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Review Article

4D Printed Stimuli-Responsive Polypills for Personalized Drug Therapy: Advances, Challenges, and Future Perspectives

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ABSTRACT

Four-Dimensional (4D) printing is transforming pharmaceutical manufacturing by enabling the development of adaptive drug delivery systems capable of responding dynamically to physiological and environmental stimuli. Among the most promising innovations in this field are 4D printed stimuli-responsive polypills, which integrate multiple active pharmaceutical ingredients within a single programmable dosage form capable of controlled and personalized drug release. These systems utilize smart biomaterials including hydrogels, shape-memory polymers, and stimuli-responsive composites that react to triggers such as pH, temperature, enzymes, moisture, magnetic fields, and light. This review explores recent advancements in 4D pharmaceutical printing technologies, adaptive release mechanisms, biomaterials engineering, nanotechnology integration, and artificial intelligence-assisted drug delivery systems. Furthermore, the review discusses the potential applications of adaptive polypills in chronic disease management, including cardiovascular diseases, diabetes, cancer, neurological disorders, and inflammatory diseases. Major challenges involving manufacturing complexity, scalability, regulatory approval, material biocompatibility, long-term safety, and ethical considerations are also critically analyzed. Emerging developments in biosensor integration, wearable health technologies, and AI-driven precision therapeutics indicate that 4D printed polypills may significantly reshape future personalized medicine. Despite current limitations, ongoing interdisciplinary advancements suggest strong future clinical potential for intelligent adaptive pharmaceutical systems.

Keywords: 4D Printing, Adaptive Drug Delivery Systems, Additive Manufacturing, Controlled Drug Release, Intelligent Drug Delivery Systems, Multi-Drug Delivery, Pharmaceutical 4D Printing, Polypills, Personalised Medicine, Precision Therapeutics, Responsive Hydrogels, Shape-Memory Polymers, Smart Biomaterials, Stimuli-Responsive Polymers.

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INTRODUCTION

Personalized medicine has significantly transformed modern healthcare systems by enabling therapies tailored to individual patient characteristics rather than applying generalized treatment approaches to all patients (Agarwal *et al*., 2023). Variations in genetics, metabolism, age, disease progression, lifestyle, and physiological conditions strongly influence therapeutic outcomes and drug responses. Consequently, conventional pharmaceutical dosage forms often fail to provide optimal therapeutic effectiveness in complex chronic diseases such as diabetes mellitus, cardiovascular disorders, cancer, neurological disorders, and autoimmune diseases (Khan *et al*., 2021).

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Recent advances in pharmaceutical additive manufacturing have accelerated the development of customized drug delivery systems capable of producing individualized doses and controlled-release formulations (Jamróz *et al*., 2022). Three-Dimensional (3D) printing technologies have already demonstrated remarkable potential in pharmaceutical manufacturing through the fabrication of tablets, implants, and multi-drug dosage forms with tailored geometries and release profiles. The regulatory approval of Spritam® by the United States Food and Drug Administration represented a major milestone validating the clinical feasibility of 3D printed pharmaceuticals (Gazzaniga *et al*., 2023).

However, conventional 3D printed pharmaceutical systems remain static after fabrication and cannot dynamically respond to physiological changes occurring within the body. To overcome these limitations, Four-Dimensional (4D) printing has emerged as a revolutionary advancement integrating smart materials with additive manufacturing technologies to create structures capable of changing their shape, functionality, or drug release behavior over time in response to external or internal stimuli (Tran *et al*., 2022).

In pharmaceutical applications, 4D printing enables the development of adaptive drug delivery systems capable of responding to pH, temperature, enzymes, moisture, magnetic fields, and biochemical signals within the body (Singh *et al*., 2024). One of the most innovative applications of this technology is the development of 4D printed stimuli-responsive polypills. These systems combine multiple active pharmaceutical ingredients into a single programmable dosage form capable of delivering drugs sequentially or selectively according to patient-specific physiological conditions (Parhi and Garg, 2025).

Stimuli-responsive smart biomaterials including hydrogels, shape-memory polymers, and nanocomposites play a central role in enabling dynamic structural and functional transformations in adaptive pharmaceutical systems (Zhang and Wang, 2023). Additionally, advancements in nanotechnology, bioprinting, biosensors, and artificial intelligence are further enhancing the precision and functionality of intelligent drug delivery platforms (Kumar *et al*., 2024).

Despite remarkable progress, several scientific and regulatory challenges remain unresolved, including manufacturing scalability, long-term material stability, reproducibility, biocompatibility, regulatory standardization, and ethical concerns regarding autonomous drug delivery systems (Kumar *et al*., 2024). Therefore, this review critically evaluates the current state of 4D printed stimuli-responsive polypills, focusing on recent technological advancements, adaptive drug release mechanisms, disease-specific applications, manufacturing challenges, research gaps, and future perspectives in personalized therapeutics (Figure 1).

METHODOLOGY

A comprehensive literature review was conducted using electronic scientific databases including PubMed, Scopus, Google Scholar, Web of Science, and ScienceDirect. Keywords such as "4D printing," "stimuli-responsive drug delivery," "adaptive polypills," "smart biomaterials," "shape-memory polymers," "personalized medicine," and "intelligent drug delivery systems" were used individually and in combination. Relevant peer-reviewed research articles, review articles, and scientific reports published in English between 2015 and 2025 were included. Additional references were identified through manual screening of bibliographies from selected articles. Studies focusing on pharmaceutical applications of 4D printing, smart polymer systems, nanotechnology integration, and adaptive drug delivery mechanisms were prioritized for inclusion in this review.

CURRENT STATE OF TECHNOLOGY

Evolution from 3D Printing to 4D Printing in Pharmaceuticals

Traditional 3D printing technologies enabled the fabrication of customized pharmaceutical dosage forms with precise geometries, programmable release profiles, and individualized doses (Jamróz *et al*., 2022). Technologies including Fused Deposition Modeling (FDM), Stereolithography (SLA), Selective Laser Sintering (SLS), binder jet printing, and semi-solid extrusion have been successfully employed in pharmaceutical manufacturing (Kumar *et al*., 2024).

However, conventional 3D printed systems remain structurally static after fabrication. The emergence of 4D printing introduced the concept of time as the fourth dimension, enabling printed pharmaceutical structures to dynamically transform in response to environmental or physiological stimuli (Agarwal *et al*., 2023). This advancement represents a transition from passive drug delivery systems toward intelligent and programmable therapeutics capable of adapting to patient-specific conditions.

Stimuli-Responsive Smart Materials

Stimuli-responsive biomaterials constitute the fundamental basis of 4D pharmaceutical printing technologies. These materials undergo physicochemical transformations upon exposure to specific environmental triggers, thereby enabling adaptive drug release behavior (Tran *et al*., 2022).

The major smart biomaterials used in adaptive pharmaceutical printing are summarized in Table 1.

pH-responsive polymers such as Eudragit®, alginate, chitosan, and cellulose derivatives enable site-specific drug release in gastrointestinal diseases and colon-targeted therapies (Parhi *et al*., 2023). Temperature-responsive Polymers including poly(N-isopropylacrylamide) (PNIPAAm) undergo reversible structural transformations in response to thermal changes, facilitating applications in inflammation-sensitive drug delivery systems (Singh *et al*., 2024).

Enzyme-responsive systems utilize disease-associated enzymes to trigger selective drug release within pathological tissues such as tumors and infected sites (Zhang and Wang, 2023). Similarly, moisture-responsive hydrogels and shape-memory polymers enable self-folding structures, controlled swelling, and programmable structural transformations for adaptive drug delivery applications (Zhang *et al*., 2021).

Multi-Drug Polypill Fabrication Technologies

Modern multi-material additive manufacturing technologies allow the fabrication of highly complex multi-drug dosage forms with programmable release characteristics (Khan *et al*., 2021). Multiple active pharmaceutical ingredients can be spatially separated within a single polypill while utilizing distinct polymer matrices and release mechanisms.

Current technological capabilities include:

- Immediate and sustained release combinations.
- Sequential multi-drug release systems.
- Personalized dose customization.
- Spatial separation of incompatible drugs.
- Layer-by-layer programmable release profiles.

These advancements hold significant promise for chronic diseases requiring combination therapy, including cardiovascular diseases, diabetes, hypertension, tuberculosis, and neurological disorders (Parhi and Garg, 2025).

Integration of Nanotechnology

Nanotechnology has substantially improved the efficiency of adaptive drug delivery systems by enhancing drug stability, targeting efficiency, and bioavailability (Kumar *et al*., 2024). Nanoparticles, dendrimers, nano-hydrogels, and liposomal systems can be integrated into 4D printed structures to facilitate precision nanomedicine.

The integration of nanotechnology enables:

- Improved tissue penetration.
- Enhanced targeting efficiency.
- Controlled nanoscale drug release.
- Reduced systemic toxicity.
- Improved solubility of poorly water-soluble drugs.

Artificial Intelligence and Digital Health Integration

Artificial intelligence and wearable biosensors are increasingly being integrated with adaptive pharmaceutical systems to enable real-time therapeutic monitoring and autonomous drug delivery (Parhi *et al*., 2025). AI algorithms may optimize individualized treatment regimens by analyzing physiological data, metabolic responses, disease progression, and therapeutic outcomes.

Mechanisms of Adaptive Drug Release

The adaptive release behavior of 4D printed stimuli-responsive polypills is primarily governed by dynamic physicochemical transformations occurring within the polymer matrix after exposure to biological or environmental stimuli (Tran *et al*., 2022). Unlike conventional drug delivery systems exhibiting fixed release kinetics, adaptive systems modify drug release patterns according to physiological conditions.

Drug release modulation may occur through:

- Polymer swelling.
- Matrix degradation.
- Shape transformation.
- Diffusion alteration.
- Structural folding or unfolding.

Physiological triggers including pH variation, temperature changes, enzymatic activity, hydration, magnetic fields, and light exposure influence the permeability, porosity, and mechanical characteristics of smart polymer systems (Singh *et al*., 2023).

These programmable responses establish the foundation for intelligent personalized therapeutics capable of improving treatment precision, patient adherence, and chronic disease management.

Applications in Disease Management

4D printed stimuli-responsive polypills possess enormous potential in chronic disease management through adaptive multi-drug administration based on patient-specific physiological conditions (Agarwal *et al*., 2022).

In cardiovascular diseases, these systems can simultaneously deliver antihypertensive agents, statins, and antiplatelet drugs while adjusting release profiles according to inflammatory biomarkers or physiological triggers. In diabetes mellitus, glucose-responsive systems may autonomously regulate insulin or antidiabetic drug release based on blood glucose fluctuations (Parhi *et al*., 2025).

Cancer therapy represents another promising application. Tumor microenvironments characterized by acidic pH, elevated enzyme activity, and localized hyperthermia may trigger targeted drug release, thereby minimizing systemic toxicity and improving therapeutic selectivity (Zhang and Wang, 2023).

Neurological disorders may benefit from sustained and programmable release systems capable of maintaining stable drug concentrations over extended durations. Additionally, adaptive systems may facilitate treatment of gastrointestinal diseases, autoimmune disorders, infectious diseases, and regenerative medicine applications (Singh *et al*., 2024).

Manufacturing Challenges

Despite promising advancements, several manufacturing challenges limit large-scale clinical implementation of 4D printed stimuli-responsive polypills (Kumar *et al*., 2024).

One major limitation involves the lack of pharmaceutically approved smart biomaterials possessing both biocompatibility and stimuli-responsive functionality. Many advanced polymers remain unsuitable for pharmaceutical applications due to safety and regulatory concerns.

Additional challenges include:

- Multi-material printing complexity.
- Drug instability during fabrication.
- Structural reproducibility issues.
- Long-term storage stability.
- High manufacturing costs.
- Scalability limitations.

Maintaining homogenous drug distribution and preserving responsive functionality during large-scale production remain particularly difficult due to the dynamic nature of stimuli-responsive materials (Parhi *et al.*, 2023).

Regulatory and Ethical Concerns

The regulatory evaluation of adaptive pharmaceutical systems remains highly challenging because current pharmaceutical guidelines are primarily designed for static dosage forms (Gazzaniga *et al.*, 2023). Regulatory agencies currently lack standardized protocols for evaluating self-transforming drug delivery systems with time-dependent properties.

Critical regulatory concerns include:

- Quality control standardization.
- Long-term safety monitoring.
- Reproducibility validation.
- Therapeutic equivalence assessment.
- Pharmacokinetic variability evaluation.

Ethical concerns additionally involve patient safety, predictability of autonomous drug behavior, cybersecurity risks associated with biosensor integration, and healthcare accessibility disparities due to high production costs (Khan *et al.*, 2021).

Table 1: Stimuli-Responsive Smart Materials Used in 4D Pharmaceutical Printing.

Material Category	Description	Examples	Applications
pH-Responsive Materials	Materials responding to pH variation	Eudragit®, alginate, chitosan	Colon-targeted delivery
Temperature-Responsive Materials	Thermally adaptive polymers	PNIPAAm	Inflammation-responsive therapy
Enzyme-Responsive Systems	Enzyme-triggered release systems	MMP-responsive hydrogels	Tumor targeting
Moisture-Responsive Hydrogels	Water-swelling structures	Hydrogel systems	Self-folding drug carriers
Shape-Memory Polymers	Stimuli-triggered structural recovery	Polyurethane SMPs	Gastro-retentive systems

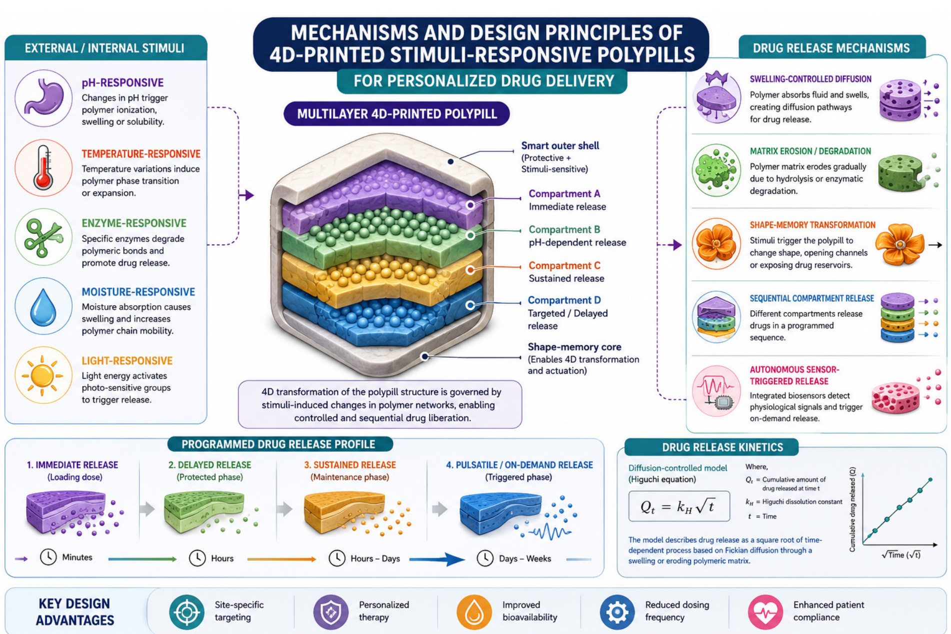

Figure 1: Schematic representation of a 4D printed stimuli-responsive polypill.

Research Gaps

Although substantial progress has been achieved, important research gaps continue to hinder clinical translation of 4D printed adaptive pharmaceutical systems.

Current limitations include:

- Insufficient *in vivo* studies.
- Limited clinical trials.
- Lack of standardized testing protocols.
- Poor understanding of long-term safety.
- Limited large-scale manufacturing studies.
- Inadequate cost-effectiveness analyses.

Most existing research remains limited to proof-of-concept or *in vitro* studies, emphasizing the urgent need for translational and clinical investigations (Kumar *et al*., 2024).

FUTURE PERSPECTIVES

The future of 4D printed stimuli-responsive polypills is expected to be strongly influenced by advances in artificial intelligence, biosensors, wearable technologies, nanotechnology, and precision medicine (Parhi *et al*., 2025).

Emerging innovations may enable:

- Autonomous glucose-responsive insulin systems.
- Biosensor-regulated cardiovascular therapeutics.
- AI-guided personalized medication algorithms.
- Closed-loop precision medicine platforms.
- Real-time therapeutic monitoring systems.

Integration of wearable biosensors with adaptive drug delivery devices may allow continuous monitoring of physiological biomarkers and dynamic adjustment of therapeutic regimens according to patient-specific needs (Agarwal *et al*., 2023).

Future advancements in smart biomaterials, bioprinting technologies, computational modeling, and regulatory science may substantially accelerate the clinical translation of intelligent pharmaceutical systems.

CONCLUSION

Stimuli-responsive polypills developed using 4D printing technology represent one of the most promising innovations in modern pharmaceutical sciences. These intelligent systems enable a transition from static drug delivery approaches toward adaptive and personalized therapeutics capable of responding dynamically to physiological conditions.

Despite considerable progress in smart biomaterials, additive manufacturing technologies, nanotechnology, and artificial intelligence integration, several technological, regulatory, economic, and ethical barriers remain unresolved. Nevertheless, interdisciplinary collaboration involving pharmaceutical sciences, biomaterials engineering, computational medicine, and digital health technologies is expected to accelerate future clinical implementation.

Overall, 4D printed stimuli-responsive polypills possess substantial potential to revolutionize future personalized drug delivery systems and precision medicine.

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ABBREVIATIONS

4D: Four-Dimensional; **3D:** Three-Dimensional; **FDA:** Food and Drug Administration; **FDM:** Fused Deposition Modeling; **SLA:** Stereolithography; **SLS:** Selective Laser Sintering; **PNIPAAm:** Poly(N-isopropylacrylamide); **MMP:** Matrix Metalloproteinase; **SMPs:** Shape-Memory Polymers; **APIs:** Active Pharmaceutical Ingredients; **AI:** Artificial Intelligence.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The author solely contributed to the conceptualization, literature review, manuscript writing, editing, and final approval of the manuscript.

SUMMARY

This review highlights the growing importance of 4D printed stimuli-responsive polypills in advancing personalized medicine through adaptive and programmable drug delivery systems. Although challenges involving scalability, regulation, and material optimization remain, continued advancements in smart biomaterials, artificial intelligence, biosensors, and additive manufacturing technologies may accelerate future clinical translation and therapeutic implementation.

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