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Review Article

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Patient-Centred Formulation Technologies for Complex Dosing Environments

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ABSTRACT

Pharmaceutical technologies increasingly permit modification of dose, dosage-form geometry, release behaviour, administration route, and production location. However, technological flexibility does not necessarily make a medicine patient-centred because the same product may perform differently when confronted with swallowing limitations, developmental or age-related gastrointestinal physiology, dose-adjustment requirements, caregiver-mediated administration, or constrained home-use conditions. This scoping review examines how formulation technologies interact with patient capability, physiological variability, administration conditions, and delivery-system requirements in complex dosing environments. A scoping-review approach was used to organize recent evidence on age-appropriate dosage forms, administration and swallowing constraints, flexible and modular dosing, three-dimensional printing, long-acting delivery, device-enabled administration, and decentralized production. Evidence was charted according to technology characteristics, patient factors, pharmaceutical state, administration conditions, and the level at which performance was demonstrated. The evidence indicates that acceptability, manufacturability, dose flexibility, dissolution behaviour, prolonged release, and portability represent distinct dimensions rather than interchangeable indicators of patient-centred performance. Paediatric and geriatric applications especially expose mismatches between standardized products and heterogeneous physiological or administration states. Flexible and digitally manufactured dosage forms can address selected dose and usability constraints, but technical success does not establish clinical benefit, biopharmaceutical robustness, or suitability across settings. Patient-centred formulation design is better treated as a problem of conditional fit among the patient, dosage form, physiological environment, and administration system. Technologies should therefore be evaluated against the dosing environment they must tolerate rather than against customization capability alone.

Keywords: *Patient-centred formulation, Age-appropriate dosage forms, Flexible dosing, Pharmaceutical 3D printing, Drug administration, Complex dosing environments*

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INTRODUCTION

Pharmaceutical product design has traditionally been dominated by requirements that can be standardized at the population level: dose strength, chemical and physical stability, manufacturability, quality specifications, and reproducible release. Patient-centred formulation design expands that problem by asking whether the resulting

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product remains usable, safe, and pharmaceutically appropriate when administered by individuals whose abilities, physiology, treatment routines, and care environments differ materially. Reviews of age-appropriate oral dosage forms have consequently emphasized that acceptability, safety, dose flexibility, access, stability, and manufacturability must be balanced rather than optimized independently [1]. A technologically sophisticated dosage form can therefore still be poorly matched to the patient if its use introduces manipulation, identification, administration, or adherence burdens that were not represented in the development pathway [2].

These tensions become particularly visible in paediatric practice. Caregiver surveys demonstrate that perceived acceptability of oral dosage forms is influenced by experience, formulation familiarity, and administration context rather than by a simple hierarchy of preferred technologies [3]. Hospital observations similarly show that younger children may require crushing, dispersion, subdivision, or other modification of conventional products and may not receive the complete intended dose after administration [4]. Such observations do not demonstrate that one alternative formulation would necessarily be superior, but they expose a recurring design failure: a pharmaceutical product may satisfy manufacturing specifications while transferring substantial dosing work to the child, caregiver, or clinical team.

Older adults present a related but distinct problem. Tablet dimensions influence acceptability in older populations, particularly when swallowing capacity is reduced [5]. Yet medicine-taking burden is not limited to swallowing. Interviews with older patients, carers, and healthcare professionals identify product recognition, handling, extraction from packaging, manipulation, and administration as separable stages at which oral solid dosage forms may become difficult to use [6]. Patient centricity therefore cannot be reduced to palatability or swallowability alone.

This review examines formulation technologies through the concept of the complex dosing environment: the combined pharmaceutical, physiological, behavioural, and logistical conditions under which a medicine must actually be prepared and administered. The central argument developed here is that customization is only one possible response to complexity. A patient-centred product must also preserve dose accuracy, pharmaceutical performance, interpretability of release behaviour, and practical administration under the conditions for which it is intended. The review consequently separates technological capability from patient suitability and distinguishes direct evidence of formulation performance from the broader clinical or translational inferences that such evidence can legitimately support.

MATERIALS AND METHODS

The review was structured as a scoping review and reported in accordance with the methodological logic of PRISMA-ScR, which emphasizes transparent identification of information sources, eligibility criteria, charting methods, and evidence selection [7]. The review question was deliberately broader than comparative effectiveness. It addressed how formulation technologies interact with patient characteristics and administration environments and where the available literature identifies boundaries between technical feasibility and patient-relevant performance.

Literature discovery covered patient-centred pharmaceutical design, age-appropriate formulations, swallowability, dosage-form manipulation, minitablets and multiparticulates, flexible or modular dosing, pharmaceutical three-dimensional printing, biorelevant dissolution, age-related gastrointestinal conditions, long-acting delivery, device-enabled administration, and decentralized manufacture. Peer-reviewed evidence published within the predefined review period was prioritized, with recent evidence used wherever it directly addressed the review domains and older sources retained for methodological or foundational patient-centred formulation concepts.

The evidence was synthesized descriptively rather than pooled statistically. Experimental formulation studies, human observational studies, clinical implementation reports, physiological studies, regulatory or methodological analyses, and focused reviews were treated as different evidence classes. Bench-scale printability, dissolution, mechanical performance, dose-content accuracy, or release testing were therefore not interpreted as equivalent to clinical acceptability, pharmacokinetic performance, treatment adherence, or therapeutic benefit.

The search interface used for the review did not expose an auditable complete database-export history from which exact retrieval, deduplication, screening, and full-text exclusion totals could be reconstructed. Accordingly, numerical review-flow counts are not reported or inferred. The reference bibliography is not treated as a surrogate for an included-study count.

PCC framework

The Population–Concept–Context framework was adapted to the pharmaceutical question rather than applied as a demographic filter alone. Population encompassed patients whose dosing requirements or administration capabilities create formulation-relevant constraints, including children, older adults, people with swallowing or handling difficulties, individuals requiring nonstandard dose increments, and patients receiving therapy outside tightly controlled clinical environments. The population definition therefore reflected functional dosing requirements rather than age category alone.

The Concept comprised formulation and delivery technologies intended to modify dose flexibility, dosage-form usability, release behaviour, administration route, or manufacturing location. These included multiparticulate and minitablet approaches, modular dosage units, extrusion-based and other pharmaceutical three-dimensional printing technologies, long-acting formulations, and device-enabled administration. Technologies were not classified as patient-centred merely because they allowed customization.

The Context was defined as the dosing environment in which the product must function. This included caregiver-mediated dosing, limited swallowing capacity, altered gastrointestinal fluid or transit conditions, repeated dose adjustment, home administration, and decentralized or resource-constrained production. This framing permitted the review to distinguish a product attribute from the environment in which that attribute becomes useful or problematic.

The review therefore used a proposed four-part interpretive distinction: patient capability, product adaptability, physiological robustness, and administration-system feasibility. These dimensions were used to organize evidence but are not presented as an empirically validated composite scale.

Search and eligibility

Eligible publications addressed at least one direct connection between a formulation or delivery technology and a patient-relevant dosing constraint. Studies were retained when they provided empirical, clinical, methodological, physiological, regulatory, or formulation evidence capable of informing the design problem. Purely promotional descriptions of technologies, non-peer-reviewed reports, and sources without usable formulation- or administration-level evidence were not used as core evidence.

Eligibility was intentionally sensitive to evidence level. A printing study could establish manufacturability, dose-content control, mechanical integrity, or dissolution behaviour without establishing acceptability or clinical effectiveness. A human gastrointestinal study could characterize fluid volume, pH, or transit without proving altered exposure for a specific product. Likewise, a patient-preference study could establish administration experience without demonstrating improved pharmacokinetics. These distinctions were retained during charting rather than collapsed into a generic designation of "successful" technology.

Because the available search environment did not provide complete native database-export counts, the review does not report numerical screening arithmetic that cannot be independently reconstructed. This methodological limitation is carried forward explicitly rather than replaced with estimated or bibliography-derived values.

Technology and patient-factor coding

Technology and patient factors were coded as separate analytical dimensions. The technology dimension described the controllable pharmaceutical property: unit size, dose modularity, disintegration behaviour, dissolution or release pattern, print architecture, depot formation, administration device, or production location. The patient-factor dimension described the condition under which that property acquired clinical relevance: swallowing capacity, manual dexterity, caregiver dependence, gastrointestinal state, dose-adjustment requirement, visual accessibility, frequency of administration, or home-use capability.

This distinction was particularly important for swallowability. An analysis of clinical swallowability assessments submitted in regulatory contexts found substantial heterogeneity in study design and measurement approaches [8]. A dosage form categorized as swallowable under one assessment framework cannot therefore be assumed to possess an invariant patient-use property independent of population, product dimensions, administration instructions, and measurement method.

A similar distinction applies to apparently flexible dosage forms. Minitablets can permit fine dose adjustment and may be suitable for patients who cannot use conventional tablet strengths, yet the practical problem of accurately dispensing, counting, packaging, and administering multiple small units has not disappeared [9]. Patient-factor coding therefore included the dosing work transferred from manufacturing to the patient, caregiver, pharmacist, or administering device.

Evidence charting

Evidence was charted by asking not only what a technology could do but also where its apparent success could become misleading. The first layer recorded the demonstrated pharmaceutical capability. The second recorded the patient or administration condition that motivated the technology. The third identified the evidence level at which performance had been demonstrated. The fourth recorded the principal transfer boundary preventing that result from being interpreted more broadly.

This approach was necessary because technically positive results can fail at different levels. A small unit may be easy to swallow but difficult to count accurately. A printed formulation may meet dose-content specifications yet display medium-dependent dissolution. A long-acting formulation may prolong drug release while introducing injection, depot, device, or persistence burdens. Conversely, failure in one configuration does not invalidate the entire technology class because material properties, dose, geometry, manufacturing conditions, physiological environment, and user characteristics can alter the result.

To make these distinctions visible without converting them into an unsupported score, **Table 1** organizes the principal kinds of misleading or incomplete success that the review must adjudicate.

Table 1. Failure-mode triage for interpreting patient-centred formulation evidence

Observed configuration	Mechanism and competing diagnosis	
Observed or apparent success state / Signal closer examination	**Likely origin of misinterpretation / Formulation or process lever**	**Patient-dependent modifier / Residual question before a patient-centred claim is justified**
Observed or apparent success state: Small or subdivisible unit appears easy to administer Signal requiring closer examination: Counting burden, loss of units, manipulation, incomplete administration	**Likely origin of misinterpretation:** Unit size treated as sufficient evidence of usability **Formulation or process lever:** Unit dimensions, packaging, dispensing method	**Patient-dependent modifier:** Dexterity, cognition, caregiver dependence **Residual question before a patient-centred claim is justified:** Can the intended dose be prepared and administered reproducibly under real-use conditions?
Observed or apparent success state: Customized dose is technically manufacturable Signal requiring closer examination: Content variation, formulation-specific printability, unstable production window	**Likely origin of misinterpretation:** Dose personalization equated with dose suitability **Formulation or process lever:** Drug loading, geometry, material rheology, manufacturing settings	**Patient-dependent modifier:** Required dose increment and frequency of adjustment **Residual question before a patient-centred claim is justified:** Does customization remain accurate and practical across the required dose range?
Observed or apparent success state: Rapid or prolonged dissolution is achieved in vitro Signal requiring closer examination: Medium sensitivity, crystallization, precipitation, delayed disintegration	**Likely origin of misinterpretation:** Release profile interpreted independently of medium and physiological state **Formulation or process lever:** Polymer, solid state, excipients, release architecture	**Patient-dependent modifier:** Gastrointestinal fluid, pH, transit, food and age-related physiology **Residual question before a patient-centred claim is justified:** Will the observed release behaviour remain relevant in the intended dosing environment?
Observed or apparent success state: Administration frequency is reduced Signal requiring closer examination: Injection, device, depot, persistence, reversibility or follow-up requirements	**Likely origin of misinterpretation:** Less frequent dosing equated with lower treatment burden **Formulation or process lever:** Depot chemistry, device design, release-controlling matrix	**Patient-dependent modifier:** Pain tolerance, self-administration ability, clinical monitoring needs **Residual question before a patient-centred claim is justified:** Is the lower frequency offset by new administration or safety burdens?
Observed or apparent success state: Production can be decentralized Signal requiring closer examination: Quality control, storage, material handling, operator dependence	**Likely origin of misinterpretation:** Portability equated with deployability **Formulation or process lever:** Printer/process design, feedstock, digital control	**Patient-dependent modifier:** Home resources, training, infrastructure **Residual question before a patient-centred claim is justified:** Can equivalent product quality be maintained outside centralized manufacture?

Note: The categories represent a proposed interpretive synthesis of the reviewed evidence. They are not a validated score, hierarchy, or ranking system. Vancouver citation numbers are intentionally excluded from the visible table.

The review-selection architecture would ordinarily be displayed at this point to distinguish source retrieval, deduplication, screening, eligibility, and inclusion from subsequent evidence charting. Because complete auditable selection-stage counts were not available, the visual architecture is retained without fabricated numerical labels.

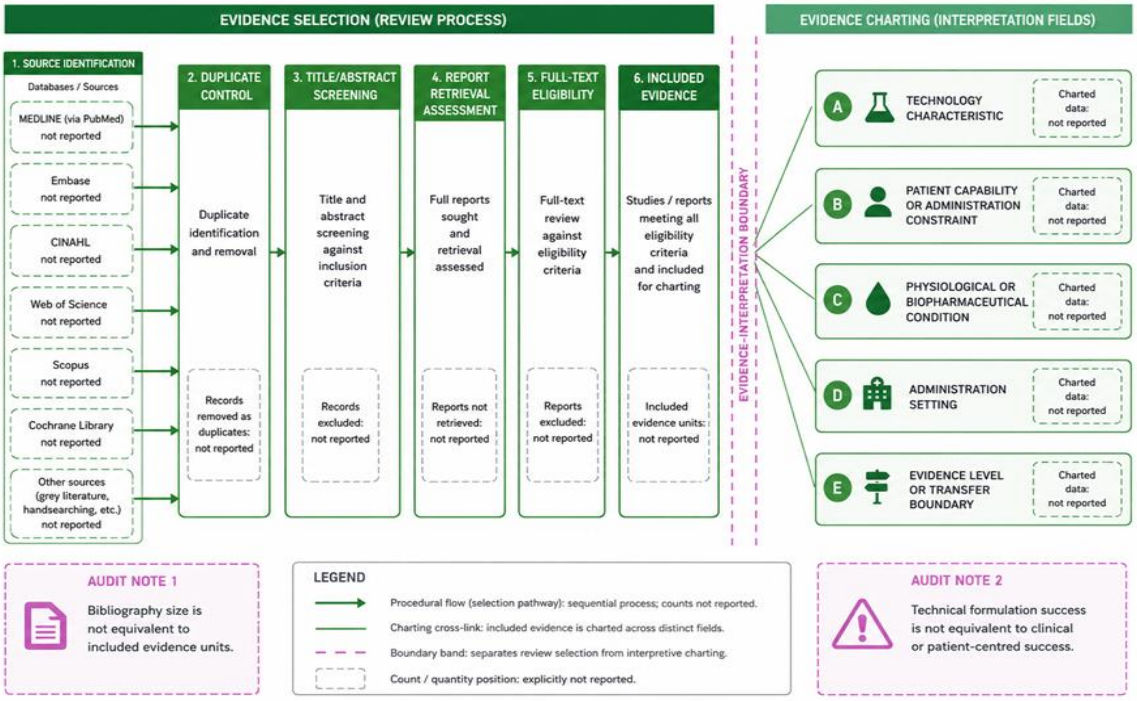


Figure 1. Selection-stage boundaries separating evidence retrieval, eligibility, and formulation-technology charting

RESULTS AND DISCUSSION

The selected literature fell into several interacting evidence domains rather than one homogeneous technology class. Patient-use studies addressed swallowing, handling, caregiver preference, product manipulation, and acceptability. Physiological studies described age-related intestinal protein expression, gastrointestinal fluid volume, pH, transit, and real-life medication intake. Formulation studies addressed dose flexibility, multiparticulates, modular units, and additive manufacture. Other evidence examined decentralized production, device-enabled delivery, and long-acting systems.

The findings consistently supported separation of technical capability from environmental suitability. Pharmaceutical technologies can modify the dosage form, but the patient-centred value of that modification depends on the constraints it is intended to resolve and on the new constraints it introduces.

Paediatric and geriatric formulations

Age-appropriate formulation design cannot be reduced to dividing patients into children, adults, and older adults. Biological maturation, functional capacity, treatment experience, disease state, and administration support vary substantially within these categories. Pediatric intestinal biology illustrates this problem. Quantitative analysis of intestinal transporter and metabolic-enzyme proteins has demonstrated age- and region-dependent expression patterns in neonatal and paediatric tissue [10]. Such data are relevant to developmental biopharmaceutics, but protein abundance alone cannot determine the absorption or exposure of an individual formulation.

Older populations are similarly heterogeneous. Magnetic-resonance measurements in fasted older adults demonstrate substantial variability in gastric and duodenal fluid volumes [11]. Wireless motility-capsule measurements further indicate that gastrointestinal transit and intraluminal pH can differ between older, geriatric, and younger groups, while also showing considerable within-group variability [12]. These observations caution against treating chronological age as a deterministic proxy for the luminal environment encountered by an oral dosage form.

Actual medicine-taking behaviour adds another layer. Older adults may consume tablets with relatively small fluid volumes, coordinate medication variably with food, or split and otherwise modify products as part of

routine administration [13]. Such conditions can differ from standardized dissolution or administration instructions. A product intended for older adults therefore needs to tolerate not merely an average age-associated physiology but a distribution of real administration states.

Flexible formulation technologies may address some of these problems. Dose-adjustable celecoxib sprinklets produced by hot-melt extrusion and fused-deposition modelling demonstrate that small printed units can provide controlled drug content while modifying solid state and dissolution behaviour [14]. Early hospital implementation has also shown that personalized three-dimensional printing can be used to prepare individualized oral medicines for children with rare metabolic disorders, although the clinical evidence remains limited to very small cohorts [15]. These findings demonstrate feasibility rather than broad superiority.

The pediatric application of advanced manufacturing also introduces constraints that are easy to overlook. Reviews of excipients used in extrusion-based three-dimensional printing emphasize incomplete age-specific safety information and the importance of considering excipient exposure relative to body weight and intended dose [16]. Personalizing the amount of active drug therefore does not automatically personalize the safety profile of the complete formulation.

Nonprinted flexible systems remain relevant. Dispersible multiparticulate formulations developed for paediatric tuberculosis demonstrate how formulation composition can influence disintegration and dissolution while supporting flexible combinations and administration [17]. Fused-deposition approaches for sodium valproate likewise show that drug loading and material rheology constrain the printable window even when the therapeutic need for flexible dosing is clear [18]. These studies collectively indicate that age-appropriate formulation requires alignment between patient need and an experimentally robust manufacturing space.

The decision problem is summarized in **Table 2** as a series of patient-formulation states rather than as a list of "good" or "bad" dosage forms.

Table 2. Decision states linking age-related dosing needs to pharmaceutical evidence and reassessment triggers

Decision context	Evidence and limits	Permitted action
Patient-centred question remaining	**Information available / Unresolved uncertainty**	**Decision state / Permissible formulation decision / Observation that should trigger reassessment**
Does flexibility reduce total dosing work rather than relocate it?	**Information currently available:** Required dose and conventional product limitations are known **Unresolved uncertainty:** Whether subdivision or manipulation preserves dose accuracy and usability	**Decision state:** Dose cannot be delivered reliably with available strength **Permissible formulation decision:** Consider smaller units, multiparticulates, modular dosing, or individualized manufacture **Observation that should trigger reassessment:** Recurrent manipulation error, incomplete administration, unacceptable preparation burden
Has the actual failure mechanism been addressed?	**Information currently available:** Patient or caregiver difficulty with conventional product is documented **Unresolved uncertainty:** Whether difficulty is driven by size, shape, packaging, identification, or administration method	**Decision state:** Swallowing or handling difficulty is present **Permissible formulation decision:** Adapt dosage-form dimensions or administration route only to the identified constraint **Observation that should trigger reassessment:** Persistent difficulty despite the modification
Is pharmaceutical performance robust to the expected physiological range?	**Information currently available:** Population-level physiological differences are documented **Unresolved uncertainty:** Individual magnitude and consequence for the specific formulation are unknown	**Decision state:** Age-related gastrointestinal differences are plausible **Permissible formulation decision:** Use age-informed biorelevant testing and avoid deterministic age assumptions **Observation that should trigger reassessment:** Release behaviour changes under relevant fluid, pH, or transit conditions
Does personalized manufacture improve the complete medication-use process?	**Information currently available:** Dose-content and manufacturability data are available **Unresolved uncertainty:** Clinical acceptability, workflow reliability,	**Decision state:** Personalized manufacturing is technically feasible **Permissible formulation decision:** Use personalization within a controlled production and validation framework

	excipient exposure, and scale-up remain uncertain	**Observation that should trigger reassessment:** Printing instability, changing dose requirement, unacceptable excipient burden, or poor administration experience
Can the product be used correctly outside controlled clinical conditions?	**Information currently available:** Intended setting and responsible user are known **Unresolved uncertainty:** Storage, counting, preparation, training, and error risks are incompletely characterized	**Decision state:** Home or caregiver administration is expected **Permissible formulation decision:** Select the least burdensome formulation compatible with pharmaceutical requirements **Observation that should trigger reassessment:** Repeated dosing error or dependence on unavailable resources

Note: The decision states are proposed synthesis derived from the reviewed evidence and do not constitute validated clinical decision rules.

Swallowing and administration constraints

Swallowability is frequently treated as an intrinsic property of the dosage form, yet the evidence indicates that it is better considered a relation between product dimensions, patient capability, administration method, and assessment procedure. Tablet size can influence acceptability in older people, but the same individual may experience additional difficulty identifying the correct medicine, extracting it from packaging, manipulating it, or coordinating administration with food or fluid. Paediatric administration can be further complicated by caregiver preparation and the need to modify products not designed for the intended age.

These constraints create an important distinction between formulation adaptation and administration transfer. A dosage form may appear flexible because it can be crushed, dispersed, divided, counted, or sprinkled, but each additional manipulation transfers a portion of dose preparation from controlled manufacture to the administration setting. The relevant question is therefore not simply whether modification is possible, but whether the final dose remains reproducible and whether the manipulation burden is compatible with the patient or caregiver.

Minitablets illustrate the ambiguity. Their small unit size can support flexible dosing and may reduce swallowing difficulty, yet large dose requirements can convert one swallowing problem into a counting or dispensing problem. Patient-centred design should therefore seek the lowest overall administration burden compatible with pharmaceutical performance rather than assuming that smaller units are intrinsically preferable.

Flexible and modular dosing

Flexible dosing technologies address a fundamental mismatch between fixed industrial strengths and variable individual requirements. Their principal advantage is not personalization as an abstract goal, but the ability to construct clinically relevant dose increments without relying on inaccurate tablet splitting, repeated liquid measurement, or complex extemporaneous manipulation.

Modular manufacturing illustrates one route to this flexibility. Bilayer dosage forms produced through droplet-deposition modelling and injection moulding demonstrate that manufacturing architecture can be used to tailor release behaviour, but successful processing depends on drug and formulation properties rather than geometry alone [19]. A modular design is therefore not a universal release-control strategy; its value depends on whether the selected material and manufacturing state provide reproducible pharmaceutical behaviour.

An alternative approach is to construct doses from standardized pharmaceutical modules. A tunable modular system developed for citalopram tapering demonstrated fine dose increments across a broad experimental range and lower bench variability than manual tablet division [20]. The pharmaceutical significance is clear: modular construction can create dose resolutions that conventional commercial strengths do not provide. The clinical implication, however, must remain narrower. Greater manufacturing precision does not by itself demonstrate improved withdrawal outcomes, adherence, or safety.

Flexible dosing should therefore be evaluated through three linked questions. First, can the required dose increment be produced accurately? Second, does changing the number, geometry, or combination of units alter disintegration, dissolution, release, or administration burden? Third, can patients, caregivers, pharmacists, or automated systems assemble and administer the intended configuration reproducibly? A technology is genuinely patient-centred only when its flexibility reduces an important dosing constraint without creating a larger pharmaceutical or administration failure elsewhere.

3D-printed and on-demand dosage forms

Three-dimensional printing extends flexible dosing by allowing dose, geometry, internal architecture, and sometimes release characteristics to be modified within a digital manufacturing workflow. The central interpretive problem is that the printed object entering the gastrointestinal tract is not the same state that ultimately governs drug availability. Printed geometry influences disintegration and release, but subsequent hydration, dissolution, ionization, supersaturation, precipitation, gastrointestinal transit, and luminal conditions can redirect performance after administration.

This distinction becomes important when conventional dissolution conditions are used to interpret individualized products. Comparative testing of immediate-release products containing poorly soluble ionizable drugs has shown that dissolution profiles can differ materially between bicarbonate-based biorelevant media and conventional phosphate buffers [21]. A favorable dissolution curve generated under one buffer system therefore cannot automatically be treated as a stable property of the dosage form across physiological conditions.

Solid-state transformation introduces another boundary. Experimental work with amorphous glibenclamide demonstrated that polymer characteristics and formulation state can alter dissolution, supersaturation, and crystallization behaviour [22]. For personalized manufacture, changing geometry or dose may therefore interact with material composition and drug phase rather than simply scaling an otherwise invariant dosage form.

Three-dimensional printing can nevertheless combine functions that conventional manufacture separates. Bupropion tablets manufactured with tactile Braille features demonstrated that dosage-form architecture can incorporate accessibility characteristics while also modifying sustained-release behaviour [23]. Such multifunctionality is potentially relevant to patients with visual impairment, but tactile accessibility, pharmaceutical release, and medication adherence remain distinct outcomes.

The broader precision-pharmaceutical literature similarly indicates that patient-specific data must ultimately be translated into manufacturable products whose quality attributes remain controllable [24]. Personalization therefore requires more than selecting an individualized dose. The resulting product must remain chemically, mechanically, biopharmaceutically, and operationally suitable for its intended environment.

Portability further expands this problem. A compact semisolid-extrusion platform has demonstrated dose-adjustable production of selected personalized formulations outside conventional large-scale manufacturing equipment [25]. This establishes technical feasibility for decentralized manufacture but does not establish equivalence of quality control, regulatory oversight, storage, operator competence, or clinical deployment across settings.

The proposed interpretation in **Figure 2** therefore separates the manufactured dosage form from the gastrointestinal states through which its apparent performance can be transformed.

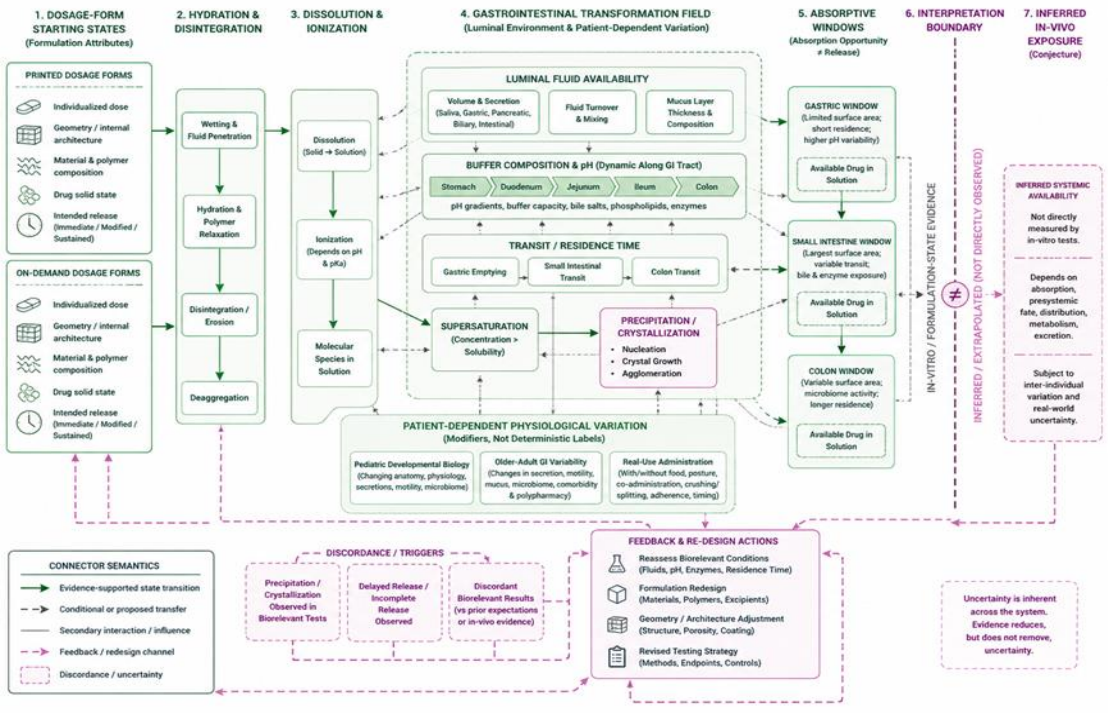


Figure 2. Gastrointestinal state changes separating printed dose architecture from oral exposure relevance

Long-acting and device-enabled delivery

Patient-centred delivery can also seek to reduce the frequency with which a patient must interact with a medicine. Device-enabled systems such as microneedles potentially support minimally invasive or self-administered delivery, but their performance depends on device design, skin interaction, manufacturing reproducibility, safety, and regulatory requirements [26]. Reduced administration frequency therefore represents one dimension of patient burden rather than a complete measure of convenience.

Long-acting injectable systems make this trade-off especially clear. PLGA-based formulations can exhibit release behaviour governed by polymer characteristics, drug distribution, degradation, diffusion, and formulation history [27]. Describing a product simply as "long acting" therefore obscures the evolving physical states that determine drug escape from a depot.

The pharmaceutical problem becomes more complex for hydrophilic drugs, proteins, and peptides because molecular properties constrain the technologies capable of retaining and releasing them over extended periods [28]. Platform selection must consequently begin with drug-specific compatibility rather than the desired dosing interval alone.

Contemporary long-acting delivery encompasses injectable depots, implants, device-assisted systems, and emerging technologies with different degrees of reversibility, procedural burden, monitoring, and release control [29]. Patient-centred evaluation should therefore examine the whole temporal administration state rather than equating longer duration with superior usability.

Table 3 makes the temporal dimension explicit.

Table 3. Temporal states governing the patient relevance of long-acting and device-enabled delivery

State and entry conditions	Evidence through time	Transition and reassessment
Governing pharmaceutical condition / Drug availability state	**Temporal state / Transition or persistence concern**	**Patient-facing consequence / Validation need before broader interpretation**
Governing pharmaceutical condition: Device, injection, implant, or application procedure **Drug availability state: Drug largely retained in delivery system**	**Temporal state:** Administration **Transition or persistence concern:** Failed placement or incomplete administration	**Patient-facing consequence:** Pain, handling, training, procedural or access burden **Validation need before broader interpretation:** Demonstrate reproducible delivery under intended users and settings
Governing pharmaceutical condition: Initial hydration, diffusion, device–tissue interaction or depot establishment **Drug availability state: Initial release or retained fraction**	**Temporal state:** Early post-administration **Transition or persistence concern:** Burst release or incomplete depot formation	**Patient-facing consequence:** Early exposure and local tolerability **Validation need before broader interpretation:** Characterize early release and local response
Governing pharmaceutical condition: Polymer degradation, diffusion, erosion, membrane transport or device-controlled release **Drug availability state: Sustained availability**	**Temporal state:** Established delivery state **Transition or persistence concern:** Interpatient or formulation-dependent release variation	**Patient-facing consequence:** Reduced dosing frequency **Validation need before broader interpretation:** Establish time-resolved release robustness
Governing pharmaceutical condition: Residual depot/device material and declining drug content **Drug availability state: Diminishing or persistent release**	**Temporal state:** Late delivery state **Transition or persistence concern:** Delayed clearance, difficult reversibility, prolonged tail	**Patient-facing consequence:** Continued exposure despite changing clinical need **Validation need before broader interpretation:** Define persistence and clinically relevant termination behaviour
Governing pharmaceutical condition: Treatment need, adverse effect, dose requirement or patient preference changes **Drug availability state: Existing system may continue releasing drug**	**Temporal state:** Reassessment state **Transition or persistence concern:** Inability to rapidly stop or retitrate therapy	**Patient-facing consequence:** Limited immediate dose flexibility **Validation need before broader interpretation:** Determine when long duration becomes a constraint rather than a benefit

Note: These temporal states constitute a proposed interpretive organization of long-acting delivery evidence, not a validated clinical classification.

Home and resource-constrained administration

Moving treatment from clinic to home can reduce travel and professional administration requirements, but it also redistributes responsibility for preparation, storage, operation, and error control. Patient-centred design must therefore evaluate what infrastructure a formulation assumes.

Real-life medicine taking among older adults demonstrates that administration commonly occurs under variable fluid, food, timing, and tablet-manipulation conditions [13]. These behaviors matter because standardized laboratory or clinical instructions may not reproduce the environment in which medicines are routinely used.

Decentralized additive manufacture illustrates both the opportunity and the risk. Pharmaceutical three-dimensional printing has been proposed as a route toward localized or point-of-care production, but implementation requires governance of digital prescriptions, material supply, equipment qualification, operator responsibility, and product release [30]. Portable printing devices extend technical accessibility [25], yet portability does not establish that equivalent product quality can be maintained in every home, pharmacy, rural service, or resource-limited environment.

Device-enabled delivery creates similar trade-offs. Systems intended for self-administration may reduce reliance on trained personnel while increasing dependence on correct device handling, skin application, storage, or disposal [26]. Resource constraints therefore interact with formulation and delivery design rather than sitting outside them.

Table 4 converts these claims into explicit adjudication questions.

Table 4. Claim-to-test adjudication for medicines intended for home or resource-constrained administration

Evidence configuration	Interpretive alternatives	Adjudication requirement
use claim / Minimum supporting observation	**Strong alternative explanation**	**Decisive test / Interpretation permitted if test succeeds**
Proposed use claim: A dosage form is suitable for home use Minimum supporting observation: Intended users can prepare and administer it under realistic instructions	Success reflects supervised demonstration rather than independent use	**Decisive test required:** Unsupervised or minimally supported usability assessment **Interpretation permitted if test succeeds:** Home administration is feasible under the tested conditions
Proposed use claim: Portable manufacturing enables decentralized personalization Minimum supporting observation: Device produces the intended dose and product characteristics	Performance depends on controlled materials, trained operators or laboratory infrastructure	**Decisive test required:** Reproducibility testing across intended decentralized environments **Interpretation permitted if test succeeds:** Decentralized production is technically reproducible within those conditions
Proposed use claim: Reduced clinic attendance lowers overall treatment burden Minimum supporting observation: Administration frequency or facility visits decrease	Burden is transferred to storage, preparation, device handling or monitoring	**Decisive test required:** Whole-workflow assessment including transferred tasks **Interpretation permitted if test succeeds:** Net administration burden is reduced for the evaluated population
Proposed use claim: A self-administered device improves access Minimum supporting observation: Users can correctly apply or operate the system	Apparent accessibility depends on dexterity, vision, cognition or training	**Decisive test required:** Population-specific human-factors testing **Interpretation permitted if test succeeds:** The device is usable for the studied user group
Proposed use claim: Product performance is robust in constrained settings Minimum supporting observation: Required quality attributes remain within specification	Laboratory robustness does not survive temperature, storage, supply or handling variation	**Decisive test required:** Stability and performance testing under intended field conditions **Interpretation permitted if test succeeds:** Pharmaceutical robustness is demonstrated within the tested environmental range

Note: The adjudication logic is proposed synthesis. Passing one test does not establish clinical superiority, regulatory acceptance, or universal transferability.

Across the reviewed evidence, patient-centred formulation emerges as a problem of conditional fit rather than technological sophistication. Conventional tablets can fail because patients cannot swallow, manipulate, identify, or dose them reliably, but advanced formulations can introduce their own counting, printing, release, device, storage, or quality-control burdens. The relevant comparison is therefore not “standard” versus

"personalized" technology. It is whether the complete medication-use configuration matches the patient and environment more effectively.

A second recurring issue is transfer between evidence levels. Swallowability assessments vary methodologically [8]. Age-related intestinal protein expression, gastrointestinal fluid volume, transit, and pH reveal physiologically relevant heterogeneity [10]. Real-life administration introduces additional variation [13]. Biorelevant dissolution studies show that apparently modest changes in test conditions can alter observed release behaviour [21]. These findings collectively argue against interpreting technical measurements as context-free product properties.

The same principle applies to long-acting delivery. Polymer composition and depot state can influence sustained release [27], while different molecular classes require different technological solutions [28]. Extending release may reduce administration frequency but can reduce immediate reversibility or dose flexibility. Patient centricity is therefore multidirectional: improving one dimension may worsen another.

This review consequently proposes that formulation performance be interpreted through four simultaneously considered planes—patient capability, product adaptability, physiological robustness, and administration-system feasibility. The proposal organizes existing evidence but has not been prospectively validated as a clinical prediction tool.

Patient-centred design framework

The proposed design framework begins with the patient capability plane, which asks what the intended user can swallow, manipulate, identify, prepare, tolerate, and administer reliably. These requirements should be specified before selecting an enabling technology.

The product adaptability plane asks which pharmaceutical characteristics can be altered without destabilizing dose accuracy or performance. Dose, geometry, unit number, solid state, release-controlling materials, packaging, and device configuration should not be assumed to be independently adjustable.

The physiological robustness plane asks whether the product remains interpretable across the physiological conditions relevant to its intended population. Pediatric maturation, older-adult gastrointestinal variability, luminal fluid volume, pH, transit, food, administration fluid, and precipitation risk can become important depending on the product. Population descriptors should identify conditions requiring evaluation, not substitute for direct biopharmaceutical evidence.

The administration-system feasibility plane considers where and by whom the dose will be produced, stored, prepared, and administered. A product intended for decentralized use must tolerate the human, material, environmental, and quality-control conditions of that setting.

A patient-centred formulation decision is therefore strongest when these four planes converge. Discordance between them should trigger reassessment rather than being hidden by a favorable result in one domain.

Evidence gaps

Several gaps limit stronger conclusions. Clinical evidence remains much thinner than formulation-development evidence for many personalized manufacturing technologies. Pediatric excipient safety is incomplete for materials increasingly considered for additive manufacture [16]. Relationships between age-related gastrointestinal physiology and performance of specific personalized dosage forms remain insufficiently characterized. Biorelevant dissolution can reveal medium sensitivity, but predictive transfer to individual exposure requires product-specific validation.

Decentralized manufacture likewise needs stronger evidence on reproducibility, digital control, material supply, operator effects, stability, and quality release outside specialist environments. Device-enabled and long-acting systems require greater attention to reversibility, persistence, human factors, local tolerability, and the full burden transferred from repeated dosing to occasional but more complex administration.

Future studies should therefore link formulation characterization to realistic administration states rather than testing technologies only under idealized conditions. Patient-centred design will require evidence connecting pharmaceutical performance, user capability, physiological variability, and delivery setting without assuming that success at one level guarantees success at another.

CONCLUSION

Patient-centred formulation technology is best understood as the deliberate matching of a pharmaceutical product to the conditions under which a specific population must use it. Dose personalization, small dosage forms, three-

dimensional printing, long-acting delivery, and self-administration can each resolve important problems, but each can also create new pharmaceutical or practical constraints. The most defensible design strategy is therefore not to maximize customization, duration, or technological novelty independently, but to optimize fit across patient capability, product adaptability, physiological robustness, and administration-system feasibility. This framework remains a proposed synthesis requiring prospective validation across products, populations, and real-world dosing environments.

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