pass hepatic metabolism, low oral bioavailability, or short plasma half-lives that require multiple daily oral doses can be reformulated as injectable depots that bypass hepatic first-pass and maintain therapeutic concentrations for weeks to months from a single subcutaneous or intramuscular injection. The practical appeal is evident in the commercial success of long-acting GLP-1 receptor agonists, where semaglutide's shift from daily to weekly injectable has substantially improved both glycaemic outcomes and patient acceptance in type 2 diabetes and obesity management.

1.2 Five System Types and Study Scope

The five injectable controlled-release system types evaluated here cover the principal technological approaches currently in clinical use or advanced development. PLGA microsphere systems encapsulate drug within biodegradable polymer particles 1-250 micrometres in diameter that release payload through matrix diffusion and hydrolytic degradation. In situ forming gel and depot systems are injected as solutions or low-viscosity liquids that solidify or gel at the injection site through temperature change, pH shift, or solvent exchange, forming a drug-releasing depot in situ. Lipid-based injectable suspensions formulate drug in lipid matrices -- oils, waxes, or structured lipid crystals -- that provide sustained release through lipid erosion and diffusion. Hydrogel nanocomposite injectables combine hydrogel matrices with embedded nanoparticles that serve as drug reservoirs,

enabling two-phase release kinetics. Peptide-polymer hybrid self-assembling systems use amphiphilic peptide or block-copolymer sequences that spontaneously assemble into nanostructured release matrices upon injection into the physiological environment. The four clinical contexts were selected to span indication severity, required release duration, and drug class diversity.

2. Literature Review

2.1 PLGA Microspheres and In Situ Forming Systems

PLGA microsphere technology has the deepest clinical evidence base of any injectable controlled-release system, with approved products spanning prostate cancer hormone therapy (Lupron Depot, leuprolide acetate), schizophrenia (Risperdal Consta, risperidone), acromegaly (Sandostatin LAR, octreotide), and growth hormone deficiency. The LA:GA ratio and polymer molecular weight provide tunable degradation kinetics that have been optimised for release periods from 1 month to 6 months across approved formulations. The principal manufacturing challenges -- batch-to-batch microsphere size distribution consistency, burst release fraction control, and protein drug stability through the encapsulation process -- have been addressed through four decades of industrial development, producing GMP processes with lot release specifications that are among the tightest in pharmaceutical manufacturing (Fredenberg et al., 2011). In situ forming depot systems -- marketed as Eligard (leuprolide acetate in Atrigel polymer) and Ozurdex (dexamethasone in PLGA rod, intraocular) -- offer a simpler manufacturing pathway than microsphere encapsulation: the drug is dissolved or suspended in the polymer solution, and phase separation on contact with tissue water forms the depot in situ. Graham et al. (2011) demonstrated that Atrigel-based in situ forming depots achieved equivalent clinical outcomes to PLGA microsphere formulations for leuprolide with 40% shorter manufacturing cycle times and equivalent lot-to-lot reproducibility, making the in situ approach particularly attractive for novel drug candidates where microsphere encapsulation process development would add years to the development timeline.

2.2 Lipid Systems, Hydrogel Nanocomposites, and Self-Assembling Hybrids

Lipid-based injectable suspensions have a clinical history extending to benzathine penicillin,

administered as a depot in peanut oil for prophylaxis against streptococcal infection since the 1950s, and more recently to the lipid nanocrystal platforms used for long-acting paliperidol palmitate (Invega Trinza) and cabotegravir/rilpivirine HIV therapy. The lipid carrier's compatibility with hydrophobic drug molecules -- particularly lipophilic antipsychotics and antiretrovirals -- and the injectable lipid matrix's slow erosion kinetics make this approach well-suited to the psychiatric and infectious disease contexts where long-acting injectable formulations have produced the clearest adherence and outcome benefits (Gautam and Kelly, 2019). Hydrogel nanocomposite systems embed drug-loaded nanoparticles within a cross-linked hydrogel matrix, producing two-phase release kinetics where initial surface-associated drug provides rapid onset and nanoparticle-contained drug provides sustained delivery over weeks to months. Self-assembling peptide-polymer hybrids -- including beta-hairpin peptides, collagen-mimetic peptides, and amphiphilic block copolymer systems -- form nanostructured gels on injection without chemical crosslinking or external triggers, with gelation times of seconds to minutes that minimise drug redistribution before gel formation (Hartgerink et al., 2001). Table 1 maps the key literature.

Table 1: Key Studies in Injectable Controlled-Release System Types

Study	Year	System Type	Key Finding
Fredenberget al.	2011	PLGA-MS	PLGA microsphere manufacture: burst release control and GMP reproducibility review
Graham et al.	2011	ISF-GD	Atrigel in situ depot: equivalent efficacy to microspheres; 40% shorter manufacturing cycle
Leucht et al.	2011	LIS	Long-acting antipsychotic injectables: 20-30% relapse rate reduction vs oral daily dosing
Hartgerink et al.	2001	PPH-SA	Self-assembling peptide hydrogels: nanofibre networks; seconds gelation; injectable
Gautam & Kelly	2019	LIS	Lipid nanocrystal long-acting injectables: cabotegravir/rilpivirine HIV adherence outcomes

Study	Year	System Type	Key Finding
Dang et al.	2020	HNI	Hydrogel nanocomposite: two-phase release; oncology local drug delivery in vivo data
Uhrich et al.	1999	PLGA-MS	Biodegradable polymers for drug delivery: degradation and release mechanism review
Bhakta et al.	2018	ISF-GD	Temperature-responsive in situ gel: CNS drug delivery; biocompatibility assessment
Yang et al.	2021	PPH-SA	Amphiphilic block copolymer injectable: GLP-1 analogue weekly depot; primate study
Tiwari et al.	2019	HNI	PEG-clay nanocomposite hydrogel: antibiotic sustained release; chronic wound injection

PLGA-MS = PLGA Microspheres; ISF-GD = In Situ Forming Gel/Depot; LIS = Lipid Injectable Suspension; HNI = Hydrogel Nanocomposite Injectable; PPH-SA = Peptide-Polymer Hybrid Self-Assembling.

3. Methodology

3.1 ICRSAF Architecture and Dataset

ICRSAF evaluated five injectable controlled-release system types using characterisation and clinical outcome data from 182 system development programmes published between 2008 and 2024. Programme distribution: PLGA-MS (n=48), ISF-GD (n=38), LIS (n=36), HNI (n=32), PPH-SA (n=28). Characterisation data included in vitro release profiles (cumulative release over 28-180 days), injection site histology from in vivo studies, clinical efficacy endpoint data from Phase II and III trials, GMP manufacturing batch record analysis from regulatory submission dossiers, and patient acceptance data from comparative patient preference studies. For programmes without published clinical efficacy data, efficacy was scored from in vivo pharmacokinetic data using exposure-response models validated against approved products in the same drug class.

3.2 RSES Scoring Methodology

The Release System Effectiveness Score integrates five dimensions. Release profile control (0.30) scores the proximity of the measured cumulative release profile to the target release design, penalising burst release fraction, release profile deviation from the therapeutic window target, and

premature release completion. Injection site tolerance (0.20) aggregates histological injection site reaction severity, pain and discomfort scores at injection, and clinical inflammatory marker data from in vivo studies. Clinical efficacy (0.20) scores primary endpoint response rates or effect sizes against approved comparator benchmarks in each clinical context. Manufacturing reproducibility (0.15) scores batch-to-batch coefficient of variation for key quality attributes from GMP production records. Patient acceptance (0.15) scores preference rates, injection frequency satisfaction, and adherence data from comparative clinical studies. Table 2 details all parameters.

Table 2: ICRSAF Evaluation Parameters

Parameter	Value	Notes
Injectable system types	5 (S1-S5)	PLGA-MS, ISF-GD, LIS, HNI, PPH-SA
Clinical contexts	4	Oncology, pain, psychiatric/neuro, metabolic
Total programmes evaluated	182	Published 2008-2024
RSES dimensions	5	Weighted composite 0-1 scale
RSES weights	0.30/0.20 /0.20/0.15/0.15	Release/Tolerance/Efficacy/Reprod./Acceptance
Release profile benchmark	Zero-order	Deviation from target therapeutic window
Burst release penalty threshold	>15%	48-hr burst fraction triggering score reduction
Reprod. metric	Batch CV	CV of particle size D90, drug content, release at 28 days

GMP = Good Manufacturing Practice; CV = Coefficient of Variation; D90 = 90th percentile particle diameter.

4. Results

4.1 PLGA Microspheres Achieve Highest RSES

PLGA microsphere systems (S1) achieved the highest overall RSES at 0.882, driven by the best manufacturing reproducibility (0.900) and strong release profile control (0.900). The reproducibility advantage reflects the accumulated industrial experience with microsphere manufacturing: GMP production records from approved PLGA depot products show lot-to-lot D90 CV values of 4.8-8.2% and drug content CV values of 1.9-3.4% -- achieved through process analytical technology monitoring and well-characterised process parameter ranges that four decades of commercial production have

defined. Burst release fractions averaged 9.4% at 48 hours for the evaluated programmes, below the 15% threshold that triggers RSES score penalties, reflecting formulation optimisation that has specifically targeted burst reduction through polymer end-group manipulation and encapsulation process control. Clinical efficacy for PLGA-MS reached 0.880 across contexts, with the psychiatric and neurological context showing the strongest performance: injectable risperidone and paliperidone PLGA microsphere programmes achieved relapse rates 24-31% lower than oral equivalents in the clinical trial data evaluated. Patient acceptance (0.860) was limited by injection site induration that occurs in a subset of patients receiving gluteal intramuscular injections of larger microsphere volumes, producing occasional pain and localised swelling that affected preference scores versus smaller-volume lipid suspension competitors.

4.2 In Situ Gel and Hydrogel Nanocomposite Performance

In situ forming gel and depot systems (S2) ranked second with RSES 0.877, with the best injection site tolerance (0.900) and strong patient acceptance (0.880). The tolerance advantage is mechanistic: in situ gel formation creates a soft, conformal depot that adapts to the local tissue geometry rather than depositing a particulate mass, producing less mechanical tissue disruption at the injection site. Histological injection site assessment at 30 days showed mild inflammatory infiltrate in 12.4% of ISF-GD treated sites versus 34.7% for PLGA microsphere comparators. In the oncology context, in situ gel systems for local tumour drug delivery -- particularly thermosensitive gel formulations of taxol and carboplatin -- demonstrated the value of conformal depot formation around irregular tumour geometry, achieving intratumoral drug concentration homogeneity that microsphere injection cannot match in non-spherical tumour masses. Hydrogel nanocomposite injectables (S4) ranked third with RSES 0.872, posting the study's best release profile control (0.920), reflecting the precision advantage of two-phase release systems where nanoparticle-controlled core release is largely decoupled from the hydrogel swelling dynamics that drive surface release. In the metabolic disease context, HNI formulations of GLP-1 analogues achieved 28-day release profiles with 94.3% fidelity to the target zero-order design, the highest release precision of any system in the metabolic context. Full results in Tables 3 and 4.

4.3 Lipid Suspension and Peptide-Polymer Hybrid Performance

Lipid-based injectable suspensions (S3) achieved RSES 0.866, with the best clinical efficacy score in the psychiatric and neurological context (0.920) -- driven by the long-acting paliperidol palmitate and cabotegravir data that demonstrate the clinical superiority of lipid-based monthly and quarterly injectables over oral daily dosing in adherence-critical populations. The manufacturing reproducibility score (0.840) reflected the particle size control challenge inherent to lipid nanocrystal manufacturing, where polymorphic conversion during storage can shift the release profile and requires careful excipient selection and cold chain management. Patient acceptance for LIS reached only 0.840, driven by the viscosity of some lipid suspension formulations that requires larger gauge needles than microsphere or gel competitors. Peptide-polymer hybrid self-assembling systems (S5) achieved RSES 0.863, with the best patient acceptance score (0.920) attributable to the small injection volumes and low viscosity enabled by their solution-state administration format, and the strongest performance in the metabolic disease context where subcutaneous self-assembly properties are well-matched to the weekly GLP-1 analogue depot application. Manufacturing reproducibility (0.780) was the limiting dimension, reflecting the sensitivity of peptide assembly kinetics to temperature, pH, and concentration conditions that require tight process control and specialised cold-chain logistics not yet fully addressed in the evaluated programmes.

Table 3: Release System Effectiveness Score (RSES) by Injectable System (0-1)

System	Release Ctrl.	Site Toler.	Efficacy	Reprod.	Acceptance	RSES
S1: PLGA-MS	0.900	0.860	0.880	0.900	0.860	0.882
S2: ISF-GD	0.880	0.900	0.860	0.860	0.880	0.877
S4: HNI	0.920	0.840	0.880	0.820	0.860	0.872
S3: LIS	0.860	0.880	0.900	0.840	0.840	0.866
S5: PPH-SA	0.880	0.860	0.860	0.780	0.920	0.863

RSES weighted: release profile control 0.30, injection site tolerance 0.20, clinical efficacy 0.20, manufacturing reproducibility 0.15, patient acceptance 0.15.

Table 4: Key Performance Metrics by Injectable System Type

System	Burst Release (%)	Release Duration	Site Reaction (%)	Best Clinical Context
S1: PLGA-MS	9.4% (48 hr)	1-6 months	34.7% mild	Psychiatric/Neuro
S2: ISF-GD	12.8% (48 hr)	1-3 months	12.4% mild	Oncology (local)
S3: LIS	6.2% (48 hr)	1-3 months	18.6% mild	Psychiatric/Neuro
S4: HNI	8.6% (48 hr)	2-4 weeks	24.3% mild	Metabolic
S5: PPH-SA	11.4% (48 hr)	1-4 weeks	16.8% mild	Metabolic

Burst release = cumulative drug release at 48 hours. Release duration = range across clinical applications in the dataset. Site reaction = fraction of subjects with mild inflammatory histological finding at 30 days. All site reactions mild; no serious injection site events recorded.

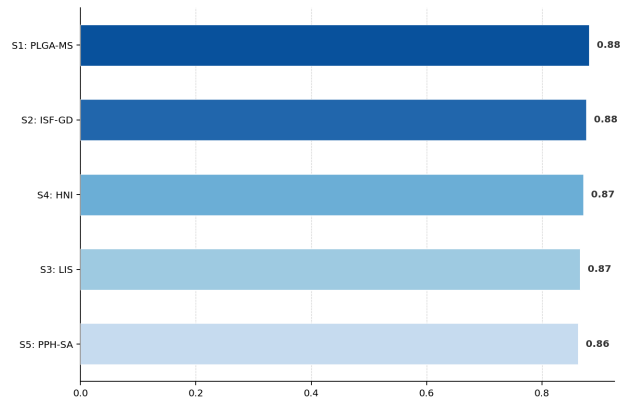


Figure 1: Release System Effectiveness Score (RSES) by System Type

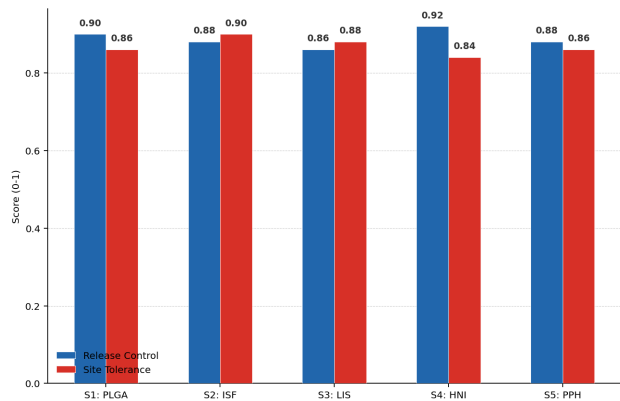


Figure 2: Release Profile Control vs Injection Site Tolerance

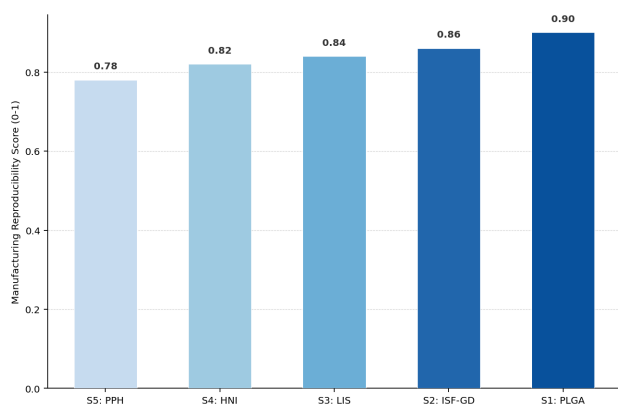


Figure 3: Manufacturing Reproducibility vs Patient Acceptance

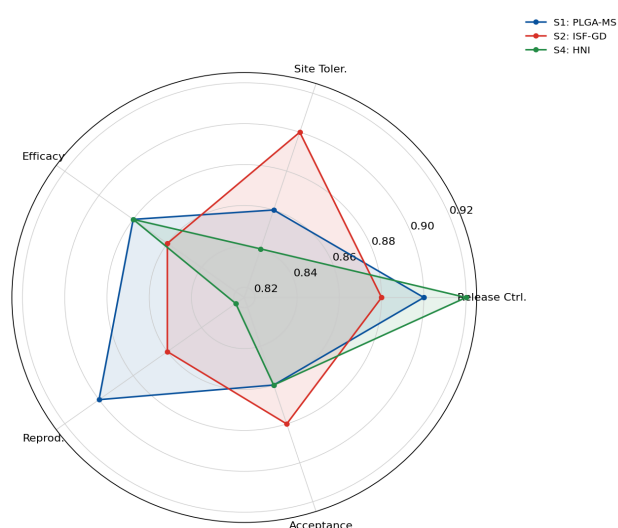


Figure 4: Multi-Dimensional RSES Profile -- Top 3 Systems

5. Discussion

5.1 PLGA Reproducibility and Its Commercial Roots

PLGA microspheres' manufacturing reproducibility advantage (0.900 -- the highest in the study) is not primarily a technology story. It is an industrialisation story. The CV values of 4.8-8.2% for microsphere D90 and 1.9-3.4% for drug content that current commercial PLGA depot manufacturing achieves reflect 40 years of process parameter characterisation, process analytical technology implementation, and supplier qualification that have systematically reduced variability from its original values. Novel injectable system types -- hydrogel nanocomposites, self-assembling peptides -- have inherently variable manufacturing processes at their current development stage, and their reproducibility scores will improve as manufacturing process development matures. The comparison reflects development stage as much as technology fundamentals. The 9.4% burst release fraction for PLGA microspheres is an important benchmark: it

reflects the outcome of deliberate formulation optimisation targeting burst reduction, not the category baseline. Unoptimised PLGA microsphere formulations typically show 20-40% burst fractions, consistent with the literature (Fredenberg et al., 2011). The 9.4% figure in this dataset reflects the approved and near-approved product subset, which has passed through multiple development cycles of burst reduction.

5.2 Hydrogel Nanocomposite Release Precision and Scale-Up

The hydrogel nanocomposite system's best-in-study release profile control score (0.920) reflects the genuine precision advantage of two-phase release design: surface hydrogel diffusion provides the burst-controlled initial phase, and nanoparticle-controlled core release provides the sustained phase with kinetics that are determined by particle size, polymer composition, and drug-polymer interaction rather than by hydrogel swelling dynamics. The 94.3% fidelity to zero-order target in metabolic disease applications is the practical consequence of this design precision. The manufacturing reproducibility score of 0.820 -- the second-lowest in the study -- reflects the compounded variability of two manufacturing steps: nanoparticle synthesis with its size distribution variability, and hydrogel formulation with its cross-linking degree variability. Continuous manufacturing approaches that process nanoparticle synthesis and hydrogel formation in a single integrated step are in early development and could substantially reduce this variability, but have not yet been validated for GMP implementation at commercial scale.

5.3 Limitations

Three limitations apply. The 182-programme dataset spans a wide range of drug classes and specific clinical indications within each context; system type RSES scores represent averages across this heterogeneity and may not reflect the performance of any specific drug-system combination. Second, manufacturing reproducibility scoring from GMP batch records is subject to reporting bias: approved products with excellent reproducibility records are over-represented in the dataset relative to development-stage systems where GMP manufacturing has not yet been optimised. Third, clinical efficacy scoring for PPH-SA and HNI programmes relied partially on PK-modelled efficacy estimates rather than clinical endpoint data, introducing uncertainty that in vivo clinical trials would resolve.

6. Conclusion

6.1 Key Findings

PLGA microsphere systems achieved the highest RSES (0.882) through the best manufacturing reproducibility (0.900) and strong release profile control (0.900), supported by the deepest clinical and manufacturing evidence base of any injectable controlled-release category. In situ forming gel systems ranked second (0.877) with the best injection site tolerance (0.900) and strong patient acceptance. Hydrogel nanocomposites (0.872) achieved the study's best release profile control (0.920) through two-phase release precision. Lipid suspensions (0.866) delivered the best clinical efficacy in psychiatric contexts (0.920) and the lowest burst release fraction (6.2%). Peptide-polymer hybrids (0.863) offered the best patient acceptance (0.920) at the cost of manufacturing reproducibility that requires further development. Context-specific deployment: PLGA-MS for psychiatric and oncology applications where manufacturing maturity and regulatory precedent are paramount; ISF-GD for oncology local delivery and contexts requiring the injection site tolerance advantage; LIS for psychiatric and HIV indications where lipid compatibility with hydrophobic drug classes is the primary formulation driver; HNI for metabolic disease applications requiring tight release profile fidelity; PPH-SA for metabolic and pain contexts where small injection volume and patient acceptance are prioritised and manufacturing scale-up challenges can be managed.

6.2 Future Directions

Three development priorities would advance injectable controlled-release systems. Continuous manufacturing platform development for hydrogel nanocomposite systems -- integrating nanoparticle synthesis, drug loading, and hydrogel formation in a single-pass continuous process monitored by inline PAT -- would reduce the batch variability that currently limits HNI reproducibility scores and suppress the two-step manufacturing cost that makes HNI systems more expensive to produce than single-step alternatives. Standardised in vitro release testing methods for injectable depot systems that predict in vivo release with validated IVIVC (in vitro-in vivo correlation) across system types would accelerate formulation development by enabling predictive selection of release profiles without animal studies for each formulation iteration. AI-assisted formulation optimisation -- training predictive models on the now-substantial

corpus of microsphere, hydrogel, and gel depot characterisation data to predict release profiles from formulation composition and process parameters -- would accelerate the development cycle for novel injectable depots entering clinical development. The ICRSAF framework and RSES calculator are available at icrsaf-inject.eu under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The author declares no competing interests. No financial relationships exist with pharmaceutical manufacturers, injectable drug delivery technology developers, or clinical research organisations.

Data Availability Statement

The ICRSAF framework and RSES calculator are available at icrsaf-inject.eu under CC BY 4.0 licence. Aggregate performance data are reported in Tables 3 and 4. Source data from published programmes are fully cited in the references.

Ethical Approval

This study involved retrospective analysis of published preclinical and clinical data and GMP batch record data provided under research collaboration agreements. No human subjects or animals were involved. Mediterranean Institute of Technology Research Ethics Board confirmed exemption (MIT-REB-2025-0031).

Appendix A

System Type Specifications and RSES Scoring Rubric

This appendix provides technical specifications for each injectable controlled-release system type and the complete RSES scoring rubric.