Available online www.ijpras.com

International Journal of Pharmaceutical Research & Allied Sciences, 2026, 15(1):44-53
https://doi.org/10.51847/4UdUjIDkNq

Original Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Self-Correcting Pharmaceutical Formulations That Sense Biological Conditions, Predict Performance Drift, and Adapt Drug Release across Changing Patient States

George Wilson[1]*, Chloe Bennett[2], Ethan Wright[1], Jack Turner[3]

[1]Department of Self-Correcting Formulations and Biological Sensing, Faculty of Pharmacy, University of Dundee, Dundee, United Kingdom.
[2]Department of Performance Drift Prediction, Faculty of Pharmacy, Newcastle University, Newcastle, United Kingdom.
[3]Department of Adaptive Drug Release and Patient States, Faculty of Pharmacy, University of Aberdeen, Aberdeen, United Kingdom.

***Email:** g.wilson@dundee.ac.uk*

ABSTRACT

Pharmaceutical dosage forms are conventionally designed around predetermined release profiles, even though the physiological conditions governing dissolution, transport, absorption, clearance, tissue access, and therapeutic need can change during use. Stimuli-responsive materials partly address this mismatch, but a material reaction to pH, glucose, enzymes, reactive oxygen species, or another cue does not by itself establish reliable patient-state interpretation or safe adaptation. This article proposes a non-empirical closed-loop formulation theory for products that sense biological conditions, estimate patient and formulation states, predict performance drift, and modify drug release within explicit constraints. The proposed Sensing–Prediction–Adaptation with Constraint and Fail-Safe architecture separates signal acquisition, signal-quality assessment, latent-state estimation, drift prediction, bounded release control, material or device actuation, response verification, and fallback behaviour. It defines self-correction as verified, uncertainty-aware adjustment of release relative to an intended release–exposure relationship, rather than simple stimulus-triggered cargo liberation. Stability is treated dynamically through cycling, hysteresis, fatigue, recovery, and reservoir integrity; reversibility requires attenuation when the triggering state resolves; and fail-safe behaviour requires a bounded release condition when sensing, prediction, or actuation becomes unreliable. Validation must use changing and confounded physiological conditions, connect material response to exposure and therapeutic consequence, and test fault states rather than only nominal performance. Manufacturing translation requires traceable material attributes, process controls, data lineage, comparability, usability, and product-specific clinical evidence. The principal contribution is an original conceptual architecture and testable evaluation logic. It remains hypothesis-generating, indication- and dosage-form-specific, and unsuitable for clinical or regulatory decision use until empirically validated.

Key words: *Formulation, Pharmaceutical formulation, Dosage form, Excipient, Manufacturability, Stability*
Received: 19 October 2025; **Revised:** 28 January 2026; **Accepted:** 01 February 2026

INTRODUCTION

Precision drug-delivery platforms can alter localization, protection, transport, and release, yet their performance remains conditioned by biological barriers and heterogeneous physiological environments. A formulation optimized around an average or baseline state may therefore preserve its manufactured attributes while producing

a different release–exposure relationship when local chemistry, tissue access, transit, disease activity, or treatment demand changes [1].

Individualized therapy cannot be reduced to selecting a different nominal dose. It requires patient information to influence product design, manufacturing, provision, and use, including the dosage form's ability to accommodate relevant variability rather than merely documenting it after development [2]. The unresolved question is how a pharmaceutical product could respond to changing conditions without converting biological noise or model error into inappropriate release.

Patient-centric product design already emphasizes that dosage-form attributes, administration conditions, acceptability, and therapeutic goals should be considered during development [3]. However, patient centricity does not itself imply autonomous adaptation. A convenient, acceptable, or personalized dosage form may still follow a fixed release program and may remain unable to distinguish altered patient need from material aging, sensor interference, or environmental change.

This Original Closed-Loop Formulation Theory Article proposes the Sensing–Prediction–Adaptation with Constraint and Fail-Safe architecture (SPAC-FS). The contribution defines self-correction, separates its functional layers, specifies their relationships, and establishes testable boundaries for stability, reversibility, validation, manufacturing, and translation. It is an original conceptual synthesis, not an empirical demonstration, clinical recommendation, regulatory framework, or claim that every dosage form should become adaptive.

From predetermined release to adaptive formulation behaviour

Predetermined release is governed primarily by properties fixed before administration, including composition, geometry, porosity, swelling, diffusion, erosion, degradation, and drug–matrix interactions. Hydrogel networks illustrate how these variables can tune loading and transport across immediate, sustained, or long-acting delivery, while the resulting behaviour commonly remains programmed around assumed use conditions [4].

Stimuli-responsive formulations add a conditional material response. Injectable hydrogels may alter swelling, degradation, permeability, or molecular transport after changes in temperature, pH, ionic environment, enzymes, or other local factors [5]. This establishes responsiveness, but the inference that produced the response is usually implicit: the material reacts to a cue without independently determining whether the cue is reliable, clinically relevant, confounded, or within the intended operating domain.

Glucose-responsive insulin systems make the distinction especially clear. They support the plausibility of demand-linked release, yet translation remains constrained by response fidelity, kinetics, safety, manufacturability, stability, and the difficulty of matching a biochemical trigger to an appropriate pharmacological action [6]. Evidence of stimulus-linked release therefore supports an adaptive mechanism, not proof of generalized self-correction.

SPAC-FS proposes a stricter hierarchy. Controlled release follows a predetermined program; responsive release changes after a detected physicochemical input; adaptive release selects a bounded action according to an inferred state; and self-correcting release additionally predicts drift, verifies the consequence, updates uncertainty, and enters a safe fallback when confidence is inadequate. These categories are proposed analytical distinctions and require product-specific empirical testing.

Biological signals and patient-state variation

Patient state is defined here as a latent, time-varying combination of physiological, pathological, behavioural, treatment, and product-interaction conditions that can modify release, absorption, exposure, or therapeutic need. Gastrointestinal pH, fluid volume, motility, transit, bile composition, food effects, and luminal contents vary within and between individuals and can materially change oral dissolution, absorption, and pharmacokinetics [7]. This route-specific evidence shows why baseline formulation assumptions may become unreliable during use.

Sex-related differences in anatomy, body composition, hormones, enzymes, transporters, renal function, immune activity, and treatment response can also alter drug disposition and the suitability of standardized dosage-form assumptions [8]. Such characteristics are not necessarily direct sensor targets; they may instead operate as contextual covariates that change how an observed signal should be interpreted.

Disease microenvironments add further complexity. Inflammatory intestinal states can change barrier integrity, immune activity, redox conditions, enzymes, mucus, microbiota-associated functions, and local physicochemical cues, creating opportunities for responsive delivery while also increasing heterogeneity and confounding [9]. Taken together, the selected evidence shows that patient state can alter both the magnitude and meaning of biological cues through gastrointestinal, sex-related, and disease-microenvironment variability [7-9].

A biological signal is therefore not equivalent to the state itself. It is an observable proxy whose informativeness depends on specificity, location, timing, measurement quality, and causal proximity to the desired release action. The architecture must distinguish target signals from contextual variables and confounders, combine multiple inputs when justified, and represent uncertainty when different states can produce similar observations. No single biomarker can be presumed sufficient across routes, products, diseases, or patients.

Proposed sensing–prediction–adaptation architecture

A closed-loop precedent exists when sensing, processing, and delivery are physically coupled. A mesoporous microneedle–iontophoresis platform has demonstrated integrated glucose monitoring and electrically controlled transdermal insulin delivery in a preclinical system [10]. SPAC-FS treats such integration as evidence that component coupling is technically plausible, while extending the formulation-level question to state interpretation, drift, constraints, verification, and fault handling. **Figure 1** presents the original conceptual synthesis for closed-loop self-correcting formulation architecture, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

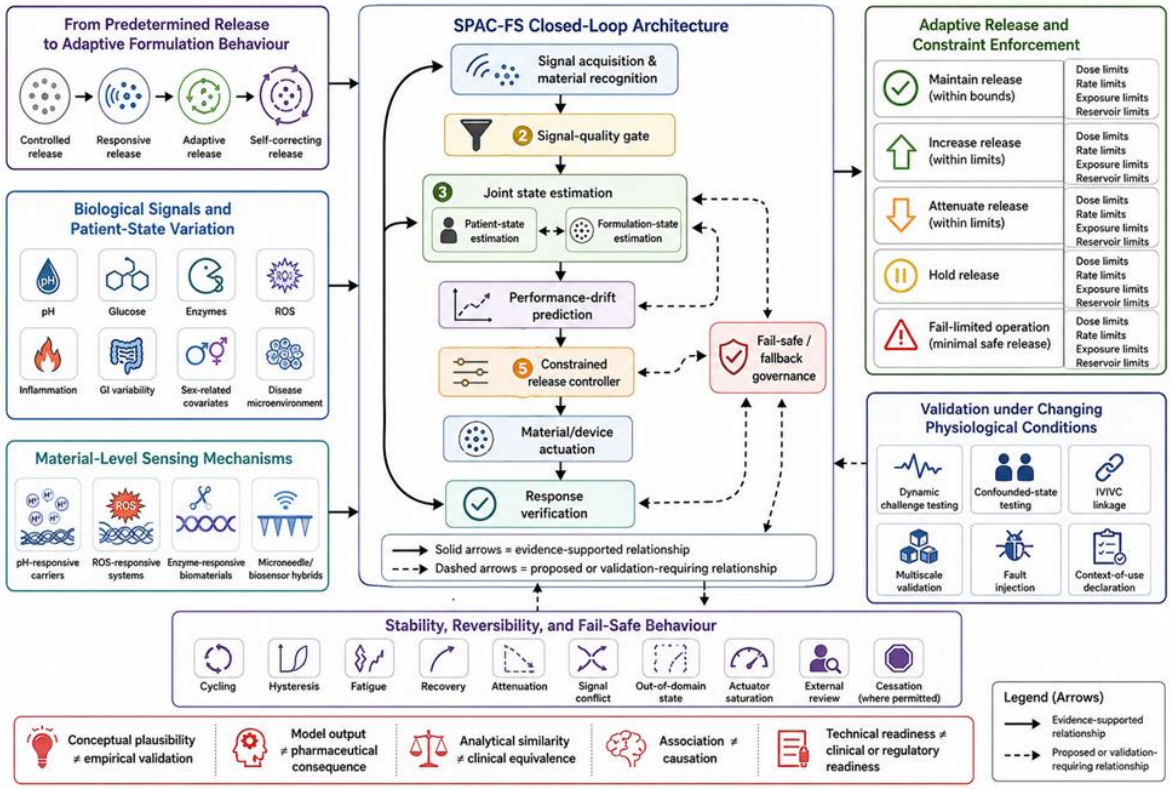

Figure 1. Closed-Loop Self-Correcting Formulation Architecture

The figure is an original conceptual synthesis developed for "Self-Correcting Pharmaceutical Formulations That Sense Biological Conditions, Predict Performance Drift, and Adapt Drug Release across Changing Patient States." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

The first architecture layer is signal acquisition and qualification. A biological or physicochemical input reaches a material recognition element or sensor, after which a signal-quality gate assesses range, plausibility, cross-reactivity, temporal coherence, and measurement integrity. A biosensor linked to an electroosmotic pump through a controllable microneedle pathway illustrates the value of separating measurement, control, and actuation rather than treating them as one undifferentiated responsive event [11].

The second layer jointly estimates patient state and formulation state. Patient-state estimation asks what physiological or pathological condition is most consistent with the available inputs. Formulation-state estimation asks whether aging, hydration, depletion, fouling, excipient interaction, structural change, or manufacturing variability has altered the product's response. A drift predictor then compares expected performance with

observed or inferred behaviour and attributes the deviation, where possible, to biology, formulation change, sensing error, or actuator fault.

The third layer selects and verifies a constrained release action. Manufacturable closed-loop patch development has shown that storage stability and production feasibility must be considered alongside sensing and delivery performance [12]. Existing closed-loop prototypes demonstrate that sensing, signal processing, actuation, and delivery can be physically integrated, although they do not validate the formulation-level architecture proposed here [10-12]. SPAC-FS therefore places dose, release-rate, exposure, tissue, reservoir, and actuator limits around every action and returns observed consequences to the estimator.

The final layer is fail-safe governance. Low signal quality, conflicting evidence, an out-of-domain state, excessive prediction uncertainty, actuator saturation, or an unverifiable response should prevent escalation and trigger a predefined fail-limited condition, external review, or cessation where product design permits. The architecture is modular: sensing may be material-based, device-mediated, or hybrid, but no implementation qualifies as self-correcting unless the complete loop and its failure transitions are prospectively demonstrated within a declared context of use.

Material-level sensing mechanisms

Material-level sensing begins when a formulation component recognizes an environmental condition and converts it into a physicochemical change. In pH-responsive carriers, protonation, deprotonation, swelling, dissolution, charge reversal, or bond cleavage can modify drug accessibility and transport [13]. Because pH ranges overlap across tissues and disease states, the response cannot alone identify the underlying patient state.

Reactive-oxygen-species-responsive systems use oxidation-sensitive bonds, polymers, or nanostructures to convert redox activity into degradation, permeability change, or cargo release [14]. Their relevance depends on local concentration, reaction kinetics, antioxidant competition, tissue distribution, and material susceptibility. Oxidative responsiveness therefore demonstrates possible transduction rather than disease-specific recognition or an automatically appropriate release decision.

Enzyme-responsive biomaterials can translate proteolytic or catalytic activity into matrix remodeling, exposure of functional groups, degradation, or altered molecular transport [15]. Enzymes may provide closer biological coupling than general physicochemical cues, but expression heterogeneity, substrate accessibility, competing enzymes, and temporal variation can weaken specificity and reproducibility.

SPAC-FS consequently classifies responsive materials as recognition elements, transducers, actuators, or combinations of these roles—not as complete closed loops. A material response becomes decision-relevant only after signal qualification, state interpretation, constrained action selection, and response verification. Material responsiveness establishes mechanistic plausibility but does not establish reliable patient-state classification, therapeutic appropriateness, or clinical safety.

State estimation and performance-drift prediction

State estimation converts incomplete observations into an inferred representation of the conditions governing performance. Physiologically based biopharmaceutics modelling illustrates how formulation properties, gastrointestinal physiology, dissolution, permeability, and absorption can be linked mechanistically, while also showing that model credibility depends on data quality, assumptions, identifiability, and context of use [16].

Pharmaceutical digital twins provide a related logic for estimating unobserved process and product states. Hybrid flowsheet models combining mechanistic relationships with process data have been applied to continuous direct compression for product and process design [17]. Transferring this logic to an adaptive dosage form is proposed, however, because a manufacturing twin is not automatically a real-time patient-state predictor.

Performance drift is defined here as a time-dependent divergence between expected and actual release-related behaviour. The proposed predictor decomposes drift into physiological change, formulation aging, manufacturing variation, sensor degradation, actuator failure, and model misspecification. Where these causes are not identifiable, the estimator should increase uncertainty rather than force a definitive classification.

A prediction becomes actionable only when confidence, model domain, and anticipated pharmaceutical consequence are declared. Observability tests must determine whether available signals contain enough information to distinguish relevant states. **Table 1** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for definitions, components, relationships, and intended uses in self-correcting pharmaceutical formulations that sense biological conditions, predict..

Table 1. Definitions, components, relationships, and intended uses in Self-Correcting Pharmaceutical Formulations That Sense Biological Conditions, Predict.

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement
Biological signal	Makes changing conditions observable	pH, glucose, enzymes, reactive species, hydration, inflammation	Evidence-supported cue enters a proposed qualification layer	Supplies state-relevant information	Specificity, temporal stability, spatial relevance, confounder testing [13]	Cross-reactivity, noise, inaccessible sampling	A signal is not equivalent to a patient state
Signal-quality gate—proposed	Prevents unreliable cues from directly changing release	Range, coherence, plausibility, sensor integrity	Rejects, weights, or flags observations before estimation	Reduces false activation	Fault injection and interference testing	Bias, dropout, delayed detection	Passing the gate does not establish clinical relevance
Patient-state estimator—proposed	Infers latent physiological or pathological conditions	Qualified signals and contextual covariates	Combines observations with mechanistic or statistical models	Supports conditional interpretation	Calibration under changing and confounded states [16]	Non-identifiability and out-of-domain inputs	Model output is not biological ground truth
Formulation-state estimator—proposed	Distinguishes biological change from product change	Material age, hydration, reservoir status, process history	Estimates evolving product capacity and response	Supports drift attribution	Stability, aging, depletion, and batch-challenge studies [17]	Hidden degradation or unmeasured process variation	Analytical similarity does not establish identical in-use behaviour
Performance-drift predictor—proposed	Anticipates divergence from intended behaviour	Estimated patient and formulation states	Compares expected and inferred release-related performance	Enables earlier corrective or fallback action	Prospective perturbation and prediction-error testing	Misattribution, model drift, delayed warning	Association does not establish the cause of drift
Constrained controller—proposed	Prevents unrestricted adaptive action	State estimate, confidence, reservoir and exposure limits	Selects an action only within a predefined feasible set	Balances adaptation with safety constraints	Controller stress tests and saturation detection [11]	Overshoot, oscillation, unsafe cumulative release	No action rule is clinically acceptable without product-specific validation
Responsive actuator	Converts a selected action into material or device behaviour	Chemical cue or controller command	Changes permeability, degradation, pumping, or release	Executes bounded release modification	Input–response, lag, capacity, and repeatability testing [10]	Delay, blockage, depletion, irreversible activation	Actuation does not prove appropriate exposure
Verification and fallback—proposed	Detects ineffective or unsafe adaptation	Observed response, confidence, constraint status	Returns evidence to the estimator or enters fail-limited operation	Supports correction and graceful degradation	Closed-loop fault and recovery testing [12]	Unobservable failure or false reassurance	Fallback behaviour must be independently demonstrated

Adaptive release and constraint enforcement

Responsive nanoparticles have demonstrated rapid and extended glucose-linked insulin delivery in preclinical models, supporting the feasibility of material-level modulation across different temporal demands [18]. Such performance does not define a universal control law because the suitable timing, magnitude, and duration of release depend on the drug, route, therapeutic window, disease state, and actuator capacity.

A glucose-responsive microneedle patch has also linked changing glucose conditions to insulin delivery in mice and minipigs [19]. This evidence supports demand-linked actuation across preclinical species, but it does not establish human dosing thresholds, long-term reliability, clinical effectiveness, or transferability to other drugs and biological signals.

SPAC-FS distinguishes hard constraints from soft objectives. Hard constraints may bound instantaneous release, cumulative dose, predicted exposure, local concentration, tissue burden, reservoir depletion, and actuator duty. Soft objectives may reduce deviation from an intended exposure or response envelope. Adaptation is permitted only within the hard constraints, regardless of predicted benefit.

Every action must be followed by verification. Failure to observe the expected release-related consequence may indicate delayed transport, insufficient actuator capacity, material degradation, sensor error, or model misspecification. The controller should then reduce confidence, limit subsequent action, or enter fallback rather than repeatedly escalating release. Preclinical responsiveness alone cannot establish a safe adaptive policy.

Stability, reversibility, and fail-safe behaviour

Conventional stability emphasizes preservation during manufacture, storage, and use. Adaptive systems additionally require dynamic stability under repeated activation. Reversible network interactions can enable reconfiguration, but cycling may introduce hysteresis, fatigue, incomplete recovery, altered transport, or competing interactions [20]. Stability testing must therefore examine response trajectories rather than only initial and final specifications.

Reversibility means that release-driving behaviour attenuates appropriately when the triggering condition resolves. Glucose-sensitive insulin designed to reduce hypoglycaemic risk supports the safety relevance of attenuating action under lower glucose conditions in preclinical evaluation [21]. It does not establish a universal fail-safe mechanism or eliminate the need to test delayed, incomplete, or excessive reversal.

The proposed fallback hierarchy includes normal constrained operation, uncertainty-limited operation, fail-limited release, external intervention, and cessation where technically possible. Triggering conditions include signal conflict, model-domain failure, excessive uncertainty, actuator saturation, reservoir abnormality, unexpected response, and failed verification. The safest fallback depends on the medicine and cannot be assumed to mean either maximum or zero release.

Fail-safe behaviour must be intentionally engineered and independently challenged. It cannot be inferred from responsive chemistry or favourable nominal performance. **Table 2** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for testable propositions, evidence requirements, and validation criteria for self-correcting pharmaceutical formulations that sense biological conditions, predict.

Table 2. Testable propositions, evidence requirements, and validation criteria for Self-Correcting Pharmaceutical Formulations That Sense Biological Conditions, Predict.

Architecture layer or process stage	Core function	Information or material flow	Interaction with other components	Validation criterion	Potential failure mode	Human or experimental responsibility	Readiness boundary
Signal observability—proposed criterion	Determine whether signals add state information	Biological condition → qualified observation	Supplies the estimator	Demonstrate incremental information beyond time and baseline conditions	False trigger, weak specificity, signal masking	Design independent target and confounder perturbations [13]	Observability does not establish clinical utility
Drift discrimination—proposed criterion	Separate physiology from product or sensor change	Qualified observations → cause-specific hypotheses	Links estimators and predictor	Ambiguous states must increase uncertainty rather than force classification	Misattribution of aging as disease change	Cross material age, storage, physiology, and sensor faults [17]	Cause attribution remains context-specific
Constrained adaptation—proposed criterion	Modify release within non-negotiable limits	State estimate → bounded controller action	Governs the actuator	No commanded action may violate predefined	Overshoot, oscillation, actuator saturation	Challenge step, ramp, oscillatory, and mixed inputs [18]	Preclinical control does not define human limits

				dose, rate, or exposure constraints			
Reversible cycling—proposed criterion	Recover after repeated state transitions	Trigger on/off cycles → material response and recovery	Tests actuator and formulation state	Preserve acceptable direction, recovery, and residual release across cycles	Fatigue, hysteresis, irreversible change	Define product-specific cycling and recovery envelopes [20]	No universal cycle threshold is proposed
Graceful degradation—proposed criterion	Enter bounded operation during faults	Fault or low confidence → fallback state	Overrides normal adaptation	Demonstrate detectable transition without uncontrolled escalation	Sensor dropout, blockage, depleted reservoir	Perform fault-injection and recovery studies [12]	Fail-safe status requires direct evidence
Response attenuation—proposed criterion	Reduce action as triggering need resolves	Falling trigger → reduced release-related action	Connects estimator, controller, and actuator	Demonstrate timely attenuation without rebound or delayed excess	Persistent action after recovery	Test partial, delayed, and fluctuating recovery states [21]	Attenuation in one platform is not universally transferable
Decision readiness—proposed boundary	Limit claims to demonstrated evidence	Validation evidence → permitted context of use	Governs all layers	Predeclare claims, uncertainty, exclusions, and human oversight	Use beyond validated population, route, or product	Independent review and product-specific qualification	Conceptual coherence is not technical, clinical, or regulatory readiness

Validation under changing physiological conditions

Validation must reproduce change, not merely compare static endpoints. Dynamic gastrointestinal simulation can reveal release sensitivity to evolving fluid composition, hydrodynamics, transit-related conditions, and other biorelevant variables that conventional static tests may miss [22]. Equivalent challenge systems are needed for other routes, with perturbations selected according to the intended biological signal and failure mechanisms.

Release testing must also connect to in-vivo performance. Development of in-vitro–in-vivo correlations for PLGA long-acting injectables shows that predictive usefulness depends on product behaviour, study design, data quality, modelling assumptions, and the intended decision [23]. A fitted relationship outside its established predictive domain cannot validate adaptive control.

Validation must therefore combine dynamic biorelevant perturbation testing with evidence linking in-vitro release behavior to in-vivo performance [22, 23]. The sequence should connect signal recognition, material transformation, release, absorption or local exposure, pharmacological consequence, recovery, and failure response. Each link requires its own uncertainty statement and acceptance rule.

Prospective testing should include target signals, plausible confounders, mixed inputs, abrupt and gradual changes, repeated cycles, sensor faults, material aging, manufacturing variation, reservoir depletion, and model-domain violations. Computational, in-vitro, in-vivo, and clinical evidence are complementary rather than interchangeable. Validation remains claim-specific and cannot establish universal readiness or regulatory acceptance.

Manufacturing and clinical translation

Manufacturing a self-correcting formulation would require traceable relationships among material attributes, process parameters, sensor characteristics, actuator capacity, software or model versions, and final product performance. Integrated data-management frameworks for continuous drug-product manufacturing illustrate the importance of interoperable information, contextualized data, and lineage across monitored unit operations [24].

Advanced delivery systems also face translational barriers arising from biological complexity, characterization, scale-up, reproducibility, manufacturing, usability, and evolving regulatory expectations [25]. Adding sensing and prediction increases the number of interacting failure modes and may complicate sterilization, packaging, storage, transport, administration, maintenance, and post-use interpretation.

A translation strategy should therefore define critical material attributes, critical process parameters, signal-response specifications, model configuration, actuator limits, release tests, fallback verification, and lifecycle change control. Batch comparability must examine functional response under dynamic challenges, not merely compositional similarity. Model or sensor changes may require partial or complete requalification depending on their pharmaceutical consequence.

Clinical translation must also address administration burden, acceptability, comprehension, adherence, monitoring, human override, and responsibility for responding to warnings or fallback states. Evidence should remain specific to the drug, dosage form, route, population, and intended use. Manufacturing feasibility, patient-centric design, and analytical performance do not independently establish clinical benefit or an acceptable benefit–risk profile.

Limitations and research agenda

Endogenous signals are frequently noisy, overlapping, spatially heterogeneous, and temporally unstable. Chemical interference can change both signal magnitude and material response, making signal fidelity a central limitation of stimuli-responsive delivery [26]. Research should prioritize orthogonal sensing, interference libraries, spatially relevant sampling, uncertainty-aware fusion, and explicit testing of biologically plausible confounders.

Prediction introduces additional limitations. Digital-twin approaches may support state updating and scenario evaluation, but data quality, transportability, interpretability, validation, update governance, and context-of-use definition remain unresolved challenges [27]. A formulation twin may also become obsolete as disease, concomitant therapy, behaviour, manufacturing inputs, or the product itself changes.

The immediate research agenda is to test observability, drift discrimination, constrained adaptation, reversible cycling, graceful degradation, and multiscale credibility across product-specific challenge sets. Ethical and governance work must define update authority, auditability, cybersecurity where relevant, human override, responsibility after failure, and equitable access. The theory remains hypothesis-generating and must not control treatment without product-specific validation.

CONCLUSION

Self-correcting formulation behaviour requires more than a responsive excipient or stimulus-triggered release mechanism. SPAC-FS proposes an integrated loop linking qualified sensing, joint patient- and formulation-state estimation, performance-drift prediction, bounded adaptation, response verification, reversible operation, and fail-limited behaviour. Its value lies in making assumptions, interfaces, failure states, and evidence requirements explicit. The architecture does not establish that autonomous adaptation is necessary, feasible, or beneficial for every medicine. Each implementation must demonstrate signal relevance, material reliability, model credibility, pharmaceutical consequence, manufacturability, usability, and acceptable performance within a declared context of use before any clinical decision role can be considered.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

REFERENCES

1. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021;20(2):101-24. doi:10.1038/s41573-020-0090-8
2. Govender R, Abrahmsén-Alami S, Larsson A, Folestad S. Therapy for the individual: Towards patient integration into the manufacturing and provision of pharmaceuticals. Eur J Pharm Biopharm. 2020;149:58-76. doi:10.1016/j.ejpb.2020.01.001

3. Timpe C, Stegemann S, Barrett A, Mujumdar S. Challenges and opportunities to include patient-centric product design in industrial medicines development to improve therapeutic goals. Br J Clin Pharmacol. 2020;86(10):2020-7. doi:10.1111/bcp.14388
4. Buwalda SJ, Vermonden T, Hennink WE. Hydrogels for therapeutic delivery: Current developments and future directions. Biomacromolecules. 2017;18(2):316-30. doi:10.1021/acs.biomac.6b01604
5. Mo C, Luo R, Chen Y. Advances in the stimuli-responsive injectable hydrogel for controlled release of drugs. Macromol Rapid Commun. 2022;43(10). doi:10.1002/marc.202200007
6. Wang J, Wang Z, Yu J, Kahkoska AR, Buse JB, Gu Z. Glucose-responsive insulin and delivery systems: Innovation and translation. Adv Mater. 2020;32(13). doi:10.1002/adma.201902004
7. Vinarov Z, Abdallah M, Agundez JAG, Allegaert K, Basit AW, Braeckmans M, et al. Impact of gastrointestinal tract variability on oral drug absorption and pharmacokinetics: An UNGAP review. Eur J Pharm Sci. 2021;162:105812. doi:10.1016/j.ejps.2021.105812
8. Madla CM, Gavins FKH, Merchant HA, Orlu M, Murdan S, Basit AW. Let's talk about sex: Differences in drug therapy in males and females. Adv Drug Deliv Rev. 2021;175:113804. doi:10.1016/j.addr.2021.05.014
9. Choi J, Shin N, Jin D, Xu E, Kwon Y, Park S, et al. Intestinal microenvironment-modulating nanomedicines for inflammatory bowel disease. J Control Release. 2026;395:114953. doi:10.1016/j.jconrel.2026.114953
10. Li X, Huang X, Mo J, Wang H, Huang Q, Yang C, et al. A fully integrated closed-loop system based on mesoporous microneedles-iontophoresis for diabetes treatment. Adv Sci (Weinh). 2021;8(16). doi:10.1002/advs.202100827
11. Luo X, Yu Q, Liu Y, Gai W, Ye L, Yang L, et al. Closed-loop diabetes minipatch based on a biosensor and an electroosmotic pump on hollow biodegradable microneedles. ACS Sens. 2022;7(5):1347-60. doi:10.1021/acssensors.1c02337
12. Liu Y, Yang L, Cui Y. A wearable, rapidly manufacturable, stability-enhancing microneedle patch for closed-loop diabetes management. Microsyst Nanoeng. 2024;10(1):112. doi:10.1038/s41378-024-00663-y
13. Liu L, Yao W, Rao Y, Lu X, Gao J. pH-responsive carriers for oral drug delivery: Challenges and opportunities of current platforms. Drug Deliv. 2017;24(1):569-81. doi:10.1080/10717544.2017.1279238
14. Saravanakumar G, Kim J, Kim WJ. Reactive-oxygen-species-responsive drug delivery systems: Promises and challenges. Adv Sci (Weinh). 2017;4(1):1600124. doi:10.1002/advs.201600124
15. Brouns JEP, Dankers PYW. Introduction of enzyme-responsivity in biomaterials to achieve dynamic reciprocity in cell-material interactions. Biomacromolecules. 2021;22(1):4-23. doi:10.1021/acs.biomac.0c00930
16. Wu D, Li M. Current state and challenges of physiologically based biopharmaceutics modeling (PBBM) in oral drug product development. Pharm Res. 2023;40(2):321-36. doi:10.1007/s11095-022-03373-0
17. Moreno-Benito M, Lee KT, Kaydanov D, Verrier HM, Blackwood DO, Doshi P. Digital twin of a continuous direct compression line for drug product and process design using a hybrid flowsheet modelling approach. Int J Pharm. 2022;628:122336. doi:10.1016/j.ijpharm.2022.122336
18. Volpatti LR, Matranga MA, Cortinas AB, Delcassian D, Daniel KB, Langer R, et al. Glucose-responsive nanoparticles for rapid and extended self-regulated insulin delivery. ACS Nano. 2020;14(1):488-97. doi:10.1021/acsnano.9b06395
19. Yu J, Wang J, Zhang Y, Chen G, Mao W, Ye Y, et al. Glucose-responsive insulin patch for the regulation of blood glucose in mice and minipigs. Nat Biomed Eng. 2020;4(5):499-506. doi:10.1038/s41551-019-0508-y
20. Webber MJ, Tibbitt MW. Dynamic and reconfigurable materials from reversible network interactions. Nat Rev Mater. 2022;7(7):541-56. doi:10.1038/s41578-021-00412-x
21. Hoeg-Jensen T, Kruse T, Brand CL, Sturis J, Fledelius C, Nielsen PK, et al. Glucose-sensitive insulin with attenuation of hypoglycaemia. Nature. 2024;634(8035):944-51. doi:10.1038/s41586-024-08042-3
22. Qiang W, Yang S, Wu P, Chen XD. Biorelevant simulation of GI variability and its impact on the release behavior of non-disintegrating formulations: A case study using DHSI-IV (NERDT) system as a novel in vitro tool. Int J Pharm. 2025;684:126161. doi:10.1016/j.ijpharm.2025.126161
23. Wang Y, Otte A, Park H, Park K. In vitro-in vivo correlation (IVIVC) development for long-acting injectable drug products based on poly(lactide-co-glycolide). J Control Release. 2025;377:186-96. doi:10.1016/j.jconrel.2024.11.021
24. Chen Y, Sampat C, Huang YS, Ganesh S, Singh R, Ramachandran R, et al. An integrated data management and informatics framework for continuous drug product manufacturing processes: A case study on two pilot plants. Int J Pharm. 2023;642:123086. doi:10.1016/j.ijpharm.2023.123086

25. Balash M, Boucetta H, He W. Factors affecting drug delivery system translation: A focus on advanced technologies, biological barriers, and regulatory challenges. J Control Release. 2025;387:114167. doi:10.1016/j.jconrel.2025.114167
26. Rathod B, Puri S. Chemical noise and signal fidelity in stimuli-responsive drug delivery systems. Int J Pharm. 2026;697:126900. doi:10.1016/j.ijpharm.2026.126900
27. Venkatapurapu SP, Clegg L, Nowojewski A, Kimko H, Olabode D, Sawant-Basak A, et al. Digital twins for accelerating drug discovery and development: Opportunities and challenges. Drug Discov Today. 2026;31(2):104617. doi:10.1016/j.drudis.2026.104617