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Advanced Formulations Can Be Designed as Adaptive Release Systems Rather Than Static Dosage Forms

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ABSTRACT

Advanced drug-delivery systems are usually evaluated as dosage forms with predefined release characteristics, yet the environments into which they release drug are variable in composition, mechanics, transport capacity, disease state, and time. This perspective argues that a useful next design step is to treat selected formulations as adaptive release systems whose performance is defined by how formulation state changes in response to physiologically or therapeutically relevant conditions. Adaptation is distinguished from simple sustained release, programmed sequential release, stimulus responsiveness, and true feedback control. Human gastrointestinal measurements, biorelevant dissolution studies, mechanistic absorption models, responsive biomaterials, implantable systems, and personalized manufacturing collectively show that release behavior can depend on gastric pH, buffering, motility, prandial composition, regional intestinal conditions, absorptive sink, local formulation-generated microenvironments, disease-associated signals, external stimuli, and patient-specific constraints. These observations do not establish a universal need for adaptive formulations. Rather, they expose conditions under which a static specification may poorly represent the product–environment interaction. The article therefore develops a proposed adaptive-release design logic in which relevant patient or physiological states are translated into formulation transformations, release consequences, downstream availability, and—where technically justified—feedback or reassessment. Particular emphasis is placed on avoiding over-responsive systems whose triggering is nonspecific, unstable, poorly coupled to exposure, or difficult to manufacture and qualify. Adaptive release should consequently be understood not as maximal responsiveness, but as controlled, evidence-bounded adjustment to states that materially influence therapeutic delivery.

Keywords: *Adaptive drug release, Stimulus-responsive delivery, Gastrointestinal physiology, Biorelevant dissolution, Feedback-controlled delivery, Personalized formulations*

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INTRODUCTION

Oral and nonoral dosage forms are commonly described by release attributes measured under controlled experimental conditions, even though the physiological environment encountered by a product is neither chemically nor mechanically constant. Direct human gastrointestinal measurements have shown substantial temporal and regional variation in luminal pH, buffer capacity, and motility, including differences associated with fasted and fed states [1]. Such variability does not make conventional dissolution testing obsolete; compendial and development tests serve indispensable quality functions. It does, however, challenge the assumption that a single release curve can fully represent how a formulation behaves after administration.

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Biorelevant dissolution and physiologically based pharmacokinetic modeling have therefore increasingly been combined to connect dosage-form behavior with gastrointestinal conditions and systemic exposure [2]. This integration is especially important because drug release is only one component of oral absorption. Mechanistic intestinal models show that solubility, permeability, convection, diffusion, regional physiology, and transporter processes can jointly determine the fraction absorbed [3]. A formulation can therefore release drug as designed yet still fail to generate the intended exposure because the downstream biological system is limiting.

The engineering literature on closed-loop drug delivery provides a useful reference point for defining a stronger form of adaptation. Closed-loop systems couple measurement of a biological state with a controller and an automated delivery response, allowing treatment output to change in relation to measured need [4]. Most pharmaceutical formulations do not possess this complete architecture. Many are instead preprogrammed, environmentally responsive, or condition-sensitive without measuring whether the resulting drug exposure or biological response was appropriate.

This perspective therefore uses adaptive release as a deliberately broader but bounded formulation concept. A formulation is adaptive when its release behavior is intentionally designed to change according to a scientifically relevant environmental, physiological, pathological, temporal, or patient-state input. True feedback-controlled release is treated as one advanced subset rather than as a synonym for all responsive systems. The central argument is not that static dosage forms should be replaced wholesale, but that products whose performance is strongly conditioned by variable states may benefit from design strategies that explicitly account for those states.

Static release assumptions

The simplest static-release assumption is that the environment into which drug is released is sufficiently stable for a single dissolution condition to represent the clinically relevant process. Human intestinal chemistry provides reasons to question that assumption for some products. Solubilization of poorly soluble drugs varies with the ratios of bile salts, phospholipids, fatty acids, and related amphiphilic components, and the direction and magnitude of those changes differ among compounds [5, 6]. Thus, a standardized medium can be analytically useful while still compressing physiologically meaningful variability.

Dynamic gastrointestinal transitions further complicate the interpretation of a nominal release profile. Experiments with weakly basic drugs have shown that the path from gastric to intestinal conditions can affect dissolution and precipitation differently across compounds and formulations [7]. This heterogeneity is important: the relevant design question is not whether gastrointestinal variability exists, but whether a particular product is sufficiently sensitive to that variability for adaptation to offer value.

Product-specific mechanistic descriptors may also matter more than bulk drug-substance properties alone. For acalabrutinib, mechanistic dissolution modeling required product-level particle and surface behavior to reproduce dissolution across conditions more faithfully [8]. The implication is not that one modeling strategy should replace conventional characterization, but that dosage-form state can modify the translation from nominal material properties to actual release behavior.

A second limitation of static reasoning is the common separation of dissolution from absorption. In an artificial gut/absorption simulator, introducing an absorptive sink changed dissolution, speciation, precipitation, and even the relative ranking of amorphous solid dispersions [9]. Removal of freely dissolved drug altered the luminal system itself. This demonstrates a reciprocal relationship: formulation state affects available drug, but removal of available drug can in turn change the formulation–solution equilibrium.

Buffer identity provides another example. Controlled comparisons have shown that precipitation kinetics of ionizable drugs can differ between bicarbonate and phosphate systems even when nominal pH is matched [10]. The practical lesson is not that one buffer is universally correct and another incorrect. Instead, the test environment must reproduce the mechanism that is relevant to the formulation question being asked.

Clinical translation adds another boundary. Mechanistic modeling of acalabrutinib showed that altered gastric pH, dissolution, transporter activity, metabolism, and administration conditions can interact in determining systemic exposure [11]. A formulation that adapts only its release rate may therefore remain ineffective if the clinically important limitation occurs downstream. An adaptive system must be designed against the controlling mechanism, not merely against the easiest variable to sense.

Dynamic gastrointestinal and tissue environments

The gastrointestinal tract can be viewed as a sequence of changing physicochemical and mechanical states rather than a uniform dissolution chamber. Simulated gastric experiments with dabigatran etexilate demonstrated that

gastric pH, mechanical stress, emptying behavior, and product architecture can combine to produce different release profiles [12]. Such results support the use of a *state envelope*: a set of plausible physiological conditions within which formulation robustness can be evaluated.

Gastric mechanics can be especially important when release and emptying occur on similar time scales. Physiologically driven dissolution combined with pharmacokinetic modeling has linked alternative gastric motility patterns with different plasma concentration profiles [13]. These patterns should not be interpreted as universally established patient phenotypes, but they show that mechanical state can become a meaningful formulation variable when drug release is rapid enough to interact with gastric processing.

Prandial conditions add compositional variability. Measurements in aspirated human intestinal fluids have shown that lipid and micellar phases change substantially between fasted, early-fed, and later-fed states and that the solubilizing consequences are drug dependent [14]. A formulation optimized against an average fed-state medium may therefore reproduce central tendency while missing clinically important variability at the edges of the physiological range.

Even when gastrointestinal release changes, exposure may remain controlled elsewhere. In analyses of rivaroxaban, gastrointestinal and pharmacokinetic determinants could not be reduced to gastric release behavior alone; permeability-related processes were important contributors to exposure [15]. This distinction creates a fundamental boundary for adaptive formulation design: changing drug availability is useful only when availability is actually rate limiting.

Regional differences also matter for delayed, enteric, extended, and colon-directed systems. Lower-intestinal dissolution studies have demonstrated that distal conditions can contribute meaningfully to absorption for some high-dose, low-solubility drugs, but the effect is product specific [16]. Human colonic-fluid measurements similarly show that colonic solubility is not uniformly poorer than small-intestinal solubility; some compounds differ substantially whereas others show comparatively similar behavior [17]. Regional adaptation therefore requires molecule-specific evidence rather than a generic assumption about where release should occur.

The formulation can also alter the environment to which it is supposedly responding. In insulin minitablets, permeation enhancers such as sodium caprate and SNAC changed local pH conditions and influenced insulin release in biorelevant media [18]. This creates a reciprocal interaction between formulation and environment. A responsive product may therefore change its own trigger conditions, introducing the possibility of self-amplification, self-attenuation, or unintended switching during release.

The same conceptual issue extends beyond the gastrointestinal tract. Tissue pH, reactive oxygen species, enzymes, glucose concentration, mechanical energy, inflammatory mediators, and microbial products can all vary over the course of disease or treatment. The design problem is consequently not simply to identify a stimulus, but to establish whether the stimulus is sufficiently specific, temporally informative, and mechanistically linked to a required change in drug availability.

Stimulus-responsive release

Stimulus-responsive systems provide the most direct pharmaceutical bridge between conventional controlled release and adaptive delivery. In intestinal inflammation, proposed and experimental delivery systems have exploited pH, transit time, microbiota-derived activity, inflammatory chemistry, and other local conditions to influence site-specific drug release [19]. These strategies illustrate an important shift: the environment is no longer treated solely as a disturbance to formulation performance but can become an input deliberately used by the formulation.

Comparable concepts are established in wound-delivery research, where pathological microenvironments characterized by reactive species, acidic conditions, enzymes, glucose changes, and external physical stimuli have been used to control material transformation and drug liberation [20]. These systems should not be extrapolated directly to oral delivery, but they demonstrate that pathological state can be encoded into material behavior.

The usefulness of a trigger depends strongly on its operating window. A pH-responsive polymeric delivery system developed for colorectal carcinoma underwent environment-dependent disassembly under acidic tumor conditions [21]. This kind of result demonstrates technical feasibility but also highlights a limitation: “pH responsive” is not itself a sufficient design specification. The relevant quantity is the relationship among material transition, actual physiological pH distribution, drug-release kinetics, and the probability that the trigger occurs in the intended location without substantial activation elsewhere.

External stimuli provide a different control mode. Ultrasound-mediated systems can modulate carrier release or alter biological barriers, creating an externally controlled input to delivery [22]. Because acoustic conditions must

be translated across devices, tissues, and models, the stimulus itself requires calibration. External triggering therefore offers temporal controllability but does not eliminate the need for a validated stimulus-to-delivery relationship.

Biochemical feedback becomes more tangible when the trigger represents the biological variable being treated. Glucose-responsive insulin microneedle systems have demonstrated preclinical release behavior that changes according to glucose state [23]. This is closer to functional adaptation because the therapeutic need and the control input are directly linked. Nevertheless, the evidence remains platform- and model-specific, and preclinical glucose responsiveness cannot be treated as evidence of established human closed-loop performance.

Responsive nanoparticle chemistry provides another layer of control. Stimulus-sensitive nanogels have been rationally designed to alter intracellular delivery according to environmental conditions relevant to therapeutic action [24]. These examples support the idea that the input–output relationship of a formulation can be engineered. However, a material response becomes pharmaceutically useful only when the resulting change in drug availability occurs at the necessary magnitude and time.

Pharmacokinetic and pharmacodynamic consequences therefore remain essential. Reviews of stimuli-responsive nanodiamond systems emphasize that surface engineering, biodistribution, stimulus sensitivity, and drug disposition must be considered together [25]. A formulation can be highly responsive yet clinically unhelpful if triggering occurs after the relevant therapeutic window, at an inaccessible site, or with insufficient change in exposure.

The microbiome creates perhaps the clearest example of both opportunity and uncertainty. Microbiome-active drug-delivery systems seek to use microbial enzymes, metabolites, or biofilm conditions as local release signals [26]. Such triggers could support spatially selective delivery, but microbial composition varies substantially among individuals, disease states, treatments, diet patterns, and time points. Responsiveness to a variable biological ecosystem therefore requires a stronger robustness standard than responsiveness to a tightly controlled laboratory trigger.

Feedback-controlled release concepts

Stimulus responsiveness and feedback control should not be treated as equivalent. A conventional responsive formulation can detect or react chemically to an environmental condition without evaluating whether the resulting release changed exposure or biological state as intended. In contrast, closed-loop delivery requires a measured state, a control relationship, an actuator or release mechanism, and some form of reassessment. Evidence from closed-loop drug-delivery engineering and implantable delivery systems supports this distinction [4, 27].

This difference is central to adaptive formulation design. A pH-sensitive carrier is responsive because local pH changes its structure. A glucose-responsive insulin system is closer to feedback because the sensed variable is related directly to therapeutic need. A device that continuously measures a biomarker, calculates a dose adjustment, releases drug, and then reassesses the biomarker constitutes a stronger closed-loop architecture. These categories should not be ranked automatically. Simpler systems may be more reliable when physiological variation is predictable enough that feedback adds little value.

A proposed formulation-specific feedback architecture can therefore be described through four functional questions. First, which biological or physiological state is being detected? Second, what formulation transformation converts that state into a release change? Third, what drug-availability consequence follows? Fourth, is the downstream state measured again, or is the system simply assuming that the programmed transformation was sufficient? Only the fourth condition creates a genuine feedback loop.

Feedback control also introduces new failure mechanisms. Biological signals may be noisy, delayed, or nonspecific; material transitions may be slow or irreversible; release may overshoot the useful exposure window; and the sensor, controller, and drug reservoir may operate on different time scales. A system that reacts rapidly to a fluctuating biomarker can become less stable rather than more adaptive. Accordingly, the design objective should not be maximum responsiveness but a response function matched to the dynamics of the biological problem.

The distinctions required to interpret such systems are compacted in **Table 1**. The table is needed because the same observed release change can imply different design conclusions depending on the governing condition, formulation transformation, downstream limitation, and whether reassessment is possible.

Table 1. Resolving when condition-sensitive release constitutes useful adaptation rather than an incomplete response

Scientific configuration		Observable support	Mechanistic test and consequence
Governing condition / Formulation transformation event	**Drug phase or availability state / Advanced-formulation question left unresolved**	**Time dependence / Biorelevant readout**	**Release or absorptive consequence**
Governing condition: Gastric pH transition **Formulation transformation event: Ionization, dissolution, or precipitation changes after gastric-to-intestinal transfer**	**Drug phase or availability state:** Freely dissolved drug may fall despite rapid initial gastric dissolution **Advanced-formulation question left unresolved:** Should the formulation adapt to gastric state, intestinal state, or both?	**Time dependence:** Minutes to early intestinal transit **Biorelevant readout:** Dynamic concentration and solid-state evolution	High gastric release can be followed by intestinal loss of available drug
Governing condition: Variable gastric mechanics **Formulation transformation event: Disintegration, erosion, mixing, and emptying change with mechanical history**	**Drug phase or availability state:** Drug may remain dosage-form associated or be released at different locations **Advanced-formulation question left unresolved:** Is mechanical state a controllable design input or only a robustness challenge?	**Time dependence:** Episodic and transit dependent **Biorelevant readout:** Mechanically biorelevant dissolution profile	Identical composition can yield different release timing
Governing condition: Fed intestinal lipid environment **Formulation transformation event: Solubilization shifts among aqueous, micellar, and lipid-associated states**	**Drug phase or availability state:** Apparent dissolved drug can increase without equivalent change in freely diffusible fraction **Advanced-formulation question left unresolved:** Which luminal phase should the formulation be optimized to control?	**Time dependence:** Changes across postprandial phases **Biorelevant readout:** Phase-resolved solubility or transfer testing	Release and absorptive availability can become partially uncoupled
Governing condition: Absorptive sink **Formulation transformation event: Removal of freely dissolved drug shifts dissolution and precipitation equilibria**	**Drug phase or availability state:** Formulation, dissolved, supersaturated, and precipitated fractions interconvert **Advanced-formulation question left unresolved:** Can an adaptive rule be designed without representing downstream sink behavior?	**Time dependence:** Continuous during intestinal uptake **Biorelevant readout:** Coupled dissolution–absorption readout	Absorption can alter the apparent release process itself
Governing condition: Formulation-generated local pH **Formulation transformation event: Excipient dissolution modifies the environment surrounding the drug**	**Drug phase or availability state:** Local ionization differs from bulk-medium expectation **Advanced-formulation question left unresolved:** Could self-modification create premature activation or self-limiting release?	**Time dependence:** Evolves as excipient and drug dissolve **Biorelevant readout:** Local pH plus release profile	Formulation can alter the trigger to which it responds
Governing condition: Disease- or biomarker-responsive material **Formulation transformation event: Trigger-induced swelling, cleavage, dissolution, or permeability change**	**Drug phase or availability state:** Drug availability rises or falls with a biological signal **Advanced-formulation question left unresolved:** Is the trigger sufficiently specific and stable across patients?	**Time dependence:** Depends on biomarker kinetics and material-response lag **Biorelevant readout:** Trigger level plus release response	Potential alignment of drug availability with therapeutic need
Governing condition: Sensor–controller–delivery system **Formulation transformation event: Measured state drives an explicit control action**	**Drug phase or availability state:** Drug output is actively adjusted rather than passively released **Advanced-formulation question left unresolved:** Does the added control layer improve robustness enough to justify its complexity?	**Time dependence:** Repeated or continuous **Biorelevant readout:** Biomarker trajectory plus delivery output	Output can be reassessed and corrected

The resulting control logic is better viewed spatially than as a simple release sequence. **Figure 1** therefore separates patient/environmental inputs from formulation transformation, drug-availability states, downstream exposure, and feedback while keeping uncertainty and qualification boundaries visible.

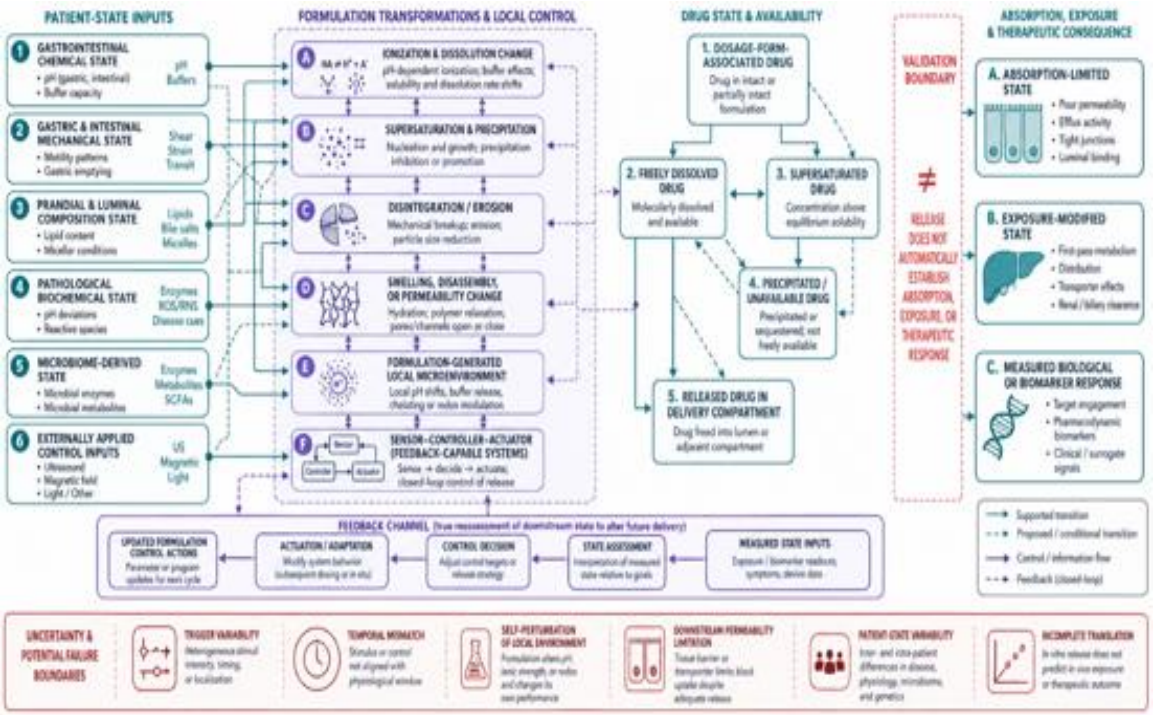


Figure 1. Patient-state signals, formulation transformations, and feedback boundaries that determine whether responsive release becomes adaptive

Sequential and pulsatile delivery

Adaptation does not necessarily require sensing. A dosage form can respond to anticipated temporal changes by encoding a predefined sequence of release events. In myocardial-infarction research, an injectable carrier was designed to provide rapid early delivery of an anti-inflammatory component followed by more sustained release of a reparative factor, matching different stages of the experimental pathological process [28]. This demonstrates programmed temporal adaptation: the formulation does not measure whether the biological state has changed, but its release sequence is constructed around an expected temporal progression.

Three-dimensional manufacturing can encode more complex profiles. Computationally designed multilayer capsules have reproduced predefined stepwise and near-zero-order release profiles by changing internal geometry [29]. Such systems demonstrate that temporal behavior can be treated as a design variable rather than an unavoidable material property. Yet matching an in vitro target curve is not equivalent to matching a patient-specific exposure requirement.

Manufacturing architecture imposes its own constraints. Bilayer tablets produced through droplet deposition modeling and injection molding showed that density, porosity, and process route can materially alter drug-release behavior, while some drug–material combinations created processability difficulties [30]. Adaptation must therefore remain physically manufacturable: a theoretically desirable temporal profile is not a useful product specification if the required structure cannot be reproduced robustly.

Multiple temporal programs can also coexist within one dosage form. Double-melt extrusion and fused-deposition manufacture have been used to create fixed-dose combinations in which acetaminophen and ibuprofen exhibited differentiated release behavior within one printed product [31]. This is important conceptually because it separates multi-program release from feedback control. A dosage form may contain several predetermined release functions and still remain open loop.

Sequential and pulsatile systems are therefore best positioned between static controlled release and true responsive adaptation. They can anticipate known changes in therapeutic need, anatomical position, or treatment timing, but they cannot correct themselves if the assumed sequence is wrong. Their usefulness depends on how predictable the underlying biological trajectory is.

Patient-state dependence

The strongest argument for adaptive release emerges when relevant physiological or therapeutic states vary substantially between patients. However, patient-state dependence should not be reduced to choosing a different release curve for each individual. Personalization must remain compatible with practical manufacturing, quality control, and clinical workflow. Hospital-based development of 3D-printed multidrug formulations for the OPERA clinical-trial setting demonstrates that patient-specific pharmaceutical manufacture can be incorporated into a real healthcare-production environment [32]. That evidence establishes feasibility of customized production, not superior therapeutic outcomes.

Patient state also includes constraints that limit what can safely be formulated. Pediatric 3D-printing literature shows that excipient selection and exposure require specific consideration because materials acceptable in adults may not have equivalent safety evidence across age groups or treatment durations [33]. Adaptation therefore cannot be defined only by responsiveness of release; it must include population-specific material acceptability.

The proposed patient-state layer in this perspective consequently includes physiological conditions, prandial state, concomitant pharmacological influences, disease-associated signals, microbial context, anatomical region, age-related formulation constraints, and other variables only when they are mechanistically relevant to the product under consideration. These factors should not be collapsed into deterministic patient labels. Some are transient, some fluctuate over hours, some change over treatment, and some influence exposure downstream of release.

An adaptive product should therefore respond only to states that satisfy three requirements: the state must materially influence the therapeutic delivery problem, the formulation must be capable of detecting or accommodating it with acceptable specificity, and the resulting release change must remain meaningful after downstream absorption and disposition are considered. This shifts personalized formulation design away from maximal customization toward selective adaptation to variables that actually control performance.

Failure modes of over-responsive systems

Responsiveness becomes undesirable when a formulation reacts to a variable that does not reliably represent therapeutic need. A trigger can be chemically real yet biologically nonspecific. Tumor-associated acidity, for example, can support pH-responsive material transformation, but the operational trigger window remains formulation- and microenvironment-dependent [21]. If the response threshold overlaps substantially with off-target physiological conditions, activation may occur too early, too late, or in the wrong compartment. The relevant design quantity is therefore not responsiveness alone but trigger discriminability across the physiological states that the product is likely to encounter.

A second failure occurs when the formulation successfully changes release but release is not the dominant determinant of exposure. Mechanistic analysis of rivaroxaban illustrates that gastrointestinal release-related factors can coexist with important permeability limitations [15]. Under such circumstances, increasing or retiming dissolution may produce little proportional change in systemic availability. This creates a proposed correct-release/wrong-exposure state: the dosage form performs as intended at the formulation level, yet downstream physiology prevents the intended pharmacokinetic consequence.

Responsive systems can also perturb their own control environment. Permeation-enhancing insulin formulations demonstrate that excipients may alter local pH while simultaneously changing drug release [18]. If the variable being sensed is modified by the formulation itself, the system can develop self-amplifying or self-limiting behavior. Such coupling need not be harmful, but it must be characterized rather than assumed to be negligible.

Biological heterogeneity introduces another instability. Human intestinal-fluid composition varies among prandial states and individuals [14], while microbiome-responsive delivery faces additional interindividual and temporal variability in microbial abundance, enzymatic activity, metabolites, and biofilm conditions [26]. A trigger calibrated to a nominal patient may therefore operate differently in another patient or in the same patient after diet, disease, medication, or microbial-state changes.

Device-enabled adaptive systems have further constraints involving sensor drift, actuator reliability, power supply, material fatigue, and long-term biocompatibility [27]. These limitations underline a broader principle: increasing the number of responsive components creates additional interfaces that must remain synchronized. Adaptation is beneficial only when the added control complexity reduces clinically relevant variability more than it introduces new sources of uncertainty.

Table 2 separates these failure states according to what is known at the moment a formulation decision must be made and what observation should trigger reassessment.

Table 2. Decision states for identifying when adaptive responsiveness should be maintained, constrained, or reconsidered

Evidence and limits	Permitted action
Information available / Unresolved uncertainty	**Formulation-state decision / Permissible design action / Observation reassessment**
Information currently available: A measurable environmental or pathological signal is associated with the intended site or state Unresolved uncertainty: Signal specificity across off-target states remains uncertain	**Formulation-state decision:** Trigger appears physiologically relevant **Permissible design action:** Preserve responsiveness but test the full physiological trigger range **Observation requiring reassessment:** Activation occurs under non-target conditions or fails within the intended state
Information currently available: Formulation transformation and drug liberation change reproducibly with the trigger Unresolved uncertainty: Downstream absorption may remain limiting	**Formulation-state decision:** Release responds as designed **Permissible design action:** Retain the release mechanism while separately testing permeability and disposition **Observation requiring reassessment:** Increased release produces little corresponding change in available or systemic drug
Information currently available: Excipient or material behavior changes local pH, ionic conditions, hydration, or other trigger variables Unresolved uncertainty: Direction and persistence of self-perturbation are uncertain	**Formulation-state decision:** Formulation alters its own microenvironment **Permissible design action:** Characterize reciprocal formulation–environment coupling **Observation requiring reassessment:** Trigger strength changes progressively because of the formulation itself
Information currently available: The relevant physiological, microbial, or disease variable differs among patients or over time Unresolved uncertainty: Operating range and probability of missed or false triggering are uncertain	**Formulation-state decision:** Patient-state signal is heterogeneous **Permissible design action:** Broaden robustness testing rather than increasing responsiveness automatically **Observation requiring reassessment:** Response becomes unstable across clinically plausible state distributions
Information currently available: Manufacturing produces the intended staged or pulsatile profile Unresolved uncertainty: Biological progression may not follow the assumed schedule	**Formulation-state decision:** Programmed temporal sequence is reproducible **Permissible design action:** Use preprogrammed release only where timing is sufficiently predictable **Observation requiring reassessment:** Therapeutic need consistently precedes or lags the programmed release phase
Information currently available: Input measurement, control logic, and release actuator communicate correctly Unresolved uncertainty: Delays, noise, drift, or actuator saturation may destabilize output	**Formulation-state decision:** Sensor-based feedback is technically functional **Permissible design action:** Maintain feedback only within validated operating limits **Observation requiring reassessment:** Control oscillation, delayed correction, persistent error, or sensor–actuator mismatch emerges
Information currently available: Patient-specific composition or geometry can be produced reproducibly Unresolved uncertainty: Safety, quality, or workflow constraints may limit customization	**Formulation-state decision:** Personalized design is manufacturable **Permissible design action:** Customize only variables with demonstrated performance relevance **Observation requiring reassessment:** Added personalization increases production variability without improving a meaningful product attribute

An adaptive-release design framework

The evidence reviewed here supports individual components of adaptive delivery, but it does not establish a single validated framework spanning oral formulations, responsive biomaterials, implants, and personalized dosage forms. The architecture proposed in this perspective therefore serves as an organizing design logic rather than an empirically validated universal model.

The first step is state identification. A candidate adaptive variable should be selected only when it materially influences product performance or therapeutic need. Examples include gastric pH, motility, prandial composition, regional luminal chemistry, disease-associated biochemical signals, microbial activity, or an externally measured biomarker. Variables that are easy to sense but weakly connected to the controlling delivery problem should not determine the design.

The second step is formulation-state transformation. The selected input must cause a reproducible physical or chemical change capable of modifying drug availability. Depending on the platform, this may involve ionization, dissolution, precipitation control, swelling, erosion, bond cleavage, permeability change, compartment opening, or actuator-driven release. Absorptive-sink studies demonstrate why this layer cannot be treated independently of the surrounding biological system: removing available drug can itself alter dissolution and precipitation behavior [9].

The third step is release-consequence qualification. A measurable change in dissolution or liberation should not automatically be interpreted as a meaningful change in exposure. The proposed framework therefore inserts an explicit boundary between formulation performance and absorption, systemic pharmacokinetics, pharmacodynamics, or therapeutic outcome.

The fourth step is control classification. Preprogrammed systems encode a release sequence in advance. Responsive systems alter release when an environmental condition changes. Feedback-controlled systems additionally reassess a relevant downstream state and use that information to modify subsequent delivery. These are distinct control modes rather than interchangeable definitions of "smart" formulation.

Finally, adaptation must pass a feasibility gate. Emerging 3D-printing technologies illustrate both the breadth of programmable solid-dose architectures and the dependence of those architectures on material properties, manufacturing parameters, process monitoring, and quality assessment [34]. Adaptation that cannot be manufactured reproducibly, stored acceptably, tested discriminately, or administered reliably remains a design concept rather than a viable pharmaceutical product.

Measurement and qualification requirements

Adaptive formulations require measurement strategies capable of separating genuine state-dependent performance from experimental complexity. Biorelevant dissolution and mechanistic modeling can link formulation behavior to physiological conditions, but such approaches remain useful only when their assumptions, discriminatory purpose, and predictive boundaries are explicit [2, 35]. The objective is not to reproduce every possible physiological variable simultaneously. It is to reproduce the variables that control the relevant product mechanism.

Qualification should therefore proceed in linked stages. First, the trigger must be measured across a physiologically plausible range rather than at a single nominal condition. Second, the formulation transformation produced by that trigger must be reproducible. Third, the transformation must generate a meaningful change in drug availability. Fourth, the relationship between that availability change and downstream exposure or response must be tested at the appropriate translational level. These four links constitute a proposed qualification architecture, not a current regulatory requirement.

Dynamic dissolution methods are particularly useful when the formulation crosses rapidly changing environments. Buffer composition, gastric-to-intestinal transition profiles, mechanical stress, absorptive sink, regional fluids, and patient-state variables should be incorporated only when mechanistic evidence indicates that they discriminate among relevant product states. Greater physiological complexity is not intrinsically more predictive.

Feedback-controlled systems require additional measurements because the controller itself becomes part of product performance. Sensor precision, response lag, actuator reproducibility, control stability, and the persistence of the trigger–response relationship must be evaluated together. A responsive material may pass conventional release testing while failing as an adaptive system if its sensed variable is noisy or its actuation occurs after the therapeutically useful interval.

Qualification must also distinguish robustness from sensitivity. A useful adaptive formulation should respond strongly to variables that matter while remaining comparatively insensitive to irrelevant variation. This creates a different optimization target from conventional maximization of stimulus response. The desirable system is not the one with the largest change in release under laboratory triggering; it is the one whose change is appropriately scaled, selective, reproducible, and connected to a meaningful downstream consequence.

For clinical translation, the decisive evidence will often require progressive linkage across in vitro, ex vivo, mechanistic-model, preclinical, and human data rather than reliance on one decisive experiment. Adaptive-release claims should consequently be stated at the level actually supported: physicochemical responsiveness, altered release, altered absorption, altered systemic exposure, or altered therapeutic response. Crossing from one level to the next requires evidence rather than assumption.

CONCLUSION

Advanced formulations need not be conceptualized exclusively as static dosage forms with a single intrinsic release profile. For products whose behavior is materially conditioned by gastrointestinal physiology, tissue state, microbial activity, temporal therapeutic need, or measurable patient variables, release can instead be designed as a controlled response to changing conditions.

The useful distinction is not between "conventional" and "smart" formulations, but among preprogrammed release, stimulus-responsive release, and true feedback-controlled delivery. Each solves a different problem and introduces different failure modes. Greater responsiveness is therefore not inherently better. Poorly discriminating triggers, mismatched time scales, self-perturbation, downstream absorption limits, patient heterogeneity, manufacturing constraints, and measurement uncertainty can all convert apparent adaptivity into unstable or clinically irrelevant behavior.

The proposed adaptive-release framework treats patient or environmental state, formulation transformation, drug availability, downstream exposure, and reassessment as separable analytical layers. Its purpose is to identify where adaptation is scientifically justified and where a robust static formulation remains preferable. Future progress will depend less on adding more triggers than on establishing which variables genuinely control performance, how reliably formulations respond to them, and whether those responses translate across the boundary from release to meaningful exposure and therapeutic effect.

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