

REVIEW ARTICLE

A Review on Four-Dimensional Additive Manufacturing of Oral Solid Dosage Forms



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Publication history: Received on 22nd June 2026; Revised on 11th August 2026; Accepted on 12th August 2026

Article DOI: 10.69613/xv825869

Abstract: Four-dimensional oral dosage forms utilize stimuli-responsive polymeric networks to execute post-fabrication conformational changes upon exposure to physiological triggers, including hydrational gradients, luminal pH transitions, localized enzymatic cleavage, and core physiological temperatures. These formulations modulate drug release kinetics via triggered surface area expansion, controlled matrix erosion, internal pore development, and spatial compartment exposure by coupling digital structural configuration with responsive polymer dynamics. Gastroretentive systems represent a primary therapeutic focus, utilizing shape-memory polymer architectures that preserve a compact geometry for oral administration and subsequently unfold or expand within gastric fluid beyond the diameter of the resting human pyloric orifice, resisting phase III migrating motor complex clearance. Similarly, site-directed colonic release, multi-active polypill isolation, and zero-order delivery kinetics are achieved by synchronizing structural kinetics with regional gastrointestinal transit. Translating four-dimensional oral architectures from concept to standard practice requires resolving significant engineering and regulatory hurdles, notably active ingredient thermodegradation during hot-melt processing, anisotropic mechanical stresses during layer-by-layer fusion, long-term shape-memory recovery drift under ambient storage conditions, and the lack of compendial quality assessment standards. This review discusses about the mechanisms, formulation variables, processing pathways, analytical characterization protocols, and regulatory pathways necessary to transition four-dimensional additive manufacturing into reliable oral drug delivery platforms.

Keywords: Four-dimensional printing; Stimuli-responsive polymers; Shape-memory actuation; Additive biomanufacturing; Gastroretentive drug delivery.

1. Introduction

Solid oral dosage forms, especially tablets and hard capsules, are the predominant route of therapeutic drug administration due to non-invasive administration, dose precision, cost-effective manufacturing, and high physicochemical stability during extended storage [1]. However, conventional single-body compressed dosage forms present fundamental biopharmaceutical limitations when applied to drugs with challenging absorption profiles [2]. Systemic bioavailability after oral delivery is governed by a dynamic physiological environment characterized by broad luminal pH transitions ranging from 1.2 in the fasting gastric lumen to 7.4 in the distal ileum, variable gastric emptying times from 15 minutes to over 3 hours, pulsatile mechanical shear forces induced by the interdigestive migrating motor complex, and site-dependent metabolic enzymatic activities [3]. Consequently, drugs that exhibit a narrow absorption window restricted to the duodenum and proximal jejunum, such as levodopa, baclofen, and riboflavin, or those vulnerable to enzymatic and alkaline degradation in distal intestinal segments, suffer from erratic pharmacokinetic profiles and low oral bioavailability when delivered via conventional immediate- or sustained-release tablets [4].

To overcome these physiological barriers, advanced pharmaceutical technology has pursued gastroretentive drug delivery systems designed to prolong gastric residence time, maintaining localized drug release within the upper absorptive segments of the gastrointestinal tract [5]. Conventional formulation approaches include low-density floating matrices, bioadhesive systems targeting the gastric mucosa, high-density swelling systems, and expanding hydrophilic matrices [6]. While functional in specific scenarios, conventional systems remain hindered by high physiological variability [7]. Floating systems depend heavily on a continuous minimum gastric fluid volume and the presence of food, bioadhesive matrices often fail due to continuous mucus turnover and rapid epithelial sloughing, and conventional swelling hydrogels are frequently cleared prematurely through the relaxed human pylorus during strong phase III migrating motor complex contractions [8].

Additive manufacturing, commonly known as three-dimensional printing, emerged as an alternative fabrication route enabling the spatial arrangement of active pharmaceutical ingredients and excipients into digital architectures that cannot be produced by

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traditional tablet tooling by utilizing computer-aided design files, three-dimensional printing allows layer-by-layer construction of customized geometries [9]. Complex inner channel networks, density gradients, and isolated multiactive chambers within a single dosage form [10]. Despite these geometrical capabilities, standard three-dimensional printed pharmaceutical devices remain intrinsically static structures post-fabrication; their shape, porosity, and macroscopic internal architecture remain unalterable following print-bed detachment, relying solely on passive diffusion, water uptake, or uniform bulk/surface erosion for drug release [11].

Four-dimensional printing introduces the temporal domain as an active design variable within additive manufacturing [12]. In this paradigm, a digitally planned structure is manufactured from stimuli-responsive functional materials that react dynamically to predefined physiological or external triggers [13]. Upon exposure to environmental changes, such as gastric aqueous wetting, localized ionic fluctuations, enzymatic cleavage, or normal human body temperature, the fabricated matrix undergoes programmed mechanical, geometrical, or functional shifts [14]. These responsive shifts encompass volumetric expansion, controlled unfolding, spatial bending, selective membrane softening, or timed porosity activation [15]. In the context of oral drug delivery, four-dimensional structural actuation allows an oral dosage form to be swallowed in a streamlined, patient-compliant geometrical configuration that dynamically morphs into an expanded, retention-competent shape within the gastric lumen, thereby sustaining localized release before eventually breaking down to facilitate physiological intestinal clearance [16]. The convergence of parametric digital modeling, advanced additive manufacturing, and stimuli-responsive biomaterials establishes four-dimensional fabrication as an important platform for next-generation personalized oral drug delivery [17].

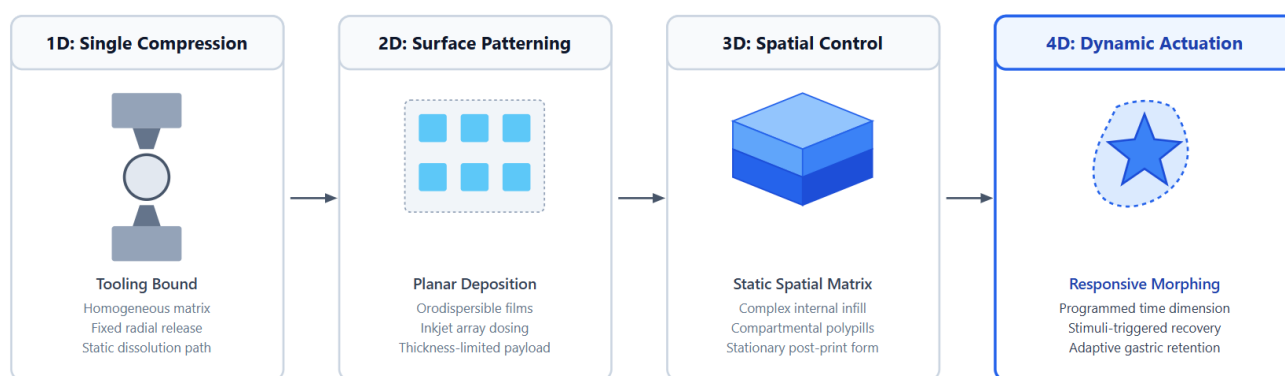


Figure 1. Evolution from conventional/additive manufacturing toward 4D pharmaceutical design

2. Principles of 4D Oral Drug Delivery

2.1. Shift from Static Additive Manufacturing to Dynamic 4D Systems

The distinction between three-dimensional and four-dimensional pharmaceutical printing resides in the functional responsiveness of the printed material network [18]. Standard three-dimensional printing is defined as a freeform fabrication process governed by Cartesian coordinates (x, y, z), yielding a static solid object whose spatial architecture remains immutable after fabrication until non-specific dissolution, swelling, or mechanical disintegration breaks the matrix down [19]. In contrast, four-dimensional printing incorporates mathematical transformations where spatial coordinates become time-dependent functions driven by environmental stimuli [20]:

$$P(t) = f(x_0, y_0, z_0, S, t)$$

where (x_0, y_0, z_0) represent the initial spatial coordinates of a material point, S denotes the localized stimulus intensity, and t represents elapsed physiological interaction time [21].

In standard additive manufacturing, post-extrusion or post-curing dimensional changes are considered structural defects, such as print warping, filament slumping, or unwanted hygroscopic swelling [22]. In four-dimensional design, such dimensional modifications are purposefully integrated into the digital model [23]. The structural changes are dictated by the localized composition, spatial polymer deposition path, printing directionality, and the physical crosslink architecture of the stimuli-responsive biomaterials [24]. Consequently, the dosage form shifts from an inert passive drug carrier to an adaptive mechanical device capable of executing scheduled physiological tasks [25].

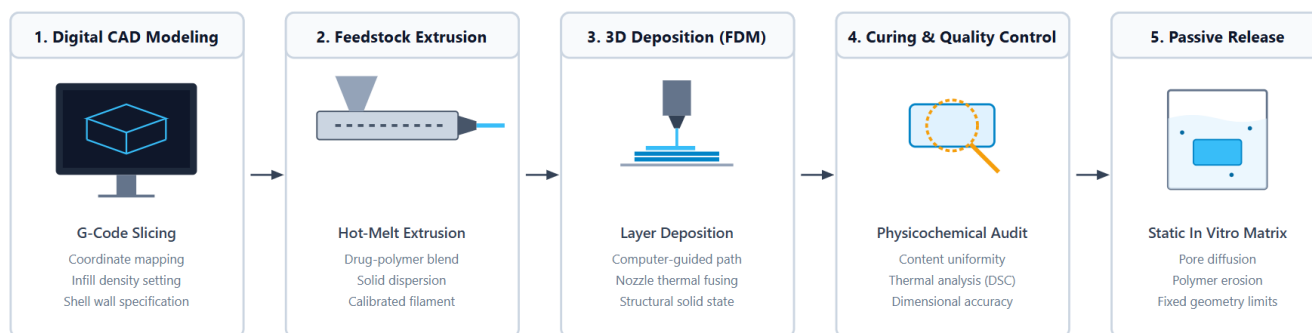


Figure 2. Simplified 3D-printed tablet manufacturing

2.2. The Time Dimension and Rate-Governing Mechanics

Time functions as a controllable design variable within four-dimensional formulation engineering [26]. The transformation sequence is mathematically governed by internal transport phenomena, heat conduction, solvent diffusion, and polymer chain relaxation kinetics [27]. When an oral tablet enters the stomach, the dynamic transformation undergoes a multi-stage physical trajectory [28]:

$$t_0 \rightarrow t_{\text{lag}} \rightarrow t_{\text{actuation}} \rightarrow t_{\text{functional}} \rightarrow t_{\text{elimination}}$$

The initial phase ($t_0 \rightarrow t_{\text{lag}}$) represents the physiological delay period where outer barrier matrices or encapsulating gelatin/hydroxypropyl methylcellulose shells dissolve, exposing the functional core while preventing premature deformation in the oral cavity or esophagus [29]. The actuation phase ($t_{\text{actuation}}$) describes the kinetic window during which the polymer network responds to surrounding solvent molecules, localized pH shifts, or core physiological temperature (37°C), executing mechanical strain recovery or anisotropic volumetric swelling [30].

The functional retention phase ($t_{\text{functional}}$) marks the sustained plateau during which the tablet retains its expanded or altered geometry, maintaining mechanical resistance against the crushing forces of gastric motility while releasing drug molecules at a programmed rate [31]. Finally, the elimination phase ($t_{\text{elimination}}$) initiates after significant active ingredient release, during which the polymeric backbones hydrolyze, crosslinking junctions dissociate, or physical erosion reduces the tablet's macroscopic dimensions below the human pyloric diameter (12.8 ± 7.0 mm), ensuring safe, unhindered clearance through the lower intestinal tract without creating bowel obstructions [32].

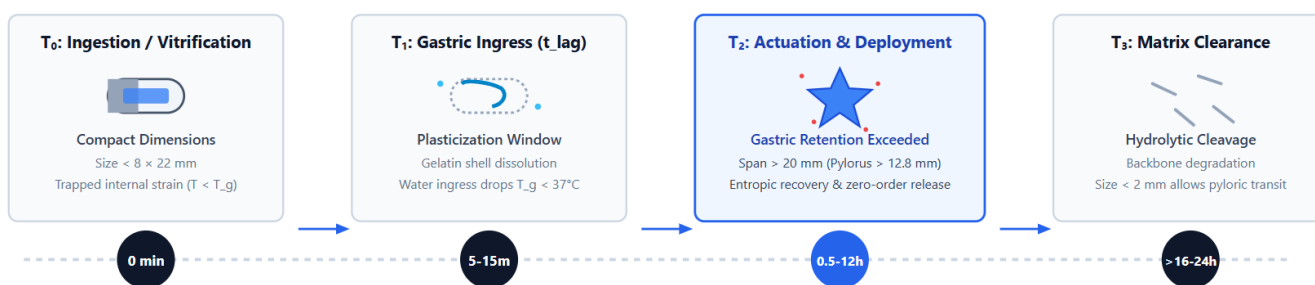


Figure 3. Programmed shape transformation over time

2.3. Integrated System Mechanics

The operational mechanics of a four-dimensional pharmaceutical tablet rely on an integrated feedback loop between the patient's internal physiological parameters, the macroscopic geometry, the micro-architecture, and the underlying material properties [33]. The structural changes must generate sufficient mechanical force to unfold or expand against the hydrostatic pressures and muscular contractions of the stomach wall, yet remain elastic enough to avoid causing mucosal abrasions or pressure-induced necrosis [34].



Figure 4. Working principle of a 4D-printed pharmaceutical system

The design process requires inverse mathematical modeling, wherein the desired final transformed geometry and drug release curve dictate the initial spatial deposition paths, layer thicknesses, and material distribution within the slicing software [35]. The operational parameters can be mapped across specific fabrication and activation stages:

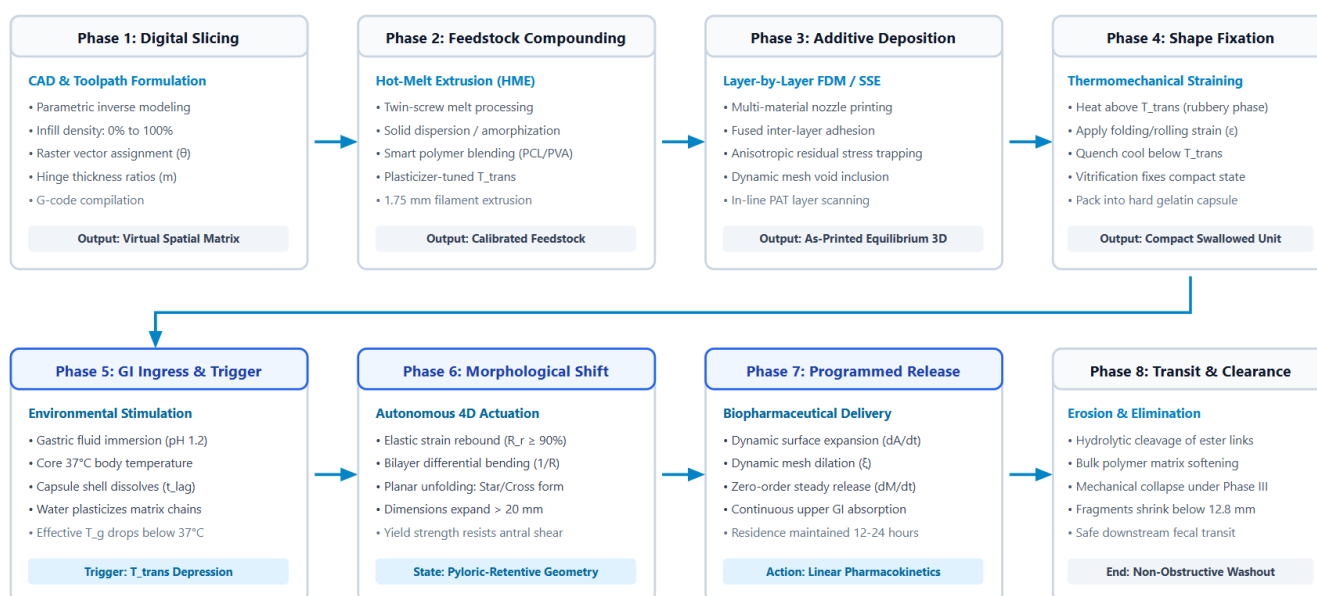


Figure 5. Eight-stage 4d Dosage Form Manufacturing & Lifecycle

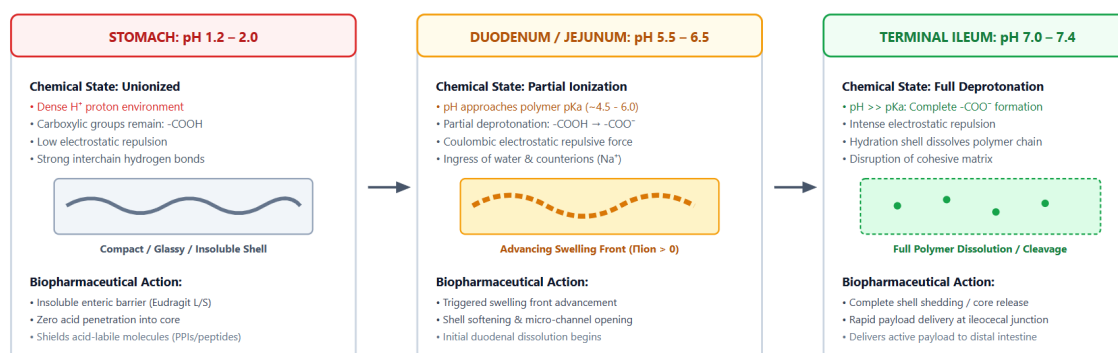
Table 1. Operational and Structural Stages in 4D Oral Dosage Form Fabrication and Biological Function

Sequence Phase	Operational Parameter	Structural State	Micro-Architectural Mechanics	Biopharmaceutical Consequence
Stage 1	Digital CAD Model Formulation	Virtual Coordinate Matrix	Slicing parameter assignments, toolpath vectoring, raster angles, infill voids	Establishes the spatial foundation for targeted mechanical deformation [36]
Stage 2	Responsive Material Selection	Raw Extrudable/Printable Media	Polymer backbone molecular weight, T_g/T_m specification, hydrophilic-lipophilic balance	Determines the environmental stimulus sensitivity and printing feasibility [37]
Stage 3	Drug-Polymer Compounding	Homogeneous Feedstock	Solid dispersion, active ingredient solubilization, polymer plasticization	Governs physical state (crystalline vs. amorphous) and matrix homogeneity [38]
Stage 4	Layer-by-Layer 3D Deposition	Solid Pre-programmed Intermediate	Inter-layer fusion, targeted anisotropic strain storage, internal void deposition	Preserves internal residual stresses within printed thermoplastic domains [39]
Stage 5	Mechanical Shape Fixation	Compact Swallowing Geometry	Polymer vitrification below T_{trans} under external compressive/folding strain	Yields a miniaturized dosage form suitable for patient administration [40]
Stage 6	Physiological Stimulus Encounter	Ingress of Gastric/Intestinal Fluids	Thermal equilibrium at 37°C , solvent wetting, protonation/deprotonation	Drives polymer segment mobility and osmotic swelling pressure generation [41]
Stage 7	Structural 4D Actuation	Expanded Macroscopic Architecture	Entropic net recovery, elastic rebound, unfolding of flexible hinge joints	Exceeds resting pyloric diameter ($> 15\text{ mm}$), preventing premature gastric emptying [42]
Stage 8	Rate-Programmed Drug Release	Dynamic Diffusional Matrix	Controlled tortuosity pathways, swelling-front advancement, surface erosion	Delivers zero-order, sustained, or targeted site-specific drug delivery [43]
Stage 9	Cleaving and Structural Clearance	Disintegrated Particulates	Hydrolytic backbone scission, ester bond cleavage, mechanical shear breakdown	Reduces dimension below 12.8 mm , promoting non-obstructive intestinal transit [44]

3. Physiological and External Stimuli-Responsive Mechanisms

3.1. pH-Responsive Polymer Systems

The human gastrointestinal tract presents a marked pH gradient that provides an autonomous internal trigger for site-specific delivery [45]. The gastric lumen maintains a strong acidic environment, typically between pH 1.2 and 2.0 in the fasted state, which increases to pH 3.0 to 5.0 postprandially [46]. The environment transitions abruptly across the pylorus into the duodenum (pH 5.5 to 6.5), the jejunum (pH 6.5 to 7.0), the terminal ileum (pH 7.0 to 7.4), drops slightly in the cecum (pH 5.7 to 6.4) due to bacterial fermentation, and stabilizes at pH 6.5 to 7.5 in the colon [47].

**Figure 6. Gastrointestinal pH Gradient and Polyelectrolyte Actuation Mechanism**

Synthetic and semi-synthetic polymers containing ionizable functional side groups react directly to these localized proton concentration shifts [48]. Polyacids, such as methacrylic acid-methyl methacrylate copolymers (Eudragit L100, S100) and cellulose acetate phthalate, contain carboxylic acid residues ($-\text{COOH}$) with dissociation constants ($\text{p}K_a$) ranging between 4.5 and 6.0 [49]. In the low-pH environment of the stomach, these carboxylic groups remain unionized, limiting electrostatic repulsion, maintaining interchain hydrogen bonding, and rendering the polymer matrix insoluble and unswollen [50]. As the dosage form passes into the alkaline regions of the small intestine, localized hydronium ion concentrations fall below the $\text{p}K_a$, causing deprotonation into carboxylate anions ($-\text{COO}^-$) [51]. The resulting electrostatic repulsion along the polymer backbone disrupts the cohesive matrix, driving solvent influx, osmotic network swelling, and gradual polymer dissolution [52].

Conversely, polybases, such as dimethylaminoethyl methacrylate copolymers (Eudragit E PO), contain tertiary amine groups ($-\text{N}(\text{CH}_3)_2$) with a $\text{p}K_b$ of approximately 6.5 [53]. In acidic gastric environments, these amine groups protonate into positively charged ammonium cations ($-\text{NH}^+(\text{CH}_3)_2$), generating charge repulsions that promote rapid dissolution and drug release [54]. In four-dimensional manufacturing, layering these opposing polyelectrolytes allows precise control over spatial deformation; an asymmetric bilayer stripe will bend asymmetrically when one layer swells while the opposing layer remains rigid, producing predictable curved geometries [55].

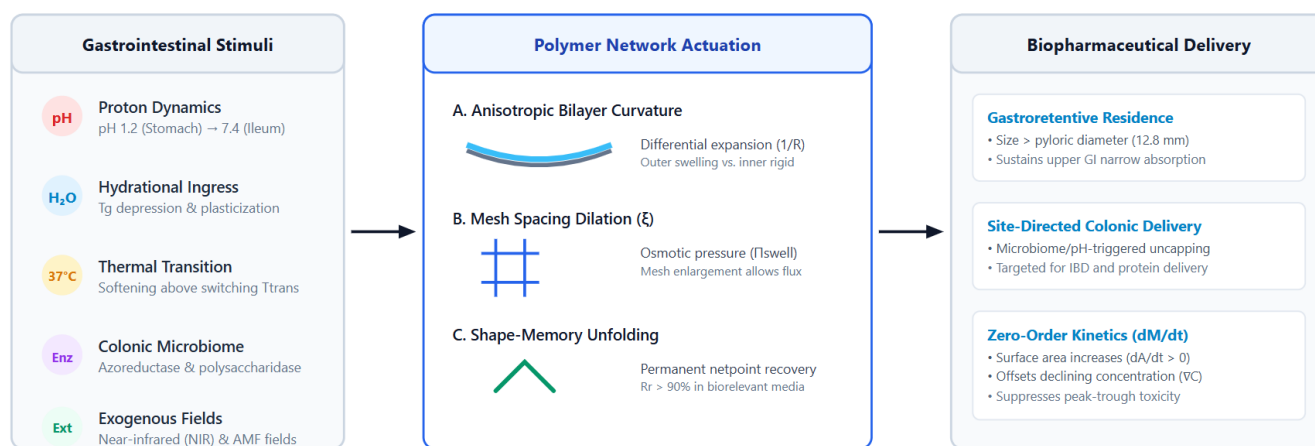


Figure 7. Stimulus-responsive transformation and drug-delivery concept

3.2. Temperature-Responsive Polymers and Shape-Memory Mechanisms

Temperature serves as an internal physical trigger for systems utilizing shape-memory polymers or responsive hydrogels that undergo phase transitions around normal human body temperature (37°C) [56]. The primary mechanism involves polymeric networks exhibiting either a lower critical solution temperature (LCST) or an upper critical solution temperature (UCST) [57]. Poly(*N*-isopropylacrylamide) (PNIPAM) is a representative LCST system with a critical transition temperature near 32°C in pure water [58]. Below this threshold, hydrophilic interactions between polymer amides and water molecules dominate via hydrogen bonding, maintaining a hydrated, swollen coil state [59]. When heated past the LCST, entropy-driven hydrophobic interactions between isopropyl groups overcome hydrogen bonding, expelling water and collapsing the network into a globular form [60].

In shape-memory polymers, mechanical actuation is driven by a two-phase structural morphology containing elastic permanent crosslinks and temporary switching segments [61]. The permanent netpoints, formed via covalent crosslinking, chemical grafting, or high-melting crystalline domains, establish and preserve the thermodynamic equilibrium geometry of the printed dosage form [62]. The switching segments consist of amorphous or semi-crystalline polymer chains that exhibit a thermal transition temperature (T_{trans}), which may be a glass transition temperature (T_g) or a melting temperature (T_m) [63].

To program a shape-memory polymer, the material is printed in its permanent, expanded equilibrium geometry [64]. It is subsequently heated above its T_{trans} , where switching domains soften into an elastic state [65]. External mechanical stress is applied to deform, fold, or roll the matrix into a compact cylindrical shape suitable for capsule encapsulation [66]. While maintaining this mechanical strain, the system is cooled below T_{trans} [67]. The switching domains vitrify or crystallize, kinetically trapping the polymer chains in a high-energy, low-entropy configuration and fixing the temporary, compact geometry [68].

Upon oral administration, exposure to physiological body fluids at 37°C reheats the switching segments above their T_{trans} , or alternatively, aqueous plasticization lowers the effective T_g down to luminal temperatures [69]. The switching segments regain chain mobility, releasing the stored entropic strain energy, and the elastic netpoints drive the matrix back to its initial expanded shape [70].

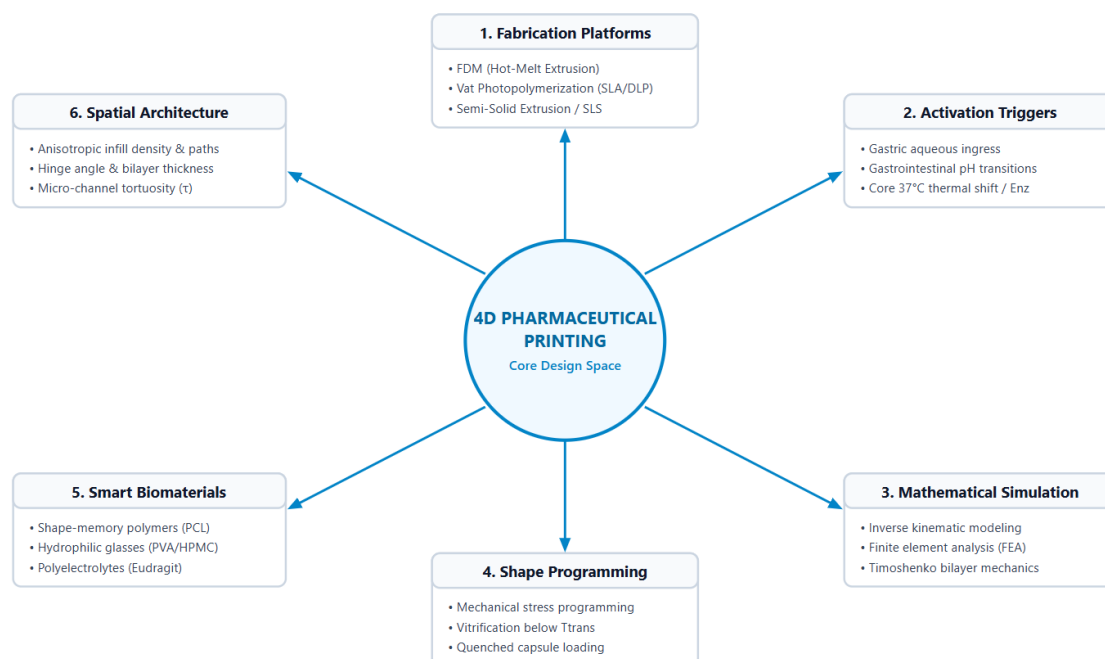


Figure 8. Major components and design factors involved in 4D printing

3.3. Water- and Moisture-Induced Activation

Aqueous fluids within the gastrointestinal tract provide a straightforward chemical driving force for four-dimensional actuation [71]. Water-induced shape recovery does not rely solely on thermal phase transitions; rather, it exploits the plasticizing action of small, polar solvent molecules on hydrophilic amorphous polymer backbones [72]. Polar polymers, such as poly(vinyl alcohol) (PVA), hydroxypropyl methylcellulose (HPMC), and poly(ethylene oxide) (PEO), exhibit relatively high glass transition temperatures in the dry solid state ($T_g > 60^\circ\text{C}$), which prevents spontaneous room-temperature shape recovery during ambient storage [73].

When submerged in gastrointestinal fluid, water molecules diffuse into the intermolecular spaces between polymer chains, forming competitive hydrogen bonds with polar functional groups [74]. This solvating action increases the free volume within the matrix, lowers the activation energy for segment mobility, and causes a depression of the glass transition temperature [75]:

$$T_{g,\text{effective}} = \frac{w_p T_{gp} + K w_w T_{gw}}{w_p + K w_w}$$

where w_p and w_w are the weight fractions of polymer and water, and K is a constant related to the expansion coefficients (Gordon-Taylor model) [76]. When the effective T_g drops below gastric body temperature (37°C), the vitrified switching segments re-enter a rubbery, elastic state, releasing stored mechanical strain and driving matrix unfolding [77].

Similarly, hydrophilic hydrogel networks generate an osmotic swelling pressure (Π_{swell}) governed by polymer-solvent mixing thermodynamics and elastic network retraction forces (Flory-Rehner equilibrium) [78]:

$$\Pi_{\text{swell}} = \Pi_{\text{mix}} + \Pi_{\text{elastic}} + \Pi_{\text{ion}}$$

This thermodynamic pressure drives rapid directional volumetric expansion, allowing tailored swelling ratios without requiring structural pre-straining [79].

3.4. Enzyme-Activated and Microbiome-Responsive Biodegradation

Enzyme-triggered transformation utilizes localized biocatalytic processes within specific physiological compartments, particularly the ileocecal region and the colon [80]. The human upper gastrointestinal tract contains limited enzymatic activity directed toward complex non-starch polysaccharides, whereas the human colon hosts a dense microbial population (10^{11} to 10^{12} CFU/mL), predominantly anaerobic bacteroidetes and firmicutes [81]. These bacteria secrete hydrolytic, reductive, and polysaccharidase enzymes, including β -galactosidase, amylase, pectinase, dextranase, and azoreductases, capable of cleaving glycosidic and azo bonds that remain stable in gastric fluid [82].

Incorporating naturally derived polysaccharides, such as inulin, pectin, guar gum, resistant starch, or sodium alginate, into printable matrices establishes an enzymatically responsive delivery system [83]. In the upper gastrointestinal tract, these materials form dense, low-permeability diffusional barriers that shield the incorporated active pharmaceutical ingredients [84]. Upon entering the cecum and ascending colon, bacterial polysaccharidases hydrolyze the polysaccharide backbone [85]. This enzymatic degradation erodes the matrix, generates structural microporosity, or detaches protective exterior printed shells, triggering controlled drug release directly at the colonic disease site [86].

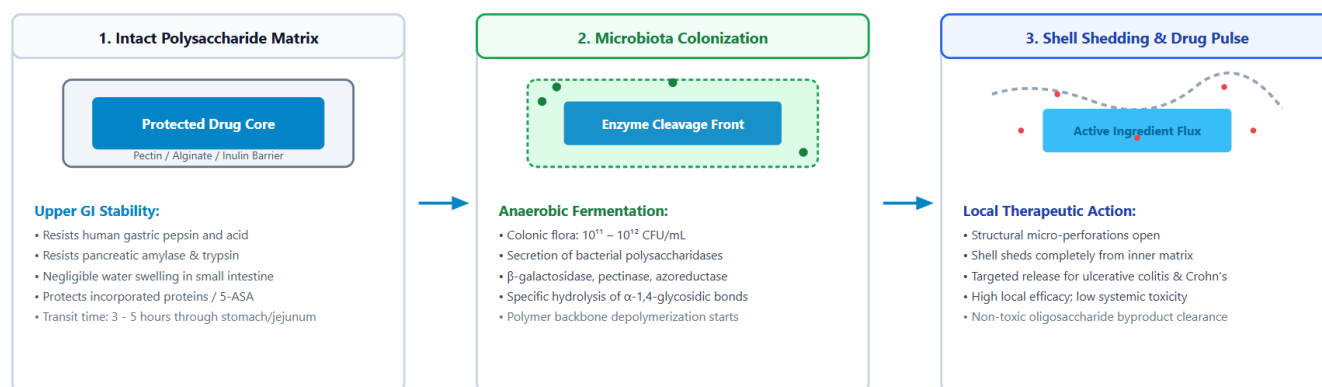


Figure 9. Microbiome-Triggered Colonic Enzymatic Degradation

3.5. Externally Actuated Stimuli

In addition to autonomous physiological triggers, structural transformations can be actuated via non-invasive external stimuli, including near-infrared (NIR) light, alternating magnetic fields (AMF), and focused ultrasound [87]. While autonomous physiological triggers are ideal for standard oral regimens, externally applied triggers provide precise on-demand control over release timing and dosing frequency [88].

Near-infrared photothermal actuation uses biocompatible photothermal transducing agents, such as gold nanorods, graphene oxide, or indocyanine green, embedded within a thermo-responsive polymer matrix (such as PNIPAM or shape-memory polycaprolactone) [89]. Biological tissues possess an optical transmission window in the near-infrared spectrum (700 to 1100 nm) where light penetration is maximized and scattering is minimized [90]. When irradiated with an external near-infrared laser, the embedded nanoparticles absorb photons and generate localized heat via surface plasmon resonance or non-radiative decay, warming the polymer matrix above its T_{trans} within seconds and triggering rapid conformational changes or drug expulsion [91].

Magnetic field actuation involves incorporating superparamagnetic iron oxide nanoparticles (SPIONs, Fe_3O_4) into printable filament extrudates or light-curable bioresins [92]. When subjected to an external high-frequency alternating magnetic field, the SPIONs produce localized hyperthermia via Néel and Brownian relaxation losses [93]. This localized thermal generation triggers shape-memory recovery or collapses hydrogel matrices to release active compounds [94]. Alternatively, uniform static magnetic fields can exert directional mechanical torque on the incorporated magnetic domains, reorienting mobile drug-delivery devices within specific gastrointestinal regions [95].

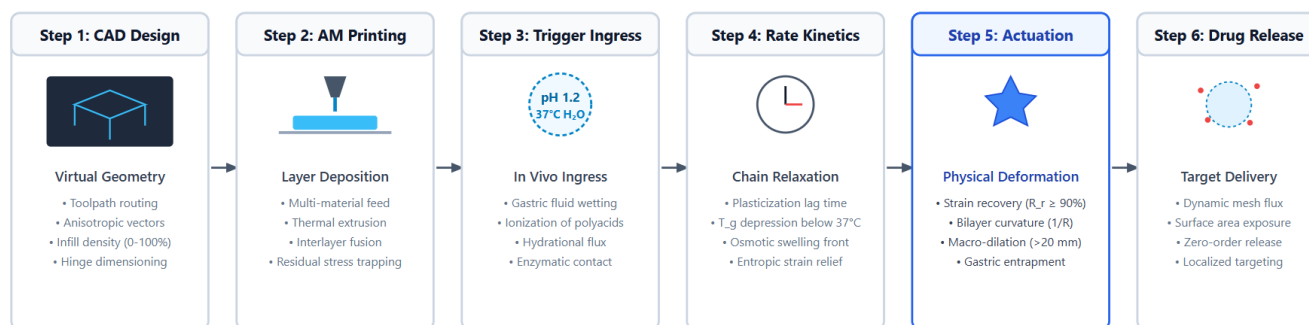


Figure 10. Multi-step process for 4D tablet printing

4. Additive Manufacturing Technologies for 4D Formulation Processing

4.1. Fused Deposition Modeling (FDM) and Hot-Melt Extrusion (HME)

Fused deposition modeling (FDM), coupled with pharmaceutical hot-melt extrusion (HME), is an established method for manufacturing solid oral dosage forms [96]. The process uses twin-screw extruders to disperse the active pharmaceutical ingredient into a molten thermoplastic carrier matrix, forming a solid molecular dispersion or solid solution [97]. The cooled, solid filament is then fed into the FDM printhead, where drive gears push it through a heated liquefier chamber and out of a small-diameter nozzle (0.2 to 0.4 mm), depositing the melt onto a build plate to construct the dosage form layer by layer [98].

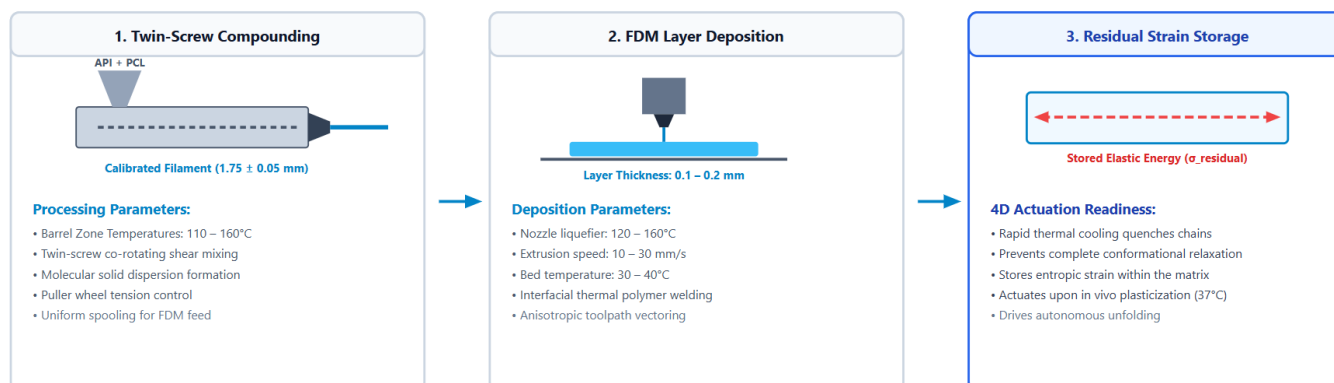


Figure 11. Hot-Melt Extrusion (HME) and FDM 4D Printing Fabrication Route

FDM offers key advantages for four-dimensional fabrication: it produces mechanically robust objects with high structural integrity and enables dual-nozzle multi-material deposition, which is essential for printing heterogeneous bilayer or segmented shape-memory structures [99]. Moreover, the directional deposition of polymer melts allows intentional storage of anisotropic residual stresses within the cooling layers; these internal stresses subsequently function as driving forces during water- or temperature-induced shape recovery [100].

However, FDM presents critical processing challenges [101]. Thermal exposure within the liquefier barrel (typically 130 to 210°C) limits the technique to thermally stable active ingredients, excluding heat-sensitive proteins, peptides, and labile small molecules [102]. Additionally, the feedstock must possess precise viscoelastic properties: excessive melt viscosity generates elevated back-pressure that leads to nozzle clogging, whereas low melt viscosity causes filament buckling or uncontrolled slumping on the build plate [103].

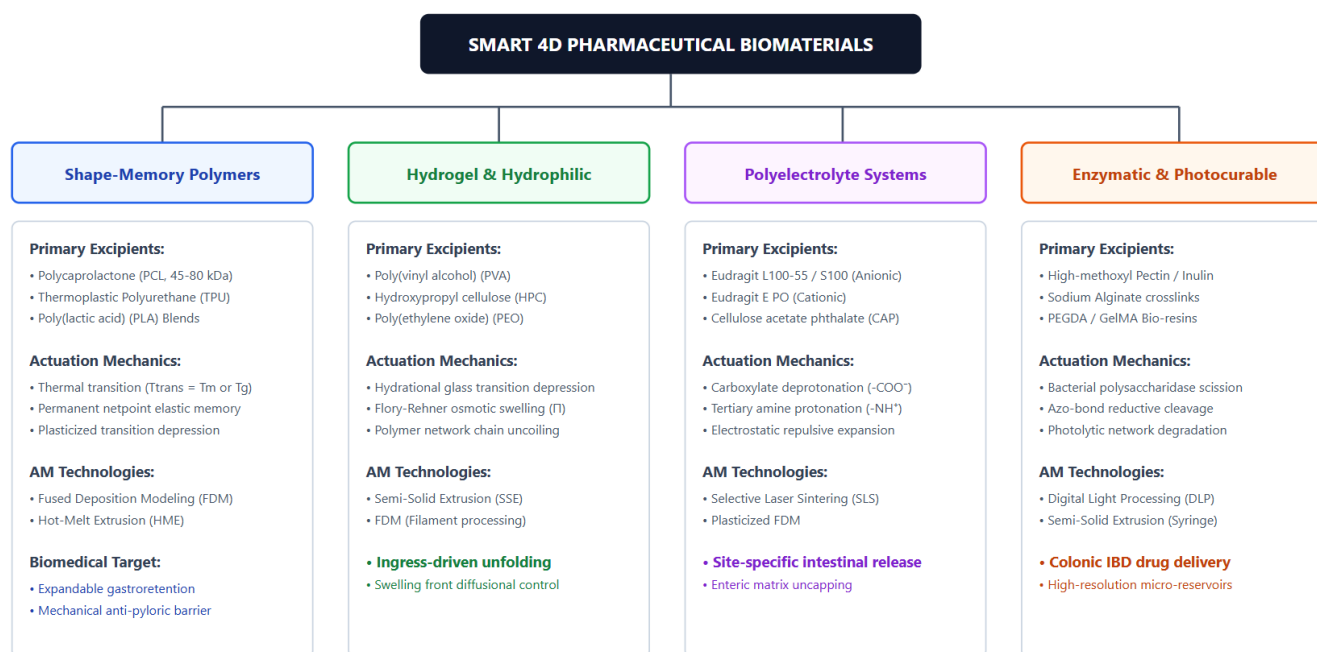


Figure 12. Classification of materials used in 4D pharmaceutical systems

4.2. Stereolithography (SLA) and Digital Light Processing (DLP)

Vat photopolymerization processes, such as stereolithography (SLA) and digital light processing (DLP), construct three-dimensional networks by selectively projecting ultraviolet (UV, ≈ 365 to 385 nm) or visible light (≈ 405 nm) into a liquid resin bath containing photocurable prepolymers, photoinitiators, reactive diluents, and suspended or dissolved active ingredients [104]. SLA focuses a scanning galvanometer-guided UV laser beam point-by-point, whereas DLP flashes a dynamic mask across an entire layer simultaneously using a digital micromirror device (DMD), significantly accelerating production speeds [105].

Vat photopolymerization operates at ambient room temperature, avoiding thermal degradation and making it well suited for thermolabile drugs [106]. It provides exceptional spatial resolution (down to 10 to 50 μm), enabling the construction of fine microfluidic networks, microporous membranes, and delicate hinge structures necessary for responsive actuation [107].

The main translational barrier for SLA and DLP in oral pharmaceuticals lies in the photopolymer chemistry [108]. Conventional commercial resins rely heavily on reactive polyacrylate or polymethacrylate monomers and toxic free-radical photoinitiators, which can cause significant cellular toxicity, mucosal irritation, or systemic damage if swallowed [109]. Developing non-toxic, biocompatible bio-resins based on poly(ethylene glycol) diacrylate (PEGDA), methacrylated gelatin (GelMA), or functionalized dextrans, paired with biocompatible water-soluble photoinitiators (such as lithium phenyl-2,4,6-trimethylbenzoylphosphine, LAP), is critical for clinical translation [110]. Post-curing washes must be rigorously validated to ensure complete extraction of residual monomers, crosslinkers, and photoinitiator fragments [111].

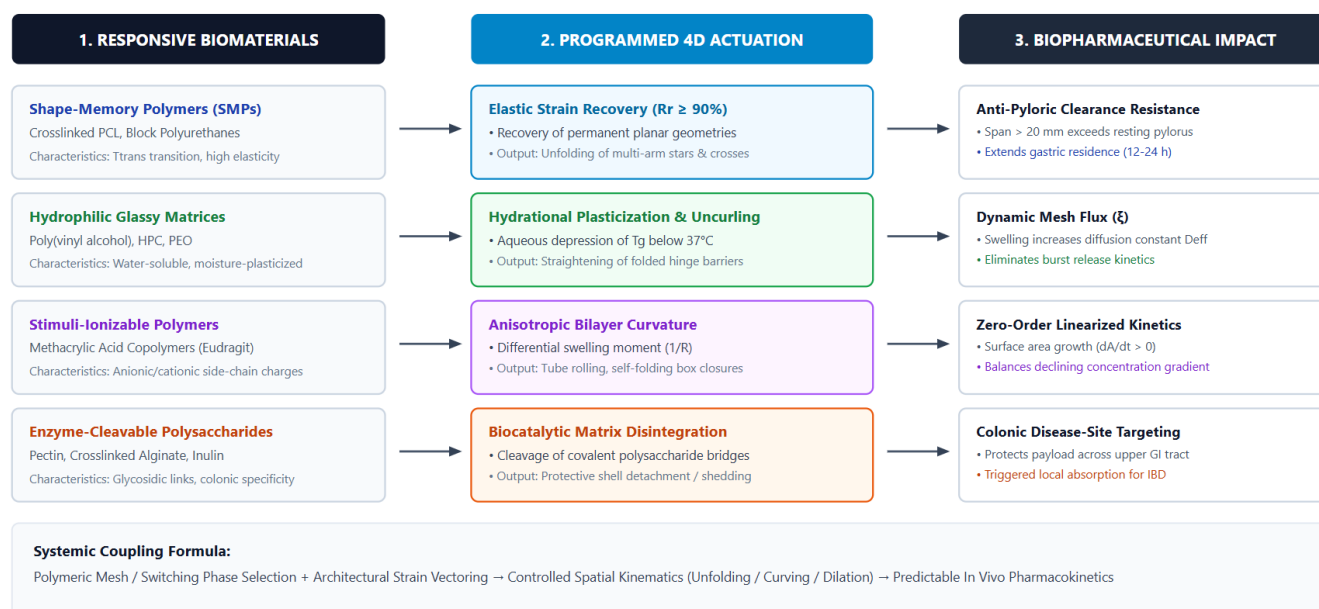


Figure 13. Smart materials and programmed responses relevant to 4D drug delivery

4.3. Powder Bed Fusion and Semi-Solid Extrusion

Selective laser sintering (SLS) belongs to the powder bed fusion category and functions by spreading thin layers of micronized drug-polymer powder mixtures across a build platform, followed by targeted scanning with a carbon dioxide or diode laser [112]. The laser energy sinters the polymer particles together by transient surface melting without requiring liquid binding agents or solvents [113]. SLS can produce porous matrix dosage forms with fast dissolution profiles [114]. However, thermal degradation risks from the laser beam, along with low mechanical strength in dynamic un-sintered regions, present challenges when engineering shape-memory structures that require robust mechanical strain recovery [115].

Semi-solid extrusion (SSE) operates by pneumatically or mechanically extruding gel, paste, or paste-like formulations through a dispensing syringe at room or mild temperatures (25 to 60°C) [116]. SSE avoids the extreme thermal degradation of FDM and the cytotoxicity risks of photocurable resins [117]. It is particularly effective for fabricating complex hydrogel networks from natural polysaccharides (such as alginate, chitosan, and carboxymethylcellulose) [118]. Nevertheless, SSE prints exhibit weak green-body mechanical strength immediately post-deposition and require extended post-processing steps (e.g., drying, ionic bath crosslinking, or solvent evaporation) that can induce shrinkage, warping, and poor dimensional reproducibility [119].

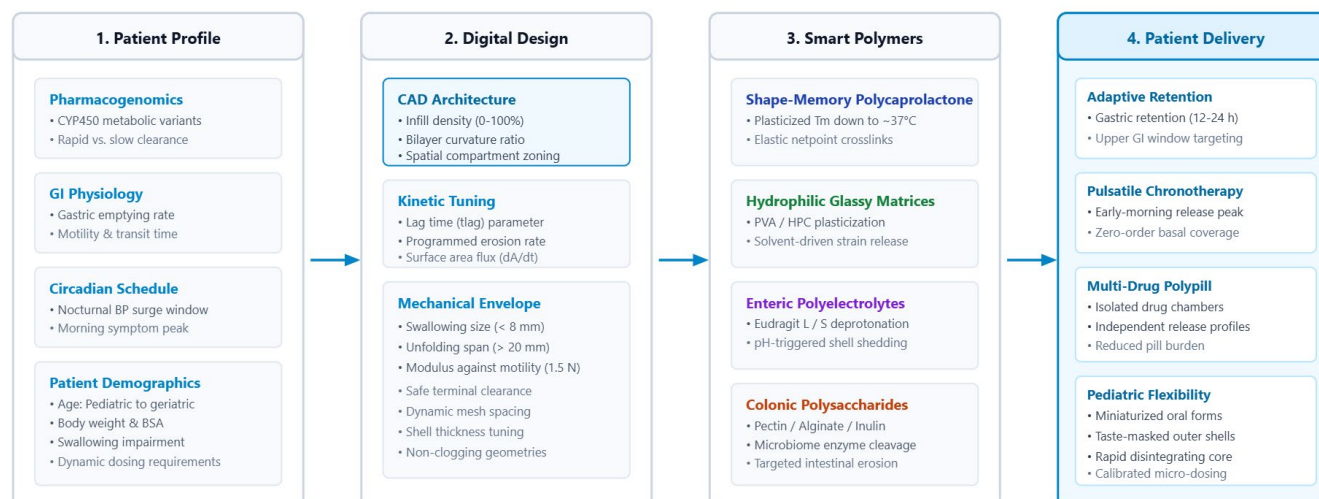


Figure 14. Role of smart polymers in personalized pharmaceutical design

5. Responsive Biomaterials and Shape-Memory Polymer Formulations

The selection of polymeric materials governs both the printing performance and the responsiveness of a four-dimensional oral tablet [120]. The polymer matrix must satisfy basic pharmaceutical requirements: it must be non-toxic, non-immunogenic, compatible with the active ingredient, chemically stable during storage, and extrudable or photocurable without degrading the drug [121]. Similarly, it must exhibit reproducible phase transitions, swelling kinetics, or shape recovery within the physiological conditions of the human gastrointestinal tract [122].

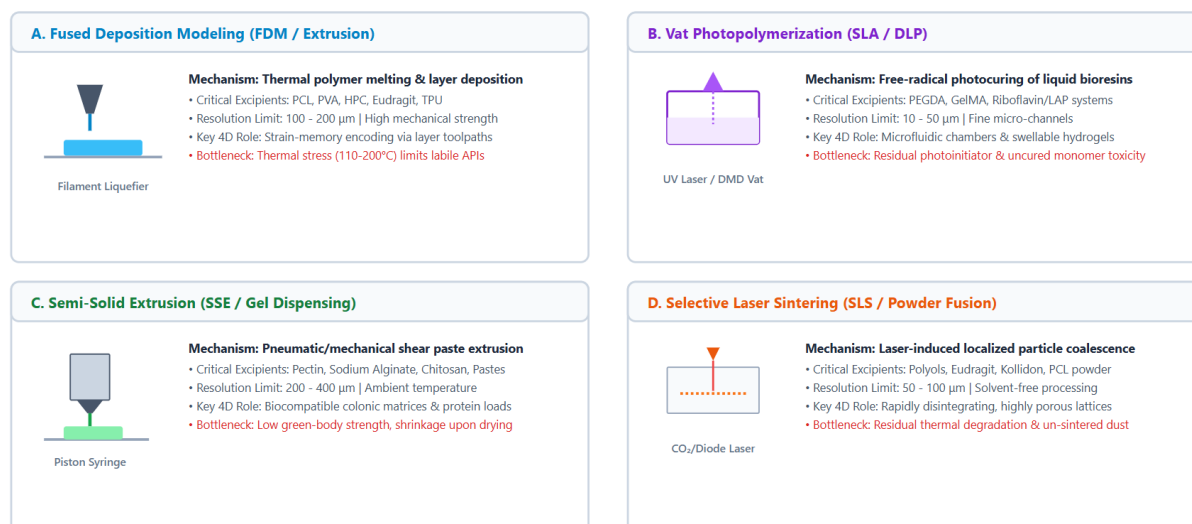


Figure 15. Major additive-manufacturing technologies used for pharmaceutical fabrication

Table 2. Comparison of Materials, Processing, and Responsiveness in 4D Additive Manufacturing

Material	Excipients	Compatible AM Method	Stimulus Mechanism	Function
Shape-Memory Thermoplastics	Polycaprolactone (PCL, M_w 45–80 kDa), Polyurethane (TPU)	Hot-Melt Extrusion + FDM	Thermal softening (T_m 58–60°C, lowered by plasticizers to $\approx$ 37°C)	Prolonged gastric retention; physical resistance against pyloric passage [123]
Hydrophilic Glassy Polymers	Poly(vinyl alcohol) (PVA), Hydroxypropyl cellulose (HPC)	Hot-Melt Extrusion + FDM	Hydrational glass-transition depression (T_g drops from 75°C to <25°C)	Water-activated deployment; erosion-based drug release [124]
Enteric Anionic Polyelectrolytes	Eudragit L100-55, Hydroxypropyl methylcellulose phthalate (HPMCP)	FDM (with plasticizers) or Direct Powder SLS	Carboxylate deprotonation at pH>5.5	Gastric protection followed by targeted duodenal/jejunal release [125]
Colonic Polysaccharides	High-methoxyl Pectin, Crosslinked Sodium Alginate, Inulin	Semi-Solid Extrusion (SSE)	Cleavage of glycosidic bonds by colonic anaerobic microflora	Site-specific release in cecum/colon; targeted treatment for IBD [126]
Photopolymerizable Hydrogels	Poly(ethylene glycol) diacrylate (PEGDA), GelMA	Stereolithography (SLA) / DLP	Isotropic solvent absorption; localized network crosslink cleavage	High-resolution microfluidic devices; rapid diffusion-controlled delivery [127]

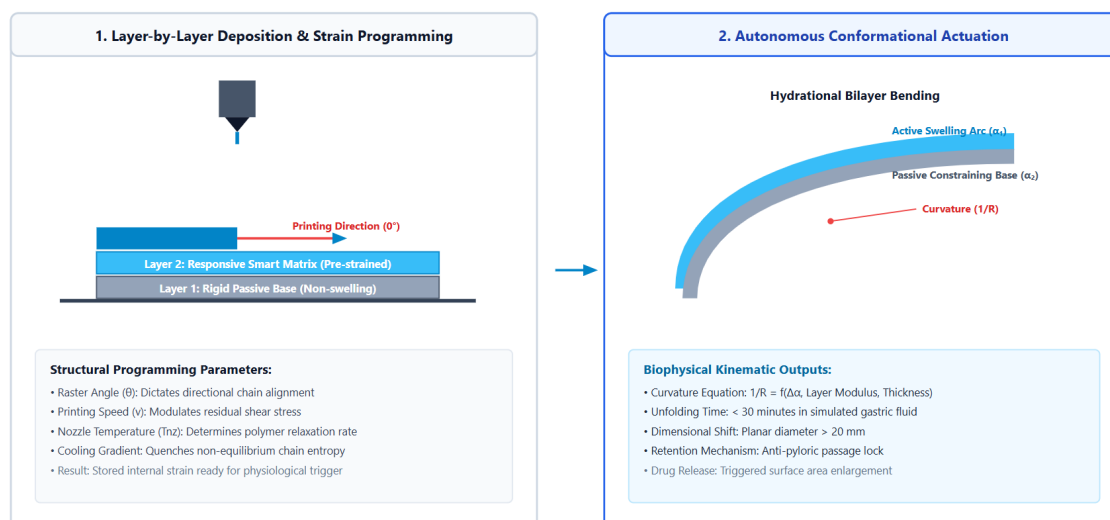


Figure 16. Layer-by-layer fabrication and structural programming concept

Thermoplastic shape-memory systems commonly employ polycaprolactone (PCL) blended with hydrophilic carriers like poly(ethylene glycol) (PEG) or poly(vinylpyrrolidone) (PVP) [128]. While pure high-molecular-weight PCL displays a melting point ($T_m \approx 60^\circ\text{C}$) above human body temperature, blending with low-molecular-weight PEG acts as a plasticizer, lowering the melting and softening transitions down toward 37 to 40°C [129]. This plasticization allows physiological gastric fluids and core body temperature to trigger the recovery of the original printed geometry [130]. Similarly, poly(vinyl alcohol) functions as a dual-action carrier; its glassy dry state provides the mechanical rigidity needed to hold a folded temporary geometry inside a gelatin capsule shell [131]. Once the capsule dissolves in the stomach, gastric water plasticizes the PVA network, depressing its T_g and releasing stored mechanical strains to unfold the structure into a wide, planar gastric-retention shape [132].



Figure 17. Overview of printing, design, and pharmaceutical applications

6. Structural Geometry and Macro-Architectural Design

6.1. Geometric Dimensions and Internal Porosity

In standard pharmaceutical manufacturing, tablet geometry is largely restricted to round, oval, or capsule-shaped geometries dictated by the physical constraints of tooling punches and dies [133]. Additive manufacturing removes these limitations, enabling digital control over macroscopic external shapes, internal cellular architectures, wall thicknesses, and interconnected pore networks [134]. In four-dimensional design, geometry serves as an active formulation parameter that dictates the kinetics of both physical actuation and drug release [135].

Porosity directly governs the rate of fluid ingress into the tablet matrix [136]. By modifying the slicing infill density (0% to 100%) and selecting distinct infill geometries (e.g., rectilinear, honeycomb, gyroid, or concentric paths), the internal surface area and channel tortuosity can be precisely adjusted [137]:

$$\tau = \frac{L_e}{L}$$

where L_e is the actual path length traversed by diffusing water molecules and L is the physical thickness of the matrix barrier [138]. Open gyroid and grid architectures provide short diffusional pathways that accelerate solvent penetration, promoting rapid water-induced shape-memory recovery [139]. Conversely, dense concentric shell designs create robust outer barriers that delay fluid access to inner responsive elements, extending the actuation lag phase (t_{lag}) [140].

6.2. Anisotropic Bilayer Actuation and Programmed Folding Hinges

Complex four-dimensional conformational changes, including self-curling, folding, and twisting, are produced by programming anisotropic material distributions or stress differentials into the printed architecture [141]. A common approach is the asymmetric bilayer strip, where two materials with contrasting swelling ratios or thermal expansion properties are fused together [142].

When hydrated, the high-swelling hydrophilic layer expands substantially, whereas the adjacent non-swelling or hydrophobic layer remains rigid [143]. Because the two layers are bonded along their interface, the resulting strain differential induces an out-of-plane bending moment, driving the structure to curve toward the non-swelling side [144]. The radius of curvature (R) of this bending actuator is mathematically predicted using Timoshenko's classical bilayer mechanics adapted for hydrogel hydration [145]:

$$\frac{1}{R} = \frac{6(\alpha_1 - \alpha_2)(1 + m)^2}{h \left(3(1 + m)^2 + (1 + mn) \left(m^2 + \frac{1}{mn} \right) \right)}$$

where α_1 and α_2 denote the isotropic swelling strains of the active and passive layers, h is total strip thickness, m represents the thickness ratio (h_1/h_2), and n is the elastic modulus ratio (E_1/E_2) [146].

By strategically placing these bilayer strips at defined hinges between rigid drug-containing compartments, flat star-shaped, cross-shaped, or polygonal structures can be designed to fold into compact cylinders for encapsulation, subsequently unfolding back into flat, extended sheets upon entering gastric fluid [147].

7. Mathematical Modeling of Drug-Release Kinetics

In a four-dimensional solid dosage form, drug release kinetics are coupled to the time-dependent geometry and porosity of the transforming matrix [148]. In a conventional non-deforming matrix, drug transport is typically described by Fickian diffusion or constant surface erosion [149]. In a four-dimensional matrix, however, the effective diffusional surface area, the diffusion path length, and the internal matrix porosity vary dynamically over time [150].

The fundamental mass transport of an active pharmaceutical ingredient through a dynamic four-dimensional polymeric network is governed by modified Fickian equations incorporating coordinate transformation and moving boundaries [151]:

$$\frac{\partial C}{\partial t} = \nabla \cdot (D_{\text{eff}}(S, t) \nabla C) - \mathbf{v}_{\text{swell}} \cdot \nabla C - k_{\text{erosion}}(t)C$$

where C is the active ingredient concentration at spatial location (x, y, z) , D_{eff} is the effective diffusion coefficient, $\mathbf{v}_{\text{swell}}$ is the velocity vector of the advancing swelling front, and k_{erosion} represents the time-dependent surface erosion constant [152]. The effective diffusion coefficient is directly influenced by the swelling ratio and local polymer network mesh size (ξ) [153]:

$$D_{\text{eff}} = D_0 \left(1 - \frac{r_s}{\xi} \right) \exp \left(-\gamma \frac{\phi}{1 - \phi} \right)$$

where D_0 represents the drug diffusion coefficient in pure fluid, r_s is the hydrodynamic radius of the drug molecule, ϕ is the polymer volume fraction, and γ is a ratio of characteristic volumes [154]. As the four-dimensional matrix expands or unfolds upon encountering physiological triggers, ξ increases while ϕ decreases, causing D_{eff} to increase dynamically over the actuation period [155].

To quantify empirical drug dissolution from swelling and shape-transforming systems, the Peppas-Sahlin model is frequently applied to decouple the relative contributions of Fickian diffusional transport from polymer relaxation/actuation [156]:

$$\frac{M_t}{M_\infty} = K_1 t^m + K_2 t^{2m}$$

where M_t/M_∞ is the fractional drug release, K_1 is the Fickian kinetic constant, K_2 is the macromolecular polymer relaxation constant, and m is the purely Fickian diffusion exponent determined by the geometry of the device (e.g., $m=0.45$ for a thin slab, $m=0.43$ for a cylinder) [157].

In a four-dimensional dosage form executing rapid shape transformation, the relaxation term ($K_2 t^{2m}$) dominates early dissolution kinetics during the actuation phase, whereas Fickian diffusion ($K_1 t^m$) governs the subsequent functional plateau [158]. Consequently, achieving a desired zero-order release profile ($dM_t/dt = \text{constant}$) requires balancing the decrease in drug concentration gradient (∇C) against the simultaneous increase in effective surface area ($dA/dt > 0$) as the printed geometry unfolds [159].

8. Biopharmaceutical Applications in Targeted and Personalized Delivery

8.1. Gastroretentive Drug Delivery Systems

Prolonging gastric residence time represents a significant biopharmaceutical application for four-dimensional additive manufacturing [160]. Human gastric emptying is governed by interdigestive migrating motor contractions [161]. In the fasted state, the stomach cycles through four distinct motility phases every 90 to 120 minutes, culminating in Phase III: intense, sweeping peristaltic contractions capable of generating localized pressures up to 100 to 130 mmHg, clearing undigested food and non-disintegrating debris larger than 2 mm through the relaxed pyloric orifice into the duodenum [162].

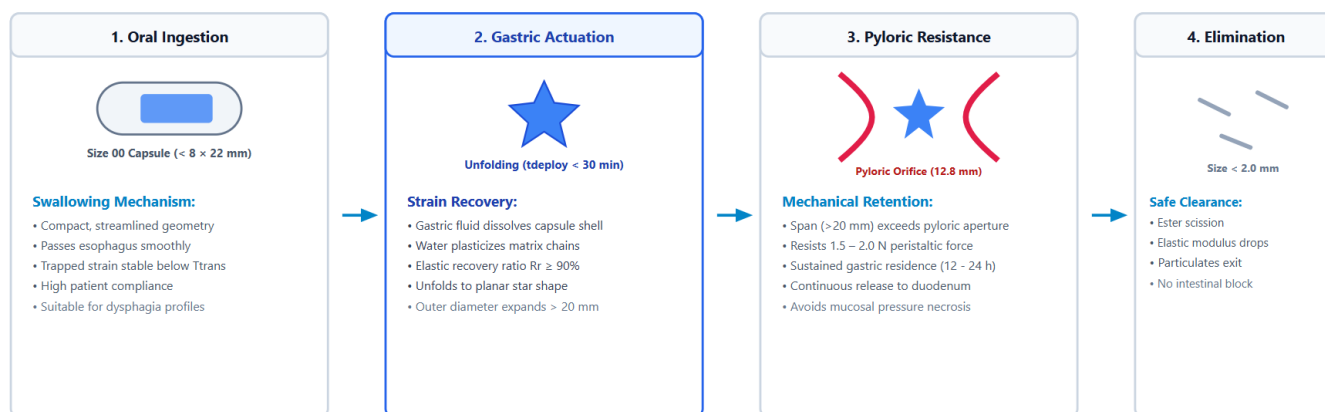


Figure 18. Gastroretentive Deployment and Pyloric Mechanical Entrapment

To resist Phase III clearing sweeps, a four-dimensional gastroretentive system must satisfy two strict mechanical and geometrical conditions:

8.1.1. Dimensional Threshold

Following oral ingestion in a standard size 0 or 00 capsule shell, the matrix must unfold, expand, or swell within 15 to 30 minutes to an outer diameter exceeding the maximum human pyloric diameter (>18 to 22 mm) [163].

8.1.2. Mechanical Rigidity

The expanded geometry must exhibit an elastic modulus and yield strength sufficient to resist compressive peristaltic forces (>1.5 to 2.0 N) without prematurely buckling or folding into an escapable shape, while remaining non-traumatic to the gastric mucosa [164].

Four-dimensional printed expandable systems, including multi-arm planar stars, cross structures, and circular cloverleaf designs fabricated from plasticized PCL, PVA, or shape-memory polyurethanes, achieve prolonged gastric retention up to 24 hours in preclinical models [165]. Following complete drug release, the connecting elastomeric joints undergo hydrolytic scission or enzymatic degradation, breaking the assembly down into individual segments below the pyloric threshold for safe clearance through the intestine [166].

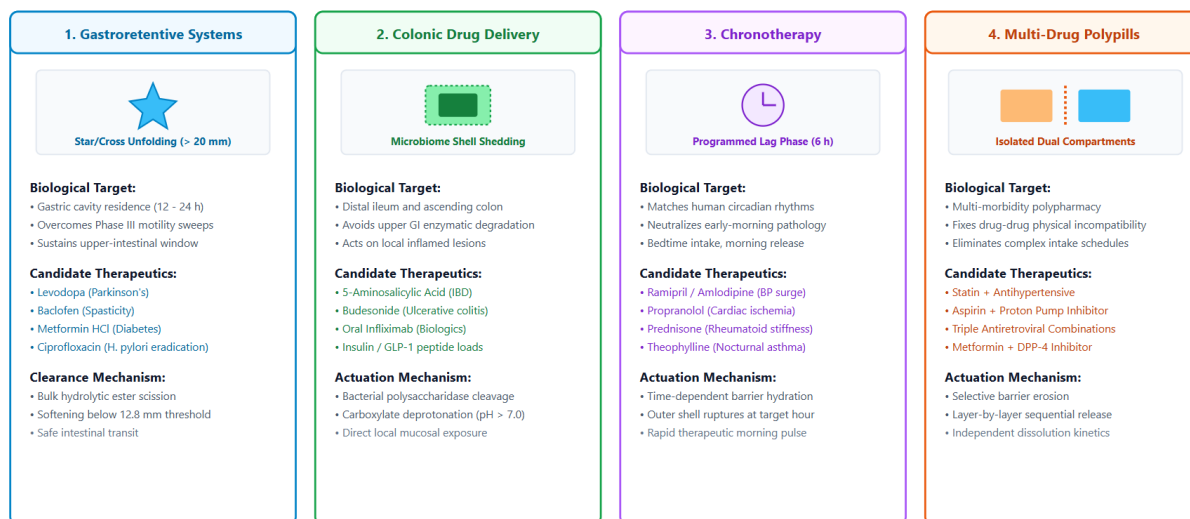


Figure 19. Major therapeutic application areas of smart drug-delivery systems

8.2 Site-Directed Colonic Delivery

Targeted drug delivery to the colon is vital for treating localized inflammatory bowel conditions, including ulcerative colitis and Crohn's disease, as well as providing systemic delivery for therapeutic peptides that are degraded by upper gastrointestinal proteases [167]. Delivering drugs reliably to the colon remains challenging due to broad physiological variations in gastric emptying rates and small intestinal transit times, which typically average 3 to 4 hours but vary widely across individuals [168]. Four-dimensional printing enables the manufacturing of multi-barrier capsules and core-shell architectures that pair enteric outer shells with microbiome-degradable internal chambers [169]. For example, a tablet can be printed with an outer shell composed of poly(methacrylic acid-co-methyl methacrylate) (Eudragit S100, which dissolves only at pH>7.0 in the terminal ileum) encapsulating an inner structural frame fabricated from high-methoxyl pectin or guar gum [170]. During transit through the acidic stomach and neutral small intestine, the outer layer shields the internal compartments [171].

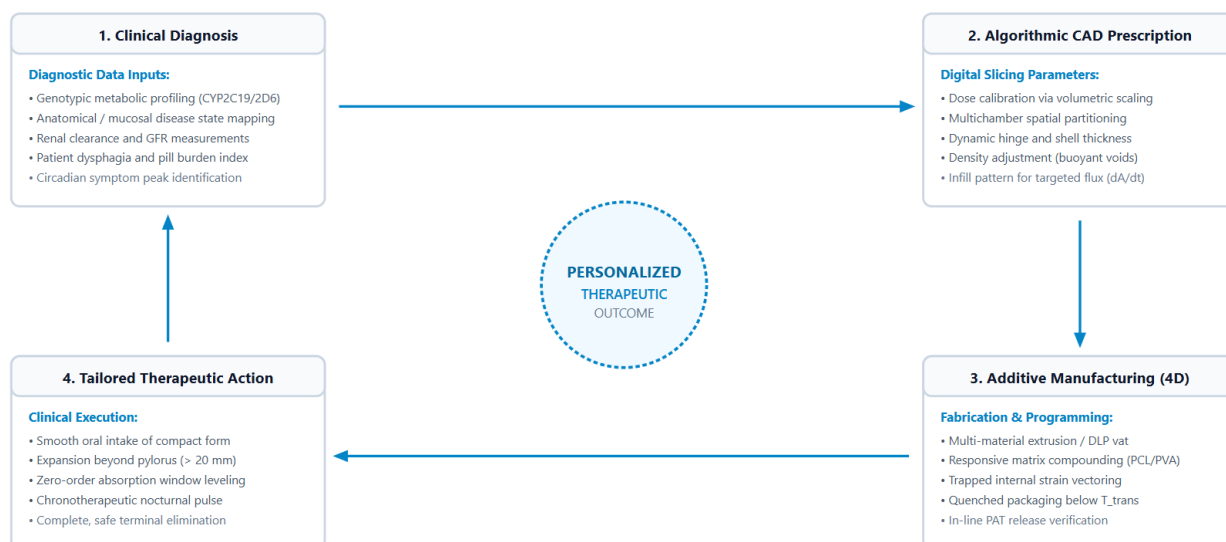


Figure 20. Personalized digital design and therapeutic-outcome concept

Upon reaching the terminal ileum, the outer enteric layer dissolves, exposing the polysaccharide frame to colonic microflora [172]. The bacterial polysaccharidases hydrolyze the glycosidic bonds, triggering structural unfolding or core matrix degradation to deliver therapeutics such as 5-aminosalicylic acid, budesonide, or infliximab directly to the ulcerated colonic mucosa [173].

8.2. Complex Multi-Drug Polypills and Chronotherapeutic Delivery

Managing chronic multi-morbidities, such as metabolic syndrome and cardiovascular disease, frequently requires taking multiple medications daily [174]. This high pill burden contributes to poor patient compliance and medication errors [175]. Four-dimensional additive manufacturing facilitates the single-step fabrication of multi-compartment polypills containing multiple active ingredients separated by stimuli-responsive partition walls [176].

Beyond simple co-encapsulation, four-dimensional designs support chronotherapeutic release profiles aligned with human circadian rhythms [177]. Pathological events such as early-morning hypertension, myocardial infarction, and rheumatoid arthritis exhibit distinct circadian exacerbations, typically peaking between 04:00 and 08:00 [178]. Using 4D digital manufacturing, a polypill can be designed with concentric geometries where an outer layer immediately delivers an evening sedative or antilipidemic drug, while an internal responsive barrier holds back an antihypertensive payload (e.g., ramipril or amlodipine) [179]. The barrier is programmed with a specific hydration lag phase of 6 hours, triggering tablet unfolding or barrier erosion to release the cardiovascular drug in the early morning before the patient wakes [180].



Figure 21. Chronotherapeutic Multi-Layer Delivery Sequence

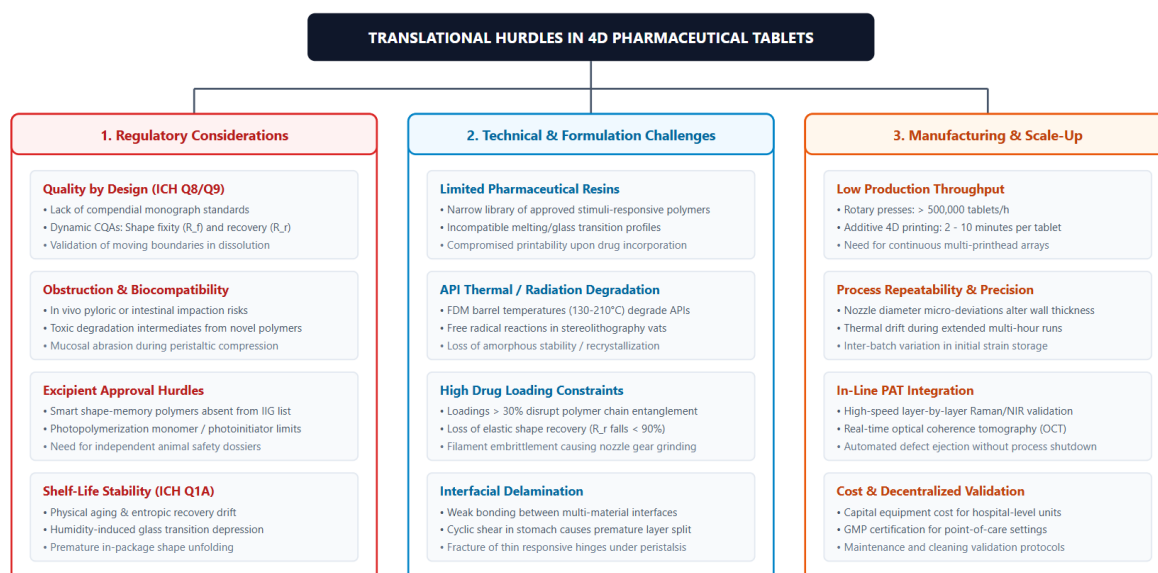


Figure 22. Regulatory, technical, and manufacturing challenges in 4D tablets

9. Quality Evaluation Protocols and Critical Quality Attributes

Standard pharmacopeial evaluations (e.g., USP, Ph. Eur.) established for conventional compressed tablets such as friability, uniform weight, breaking force, assay, and static paddle dissolution are insufficient to fully evaluate four-dimensional oral solid dosage forms [181]. Because 4D tablets are dynamic mechanical systems that change conformation in response to environmental conditions, analytical evaluation requires additional quantitative metrics characterizing the kinetics, magnitude, and reproducibility of the structural actuation [182].

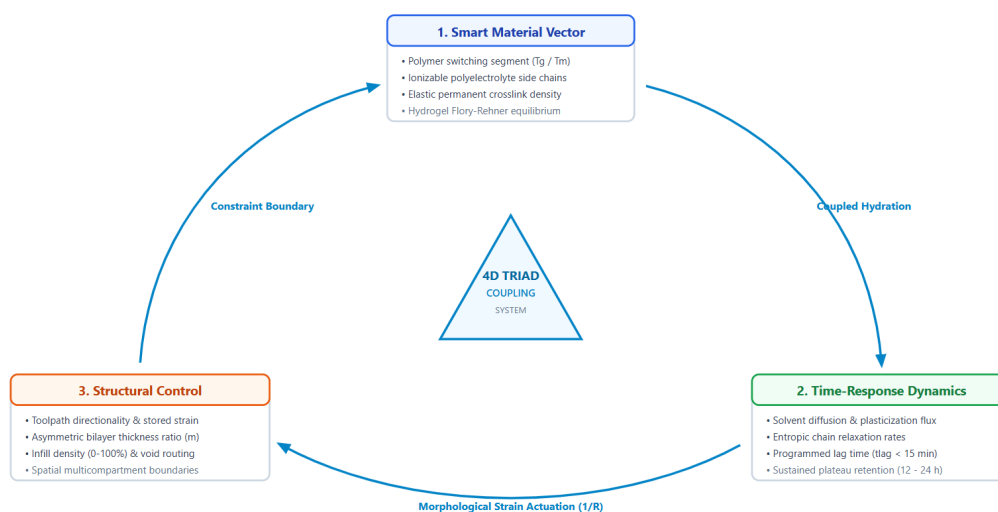


Figure 23. Integrated 4D printing process highlighting smart material, time response, and structural control

Table 3. Critical Quality Attributes (CQAs), Analytical Protocols, and Compendial Acceptance Thresholds for 4D Dosage Forms

Critical Quality Attribute (CQA)	Analytical Method	Acceptance Criteria
Active Ingredient Assay & Potency	Reversed-Phase HPLC / UPLC with UV/MS detection	95.0% to 105.0% of nominal target dose across printed batches [183]
Dose Content Uniformity	Ph. Eur. 2.9.40 / USP <905> Uniformity of Dosage Units	Acceptance Value (AV) < 15.0 (L_1 parameter for n=10 units) [184]
Polymorphic State & Solid Dispersion	Powder X-ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC)	Complete amorphization or maintained stable polymorph; no unwanted recrystallization [185]
Green-Body Dimensional Accuracy	High-resolution micro-computed tomography (μ -CT), Digital Micrometer	$\pm 5.0\%$ variance against CAD digital volumetric specifications [186]
Layer Adhesion & Interfacial Strength	Diametral compression testing, dynamic mechanical analysis (DMA)	Breaking force >1.5 N to prevent delamination under gastric motility shear [187]
Shape Fixity Ratio (R_f)	Dynamic Image Analysis: $R_f = (\epsilon_{\text{fixed}} / \epsilon_{\text{applied}}) \times 100\%$	$\geq 95.0\%$ retention of temporary deformed swallowing state at 25°C [188]
Shape Recovery Ratio (R_r)	Dynamic Image Analysis: $R_r = [(\epsilon_{\text{fixed}} - \epsilon_{\text{recovered}}) / \epsilon_{\text{fixed}}] \times 100\%$	$\geq 90.0\%$ restoration of target expanded geometry in biorelevant medium [189]
Actuation Lag Time (t_{lag})	High-speed photographic recording in USP Apparatus 2	Within defined operational bounds: . (prevents esophageal deployment) [190]
Full Deployment Time (t_{deploy})	Video monitoring in biorelevant dissolution baths	≤ 30 min to ensure full deployment prior to Phase III gastric sweeps [191]
<i>In vitro</i> Dissolution Profile	USP Apparatus 2 / 4 with automated autosampler; simulated gastric fluid (FaSSGF)	Similarity factor $f_2 \geq 50$ compared against reference target release kinetics [192]
<i>In vitro</i> Pyloric Passage Resistance	Modified mechanical gastric simulator mimicking Phase III antral shear	Device maintains spatial dimensions >20 mm against 1.5 N cyclic force [193]

The shape fixity ratio (R_f) evaluates the ability of the polymer switching segments to lock in the mechanical strain applied during programming, preserving the compact capsule form during packaging and handling [194]. The shape recovery ratio (R_r) quantifies the extent to which the permanent crosslinks restore the functional geometry upon encountering physiological body heat or fluid [195]. Additionally, tracking layer adhesion is critical for printed matrices; insufficient thermal fusion or light-curing depth can cause delamination along layer boundaries when subjected to cyclical gastric shearing [196]. X-ray micro-computed tomography (μ -CT) provides non-destructive three-dimensional visualization of internal pore channels and interfacial layer boundaries, verifying that internal print architecture matches the input digital slice file [197].

**Figure 24. Scheme of 4D-designed tablet development**

10. Technical Bottlenecks and Scale-Up

10.1. Technical and Formulation Engineering Barriers

Translating four-dimensional oral drug delivery systems from benchtop proof-of-concept to clinical utility requires overcoming several material and processing hurdles [198]. The current library of pharmaceutical-grade, biocompatible excipients possessing suitable stimuli-responsiveness remains narrow [199]. Most commercial shape-memory polymers and smart hydrogels were developed for industrial prototyping or tissue engineering scaffolds and lack established regulatory safety records for oral ingestion

[200]. Incorporating high drug loadings ($> 30\%$ w/w) often compromises responsiveness by disrupting polymer chain entanglement, interfering with crystalline domain formation, or altering the glass transition temperature [201].

Maintaining long-term stability during storage presents another engineering challenge [202]. Polymers held in a temporary, high-energy vitrified state are susceptible to physical aging [203]. Ambient fluctuations in storage temperature and relative humidity can accelerate secondary relaxations, causing gradual loss of the fixed temporary shape (unwanted premature deployment) or increasing the actuation lag time beyond safe physiological limits [204]. Formulations must therefore be developed with high dry glass transition temperatures ($T_g > 50^\circ\text{C}$) and packaged in specialized moisture-impermeable blister packs to prevent ambient plasticization prior to ingestion [205].

10.2. Industrial Scale-Up and In-Line Process Analytical Technology (PAT)

Traditional rotary tablet presses can produce over 500,000 tablets per hour [206]. In comparison, additive manufacturing techniques such as FDM and semi-solid extrusion remain batch-limited, often requiring several minutes to produce an individual dosage form [207]. Scaling four-dimensional printing for industrial production requires moving away from single-nozzle printers toward multi-nozzle, continuous conveyor-belt platforms or high-throughput digital light processing systems capable of curing complete multi-tablet arrays simultaneously [208].

Industrial scale-up must adhere to Quality by Design (QbD) principles (ICH Q8(R2)), supported by continuous Process Analytical Technology (PAT) [209]. Key critical process parameters (CPPs) including barrel zone temperatures, screw torque, printhead speed, nozzle shear rates, and layer cooling times must be continuously monitored and controlled within validated operational design spaces [210]. In-line near-infrared (NIR) and Raman spectroscopy can quantify drug solid-state form and matrix uniformity immediately before deposition [211]. Simultaneously, high-speed machine vision systems and optical coherence tomography (OCT) can detect layer-by-layer defects, interfacial delamination, or dimensional deviations in real time, preventing defective dynamic matrices from moving downstream [212].

10.3. Regulatory Expectations and Quality Risk Management

Regulatory agencies, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have established initial guidance for additive manufacturing of medical devices and solid oral dosage forms (e.g., FDA Guidance *Technical Considerations for Additive Manufactured Medical Devices*) [213]. However, formal regulatory frameworks for four-dimensional dosage forms remain in development [214]. Because four-dimensional dosage forms incorporate moving components and mechanical actuation, they operate at the interface between traditional oral tablets and dynamic medical devices [215]. Regulators require comprehensive quality risk assessments (ICH Q9) addressing the risk of physiological failure [216]. The primary clinical risk is gastrointestinal obstruction: if a gastroretentive tablet fails to degrade or soften following drug exhaustion, the rigid matrix may impact against the pylorus or ileocecal valve, causing bowel obstruction requiring surgical intervention [217]. Consequently, regulatory submissions must provide definitive preclinical proof of matrix breakdown via hydrolytic, enzymatic, or mechanical erosion under biorelevant conditions [218]. Stability protocols (ICH Q1A(R2)) must also track dynamic performance attributes such as R_f , R_r , and actuation kinetics across standard accelerated and long-term shelf-life stability intervals [219].

11. Conclusion

Four-dimensional printing combines additive manufacturing, stimuli-responsive polymer chemistry, and computer-aided digital design to create dynamic oral solid dosage forms. These programmed delivery systems can alter their geometry, mechanical modulus, and internal architecture over time by utilizing physiological environmental triggers such as hydrational shifts, localized pH transitions, core body temperatures, and bacterial enzymatic cleavage. This responsive behavior provides viable engineering solutions for challenging drug delivery scenarios, such as extending gastric residence for drugs with narrow upper-intestinal absorption windows, targeting payload delivery directly to colonic disease sites, and automating multi-phase chronotherapeutic regimens. Adopting four-dimensional additive manufacturing into standard clinical practice requires developing expanded libraries of pharmaceutical-grade, biocompatible smart excipients that combine stable printability with reliable physiological responsiveness. Industrial adoption will depend on continuous multi-nozzle and light-based manufacturing systems equipped with in-line process analytical technologies to ensure batch-to-batch reproducibility. When supported by standardized pharmacopeial testing and clear regulatory guidelines, four-dimensional additive manufacturing provides a versatile platform for engineering next-generation, patient-specific oral drug delivery systems.

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