

3D-Printed Polypills in Precision Medicine: Transforming Multidrug Therapy For Metabolic Syndrome

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Abstract

Advanced 3D printing technology enables the production of customized polypills where multiple drugs are arranged in distinct regions and finely tuned control over each drug's dose release kinetics, and geometry by using technologies such as extrusion, stereolithography (SLA), and multi-material inkjet printing. It includes designing specific drug-polymer matrices, layered architectures, with controlled drug kinetics via infilled patterns, shell thickness, and Hot-Melt Extrusion filament, supporting flexible and patient-specific multi-drug therapy. In current research, Emerging Metabolic Syndrome polypill formulations together with statins, antihypertensives, antidiabetic drugs include GLP-1 receptor agonists and DPP-4 inhibitors, low-dose aspirin, and anti-obesity agents, with careful tuning of compatibility and release profiles using layered 3D printing, polymer matrices, and pH-responsive coatings. Precision-driven 3D printed Metabolic Syndrome polypills leverage pharmacogenomics, digital health data, and point-of-care production systems to tailor treatment for each patient. To ensure optimal and personalized drug exposure, metabolic syndrome polypills are evaluated using content uniformity, physicochemical and dissolution studies, release kinetics modeling, preclinical pharmacokinetics, and IVIVC-guided or virtual bioequivalence assessments. At Present, 3D printed polypills are governed by conventional drug device and GMP regulations, supported by the US FDA, EMA, and ICH (Q8-Q12). From experimental to clinical use, 3D-printed polypill production depends on multi-printer networks, QbD-based process control, PAT-enabled real-time monitoring, efficient material management, and cost-effective approaches for customized, low-volume manufacturing. Futuristic development in 3D printed polypills will focus on AI-driven formulations and geometries, 4D-responsive tablet system manufacturing models, cutting-edge organ-on-chip and PBPK models, and convergence with digital therapeutics and precision nutrition platforms to achieve truly personalized cardiometabolic therapy.

Keywords: 3D printing, Polypills, Metabolic Syndrome, pharmacogenomics, Multilayer.

1. Introduction

Metabolic syndrome, also known as syndrome X, refers to a cluster of metabolic abnormalities, including insulin resistance, hypertension, Central obesity, and atherogenic dyslipidemia, which together elevate the risk of cardiovascular disease. The metabolic syndrome is not considered an absolute risk factor for example, age, gender, smoking and LDL cholesterol level. The metabolic syndrome is diagnosed or identified when 3 or more metabolic abnormalities are present [1].

According to (National cholesterol education program) ATP III criteria these abnormalities includes increased fasting blood glucose level (≥ 100 mg/dL or treatment of hypoglycaemia), increased triglyceride levels (≥ 150 mg/dL or treatment for hypertriglyceridemia), reduced High Density Lipoprotein (HDL) cholesterol (< 40 mg/dL in men and < 50 mg/dL in women or specific therapy), elevated blood pressure ($\geq 130/85$ mmHg or antihypertensive treatment), and increased waist circumference (> 102 cm in men and > 88 cm in women).

Under the International Diabetes Federation (IDF) 2006 guidelines, for the diagnosis of metabolic syndrome, the Central adiposity, an obligatory component defined by a waist circumference > 80 cm in women and > 94 cm in men [2].

According to the (World Health Organization) 1999 criteria, metabolic syndrome is diagnosed when insulin resistance or impaired glucose metabolism is present (fasting plasma glucose > 6.1 mmol/L or 110 mg/dl, or 2-hour plasma glucose > 7.8 mmol/L or 140 mg/dl), as an essential criteria, together with any two or more of the following metabolic abnormalities, including reduced HDL cholesterol, elevated triglycerides, central obesity (waist-hip ratio > 0.9 in men or > 0.85 in women, or BMI > 30 kg/m²), and hypertension ($> 140/90$ mmHg [3].

1.1 Global Burden and Prevalence of Metabolic Syndrome

Globally, the prevalence of Metabolic Syndrome nearly doubled from 14.7% in 2000 to 31% in 2023 in women, while in men it increased from 9% to 25.7%. In 2023, approximately 1.54 billion adults were affected by metabolic syndrome. In both men and women, frequency increases in 196 countries and territories. Worldwide, 1.4 billion adults aged 30- 79 were associated with hypertension in 2024, representing 33% their age group, and around 600 million people are unaware that they have hypertension. The global prevalence of diabetes and obesity is rising, and in 2019 approximately 463 million adults were living with diabetes worldwide. An approx. 252 million adults are living with diabetes, and unconsciously they have the issue. Diagonally low income 58.7%, middle income 45.5%, and high income 28.9% of grownups are alive with diabetes undiagnosed. The peak quantity of undiagnosed diabetes is found in Africa, 72.6%, followed by the western pacific 50.0% and Southeast Asia, 42.7% [4].

1.2 Current treatment where patients take multiple medications daily

Polypharmacy may offer clinical benefits for patients managing multiple chronic conditions concurrently, as it aims to, improve patient comfort, and delay disease progression. However, a growing proportion of elderly patients are prescribed an excessive number of medications, which has been shown to adversely affect their overall health outcomes. The integration of personalised medicine into pharmaceutical care for chronic diseases remains limited due to conventional manufacturing processes and inadequate drug delivery systems. Studies have reported that more than 50% of elderly patients experience adverse drug reactions at approximately three times the rate of younger populations, while nearly 50% demonstrate non-adherence to prescribed medications — both of which contribute to suboptimal treatment outcomes and a significant rise in healthcare expenditure. The consequences of inappropriate polypharmacy extend across both physical and mental health domains, including increased mortality rates, higher rates of hospitalisation, greater risk of accidental falls and injuries, progressive physical frailty, and accelerated cognitive decline [5].

1.3 Explain why 3D printing enables personalised multidrug therapy

Now one of the biggest clinically significant advantages of 3D printing is its capacity to fabricate compound, multicomponent dosage forms, usually referred to as polypills, that would be problematic or terrible to produce through conventional manufacturing. Unlike traditional tablet compression, additive manufacturing allows separate drug-loaded sections to coexist within a single solid unit, each retaining its own release form without interference from neighbouring components. Extrusion-based 3D printing shows this principle early on, with researchers successfully constructing a five-drug polypill in which two separate, well-defined release profiles were achieved instantaneously within one tablet. Through an advanced SLA approach, researchers produced multilayered polypills incorporating six distinct active pharmaceutical ingredients

2 3D printing technologies in pharmaceutical fabrication

2.1 Fused Deposition Modelling (FDM / FFF)

Over the past decade, 3D printing has found a genuine place in pharmaceutical manufacturing, with techniques such as FDM, inkjet printing, offering something distinct to formulators. Of these, FDM has become the go-to choice for many it works by pushing heated polymer filaments through a nozzle, stacking material one thin layer at a time until a complete structure takes shape. Materials such as PLA, PVA, HPC, HPMC, and ethyl cellulose typically serve as the carriers or matrices that hold the drug in place throughout this process. One clever workaround that emerged involved blending thermostable fillers like talc into HME-processed filaments, which pulled printing temperature down to roughly 110° Celsius a practical solution for protecting APIs that would otherwise degrade under heat. FDM does have its frustrations, though.

2.2 Stereolithography (SLA) / Digital Light Processing (DLP)

3D printing has demonstrated significant potential to revolutionise drug distribution systems. In 2015, the Food and Drug Administration (FDA) permitted the first 3D-printed drug, Spritam (levetiracetam), for the treatment of epilepsy. Stereolithography apparatus (SLA) and digital light processing (DLP)-based vat-polymerisation methods are highly effective procedures of bioprinting. While SLA and DLP are mutually layer-by-layer fabrication methods, DLP uses projected planar light patterns and is thus faster than SLA, which depends on raster scans [36]. Vat photopolymerization methods such as SLA, DLP, and continuous liquid interface production (CLIP) use light radiation to form compact objects from a photoreactive liquid resin. These procedures

offer great feature tenacity, a smooth surface texture, and avoidance of drug thermal degradation. This SLA printer generates solid matter by consuming a laser beam to photopolymerise monomers. In this work, polyethylene glycol diacrylate (PEGDA) was used as a monomer, and diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide was used as a photo-initiator [6, 7].

2.3 Inkjet printing

Inkjet printing (IJP) is a reliable manufacturing method that easily deposits ink materials, layer-by-layer, to create 3D objects or 2D designs with detailed control over their structure and arrangement. In inkjet printing, droplet deposition is classified: 1 Continuously inkjet and 2 drop-on-demand (DoD) instrument. DoD inkjet printing is classified into the mechanism by which droplets are formed: "Thermal and piezoelectric inkjet printing. The drug is organised by small droplets and perfectly binds these droplets into thin layers of powder to form more than a few solid units, and overlapped layer by layer. The inkjet technique gives a high spatial resolution of-up to 50 μm and the co-deposition of several inks [8]. It is used for multi-drug holding medicine preparation, the inks used by machine: a kind of solvent that minimises surface tension and improves droplet ejection. Like 40% aq. isopropanol with 4% glycerine and 0.1% PVP K30, the properties of the printing ink directly impact droplet formation, viscosity, density, and surface tension.

2.4 Binder jetting

Liquid binders are mostly applied to the powder bed to form and couple each layer. In binder jetting, elements are attached using a liquid binder and make a layer by spraying the binder as fine droplets through a printing nozzle onto the powder. The binder is sprayed into the powder as tiny droplets through a printing nozzle, where it binds to a particle to make a 3D printing structure. In binder jetting, the layer-by-layer moulding of powder particles using a liquid binder results in the formation of a tablet with high porosity and enlarged interparticle spacing. This porous structure provides the quick penetration of dissolution media onto the tablet matrix. The 3D printed tablet shows rapid disintegration, in a within a few seconds. A great achievement in the pharmaceutical manufacturing industry in the year 2015, at a time when the FDA officially accepted the world's first 3D printing formulation (levetiracetam). The first three-dimensional (3D) drug product was formed using the binder jetting technology.

2.5 Semisolid extrusion [SSE]

Semisolid extrusion [SSE] is a subclass of material extrusion 3D printing, and with the help of sequential deposition of layers of gel or paste, makes objects of any chosen size and form. SSE 3D printing has the benefit of allowing ambient temperature printing, which is particularly beneficial for the 3D printing of thermosensitive drugs. SSE permits the use of an extensive range of material which is not suitable for other methods, such as FDM or DPE. A binary HPMC + PVP systems, have been successfully used as ink bases, with SiO_2 added as a disintegrant. SSE gives micro-extrusion-based 3DP expertise in the pharmaceutical field due to its ease and potential for on-site manufacturing, which provides covering dose, release profile, size, shape, and colour [9].

2.6 Selective Laser Sintering (SLS)

The modulation of the porosity of printed materials appears to be the most interesting outcome of this technology for pharmaceutical applications. A typical SLS apparatus consists of five key components: (i) a building platform, (ii) a laser, (iii) Galvano mirrors, (iv) a powder reservoir platform or hopper, and (v) a mechanical roller. The SLS process is particularly advantageous for mass production. Porous tablets fabricated via SLS can disintegrate orally within seconds. Still, SLS is capable of producing amorphous solid dispersions in a single step, eliminating the multi-step processes required by conventional manufacturing systems. Compared to other methods, SLS offers numerous advantages, including compatibility with a wide variety of raw materials, high component complexity, rapid manufacturing, reduced production costs, and efficient resource utilisation. Additionally, SLS reduces medication risks by printing the exact dose strength required to meet each patient's therapeutic profile. A further practical benefit is that unsintered powder can be recovered and reused across multiple print cycles. Despite these advantages, SLS is not without limitations [10].

3D PRINTING TECHNOLOGIES IN PHARMACEUTICAL FABRICATION

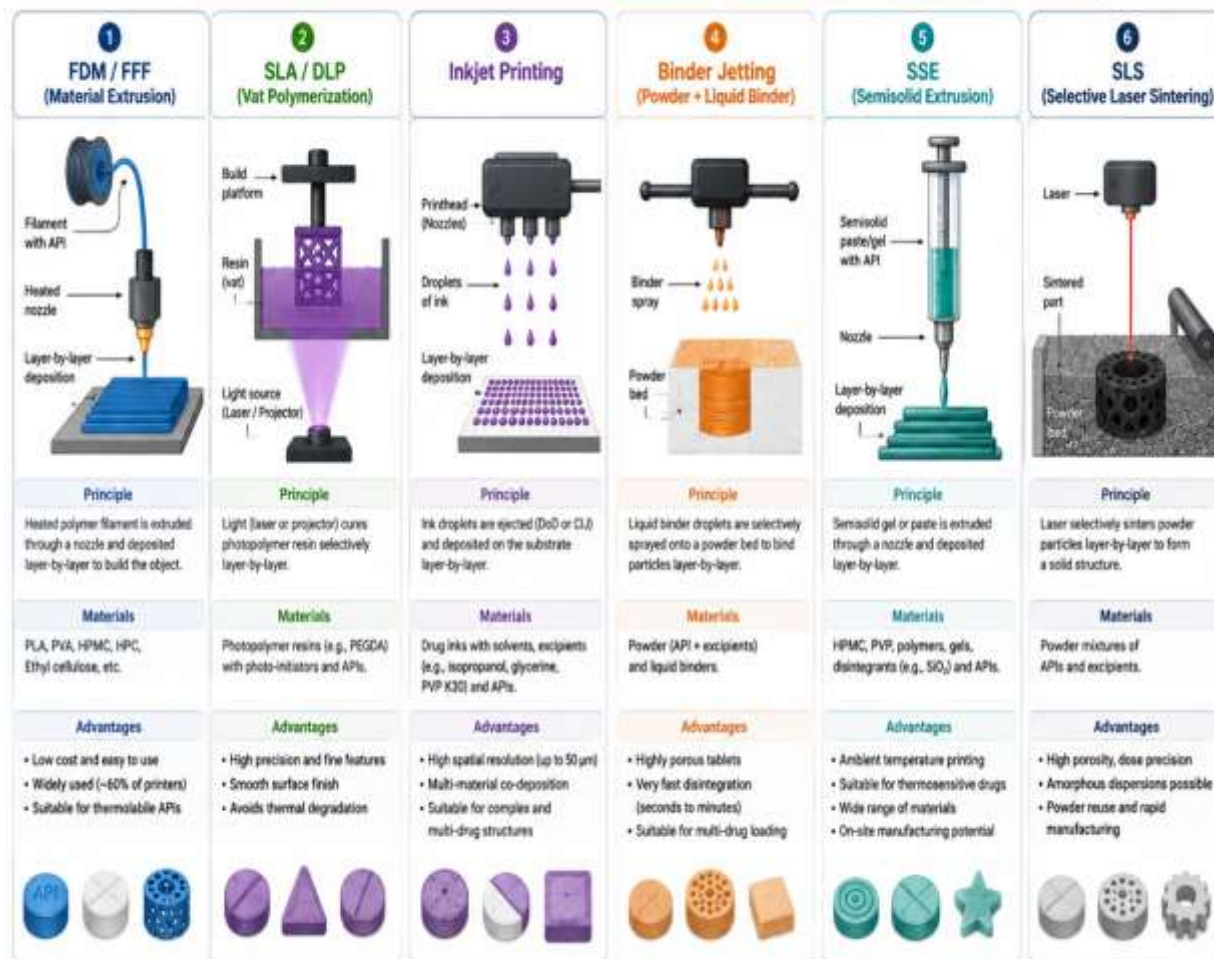


Fig. 01 Various 3D Printing Technologies

3 Polypill Design Strategies Using 3D Printing

3.1 Drug-Polymer Matrix Selection

Amorphous solid dispersions (ASDs) are progressively working to improve the bioavailability of poorly soluble molecules by increasing the rate and amount of dissolution during drug product development. Hydrophilic polymers, containing PVP, PVPVA, and HPMC, drug release in low drug-loading ASDs is polymer-controlled. The miscibility of indomethacin in HPMC is greatly higher compared with the indomethacin-HPMCAS system, in these solid dispersions, demonstrating that miscibility can strongly affect physical stability. HPMC-AS is an enteric-functional amphiphilic polymer mainly suited for pH-triggered release and gives spring-parachute dissolution improvement [11]. Polymethacrylates (Eudragit E, L, S, FS) are amongst the most commonly used excipients for making ASDs in enteric submissions. Polymer choice is of great standing for the reason that it affects the stability, solubility, dissolution rates, manufacturing process, and bioavailability of the ASD. DSC is the main thermal critical tool for drug-polymer compatibility. A single glass change temperature between the amorphous drug and polymer, as checked by controlled DSC, shows miscibility [12].

3.2 Controlling Drug Release Profiles

Drug release in polypills is primarily tuned by the choice and proportion of polymers and excipients in each compartment. Hydrophilic, swellable polymers such as HPMC or Soluplus retard release via gel-layer formation,

while hydrophobic or erodible polymers. PVA-based tablets containing 70% fluconazole disintegrated in less than 3 minutes, whereas formulations with 40% and 20% drug content did not meet this threshold. Porous preparations show quick disintegration and therefore fast drug release. HPMC-AS LG dissolved at roughly pH 5.4, and 100% of drug was out from 20% infill tablets in less than one hour after the pH shift [78]. Fill density needed a significant impact ($F(11,24) = 15,271.147$, $p < 0.0001$) with a strong negative association ($r > -0.99$; $p < 0.0001$) with release performance 20% infill proved the fastest and most complete release. Tablets containing 25% w/w HPMC as a release modifier gives 95% drug release in 24 hours, compared with only 17.8% without HPMC; fill density and shell viscosity had a significant role, comparative effect on release performance. Tablets with a concentration of more than 0.9 g/cm³ are inclined to sink to the lowest of the dissolution vessels [13].

3.3 Hot-Melt Extrusion (HME)

Hot Melt Extrusion (HME) is a constant pharmaceutical manufacturing method that has been widely explored for solubility enhancement and taste masking of active pharmaceutical ingredients. The benefit of consuming HME to produce polymer filaments for FDM

printing is that a homogenous solid dispersion of two or additional pharmaceutical excipients can be made, and a thermostable drug can even be incorporated in the filament composition. HME is a solvent-free, single-step method that can be coupled with an FDM 3D printing method for founding a nonstop manufacturing line. Twin-screw extrusion or its speciality, is grouped with single-screw extrusion that can carry filaments with improved tensile assets compared to only single-screw extrusion. The HME method permits the adaptation of the API to a shapeless form, or the dispersion of API at the molecular level, which can result in enhanced bioavailability [14].

3.4 Multi-Drug Loading Strategies

3D printing is the process of forming objects layer by layer using digital models. And additive manufacturing creates objects by the gradual addition of material until the final geometry is achieved. Advanced techniques such as fused deposition modelling (FDM) employing controlled sequential deposition mechanisms. It provides the controlled placement of drugs, allowing the creation of dosage forms with separate layers, compartments, or structures in which multiple APIs (Active pharmaceutical ingredients) are placed in separate compartments. Moreover, research shows that tablets were fabricated with separate compartments for individual drugs [15]. The amount of drug loading can be tailored by adjusting the composition of the printing matrix, while inkjet printing also allows precise control over dose combinations and the kinetics of drug release.

3.5 Dose Flexibility and Special Populations

Many pediatric designs need dose handling to either manage prescribed doses per age/body weight or to minimise acceptance issues. Excruciating a large tablet into divided pieces is the most dominant and modest practice for using solid dosage systems. The individual wreckages formed might not meet the planned dose owed to the possible difference in weight, content uniformity and the effect on drug dissolution, as well as following metabolism. Entirely mini-tablets shaped had outstanding content uniformity and their tag claim standards with acceptable range, showing that HME dealing tracked by 3D printing promotes content uniformity even for mini-tablets holding low drug doses (0.19 mg) [90]. For renal/hepatic issues with reformed pharmacokinetics, 3D printing fabricates instant low-dose alternative CAD alterations, ensuring safety without the inventory of multiple assets [16].

4. Lipid-Lowering Agents

HMG- CoA reductase inhibitors, commonly referred to as statins, are prescribed alongside diet and exercise to manage hypercholesterolemia. These drugs work by decreasing the level of total cholesterol, LDL cholesterol, and triglycerides, while raising HDL cholesterol. While each statin has specific FDA- approved indications, they are mainly used for preventing and managing ASCVD events such as heart attacks and strokes. Drug selection is guided by patient- specific needs, drug properties, and recommendations from the 2018 cholesterol guidance. Despite this flexibility, taking the medication at the same time daily is advised to ensure better compliance and stable plasma levels. Some research suggests that alternate day dosing strategy to decrease treatment cost and adverse effects, but the majority of clinical outcome data support daily use [17]. In pharmaceutical formulations, statins face stability challenges, especially in the FDM technique, where high processing temperatures can compromise drug stability.

4.1 Antihypertensives

A polypill is a fixed-dose combination (FDC) containing therapy with three or more active ingredients in a single pill cell, planned to reduce the pill weight and reach a large protective effect against cardiovascular disease (CD) with negligible adverse effects. The best-known triple fixed combination dose (FCD) is one that comprises the CCB amlodipine (AML), the ARB valsartan (VAL), and the diuretic HCTZ. Affected person with metabolic syndrome, lisinopril (ACE-I) is linked with a lower rate of newly diagnosed diabetes compared to amlodipine, and both drugs demonstrate similar cardiovascular results. Later oral medication of the single-pill triple combination in healthy grownups, peak plasma ratios of HCTZ are reached in about 2 hours, valsartan in about 3 hours, and amlodipine in around 6 hours. Valsartan (VAL) is an oral antihypertensive drug that goes to the BCS class II [18]. This low oral bioavailability is because of the pH-dependent solubility of VAL, with low solubility at a pH of ≤ 3 slight drug release at pH < 4.5 , but worthy and complete release of both drugs at pH 6.5.

4.2 Antidiabetics

Oral semaglutide was accepted by EMA and FDA in 2020, and is the first orally available GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus in adults. Its efficacy in glycemic regulation, weight decrease, and safety has been proven in the [PIONEER] clinical trial program. Additionally, it has revealed cardiovascular safe activity clinically comparable

to placebo, contributing to a convenient alternative to injectable therapies. GLP-1 receptor agonists are normally administered via the injectable route; however, semaglutide is offered in both subcutaneous and oral formulation, showing a Major improvement. It is accepted as a secondary mediator for glycemic control in type 2 diabetes mellitus and is under inquiry for anti-obesity guidance. DPP-4 inhibitors demonstrate minimal drug-drug interaction. Reduce HbA1c by almost 0.5-0.9% and may slightly decline the body weight [19].

4.3 Antiplatelet Agents

Low doses of aspirin (75–100 mg) need enteric-coated sheets in 3D-printed polypills to curtail gastric irritation and ulceration risk. Aspirin prevents cyclooxygenase in the stomach's acidic atmosphere, theoretically causing mucosal damage, erosions, or bleeding, even at low doses. Enteric coatings liquify in the small intestine at higher pH, with delayed release and defend the gastric lining while providing protective antiplatelet efficacy. In polypill strategies, multi-layer extrusion or stereolithography is used on pH-sensitive polymers. As external enteral shells around aspirin sections. This separates aspirin from gastric acid without bargaining immediate-release contours for other drugs like statins [20]. Clopidogrel responsive with many polymers requires secluded compartments in polypills to stop ruin or interactions during printing procedures like FDM or SLA.

4.4 Anti-Obesity Agents

Orlistat, phentermine/topiramate ER, and GLP-1 founded combo similar to oral semaglutide with metformin characterize key anti-obesity agents with different mechanisms, but each postures gives unique challenges for fused deposition modeling (FDM) in polypill progression. Their oily, controlled-substance, or evolving combo makes filament extrusion, multi-API integration. Orlistat behaves like a lipase inhibitor, but its integrally oily and waxy properties delay uniform filament construction during hot-melt extrusion for FDM, increasing poor flow, inconsistent drug-polymer miscibility, and nozzle clogs. CNS-acting drug (phentermine and topiramate) follows a control pathway, complicating 3D-printed polypill consent because of fixed dose need, misuse potential, and REMS requirements [21].

4.5 Drug-Drug Physicochemical Compatibility

Drug-drug physicochemical compatibility is serious in multi-layer polypill designs, particularly for FDM 3D printing, where issues like pH mismatch, hygroscopicity, thermal stability, and co-crystal construction can reduce stability. There is highlight screening via DSC, FTIR, and TGA to identify risks in fixed-dose combinations (FDCs). Metformin is like an alkaline/acid-base character which is relatively unstable at alkaline pH and inclines to be more soluble in acidic to neutral media, although amlodipine is an acid-sensitive drug that can be destroyed at low pH. Metformin hydrochloride is hygroscopic revelation to moisture, which can cause swelling and form a cake and mobility changes [22].

5 Personalizations and Patient Profiling

5.1 Precision Medicine in Metabolic Syndrome

Exactness medicine in (Metabolic Syndrome) changes from one-size-fits-all schedules to biomarker-determined, phenotype-specific therapy with dosage and agent choice directed by separate risk shapes and

digital-device data. It knows drug quality and dose, statin intensity, and adjuncts, 24-h ambulatory BP refines antihypertensive dosing. Visceral-predominant overweightness shows a stronger connection to insulin resistance dyslipidemia, and hypertension [23]. Lifestyle-intensive, GLP-1 RA- or SGLT-2-inhibitor-based treatments that reduce visceral fat and improve cardiometabolic risk. Insulin-resistant (high HOMA-IR, normal/high C-peptide) answers best to metformin. Wearable-derivative statistics (step count, heart-rate variability, sleep, CGM, and activity-time contours) build that build digital model of inactive vs active, steady vs labile glucose, and expectable inconstant BP forms.

5 . 2 Pharmacogenomics Relevant to Metabolic Syndrome Drug Combinations

Pharmacogenomics plays a critical key role in enhancing drug blending for Metabolic Syndrome, where genetic variants give efficacy and safety of statins, antihypertensives, antiplatelets, and antidiabetics. CYP2C9 and CYP3A4 polymorphisms adjust statin breakdown, with reduced CYP3A4 activity increasing exposure to atorvastatin and simvastatin, enhancing toxicity risks CYP2C9 variants primarily affect drugs like fluvastatin or rosuvastatin [24]. ACE gene pullout/removal (I/D) polymorphism expects response to ACE inhibitors or ARBs; D/D genetic constitution connects with higher ACE activity, inferior response in some people, and enlarged cardiovascular risk. CYP2C19, a poor metabolizer enzyme (*2/*2 or *2/*3) display reduced clopidogrel initiation, enriching platelet reactivity and main adverse cardiovascular actions in Metabolic Syndrome patients on dual therapy. SLC22A1 (OCT1) alternate lessen metformin uptake into hepatocytes, fading glycemic response, and increasing therapeutic failure rates [25].

5.3 Digital Health Integration

Digital health devices increase polypill medication for Metabolic Syndrome, which provides real-time data and self-medication, connecting patient care with on-demand 3D printing drug design. Continuous glucose monitors like Dexcom or Freestyle Libre deliver minute-by-minute glycemic trends make personalise a polypill for metformin-combination. Ambulatory BP devices provide cuffless chasing via PPG sensors, warning of hypertension shocks that need immediate ACEI/ARB dose pinches in printed polypills. Electronic health records need patient vital organ, pharmacogenomics (e.g., SLCO1B1 variants), and systems to auto-generate 3D printed files for custom statin-antihypertensive polypills, confirming fixed layering for release shapes [26, 27].

5.4 Dose Individualization Algorithms

This algorithm optimizes 3D-printed polypills for metabolic syndrome by modifying or designing multidrug doses to patient-specific needs. They participate in PK-PD modeling, machine learning, and Bayesian updates for precision therapy. Population PK models for Metabolic syndrome patients, justification for covariates like age, BMI, renal function, and comorbidities to examine drug exposure in multidrug schedules. Machine Learning Models(e.g., XGBoost, neural networks) fuse genotype (SNPs), phenotype (biomarkers, lifestyle), and EHR data to show maximum drug response [28]. They guess Metabolic syndrome risk and drug action, enabling polypill customization via multi-task deep learning. Highly accurate new models for dynamic personalization. Bayesian Individualization bayesian methods use old population PK data, which is updated with TDM concentrations via MAP assessment for new dose estimates [29].

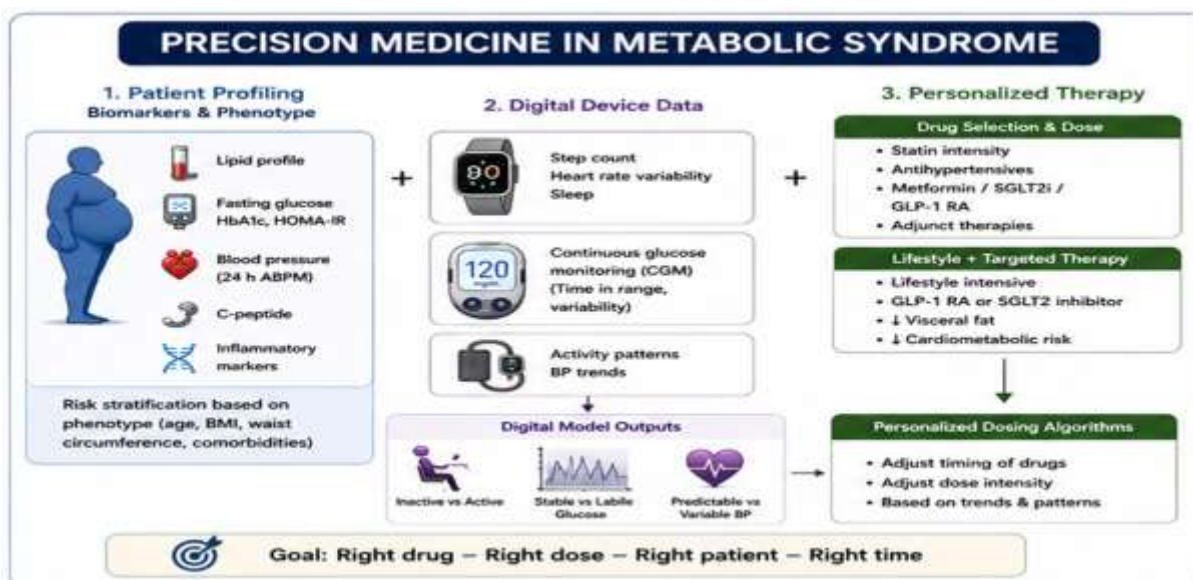


Fig. 02 Precision Medicine in Metabolic Syndrome

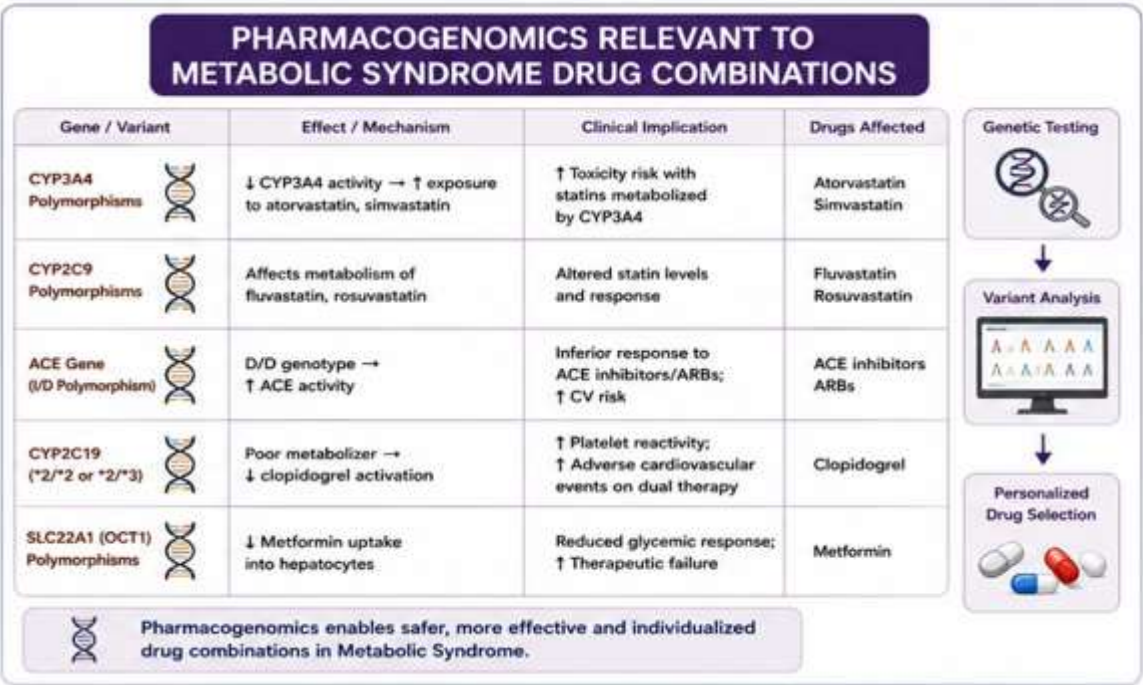


Fig. 03 Pharmacogenomics Relevant to Metabolic Syndrome Drug Combinations

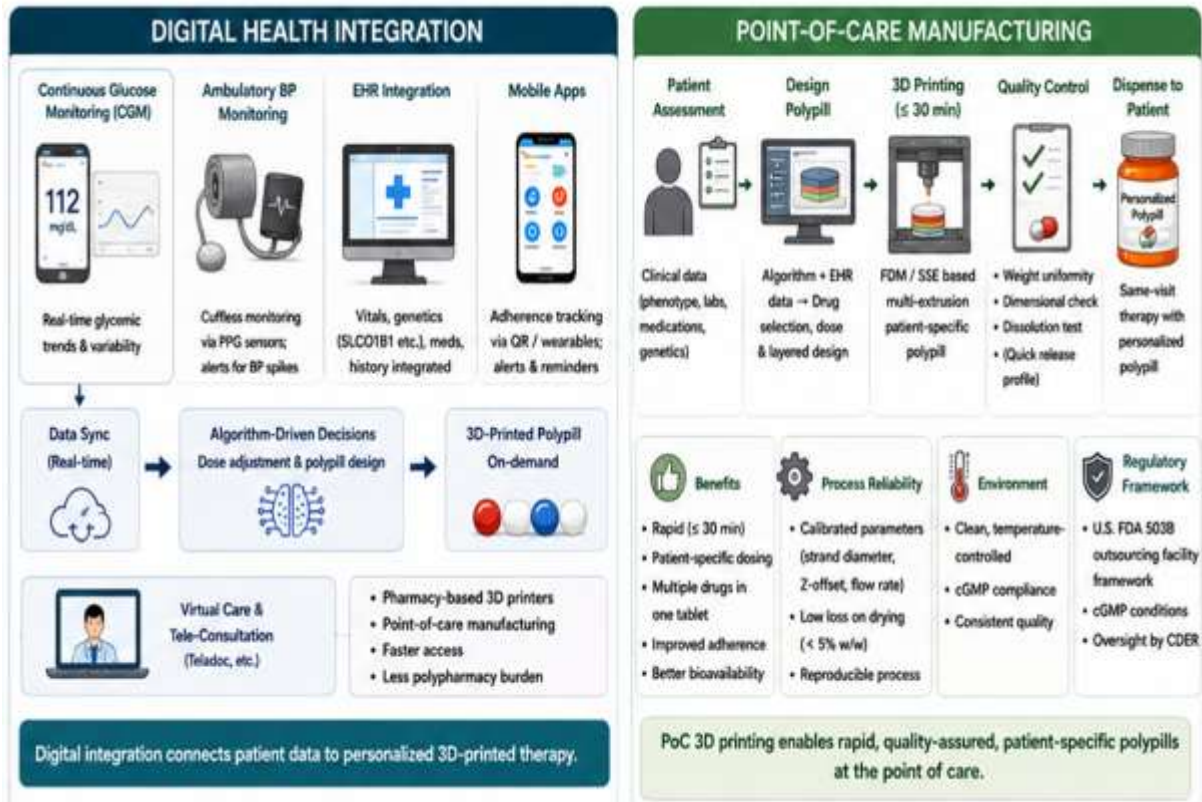


Fig. 04 Digital Health Integration and Point-of-Care Manufacturing

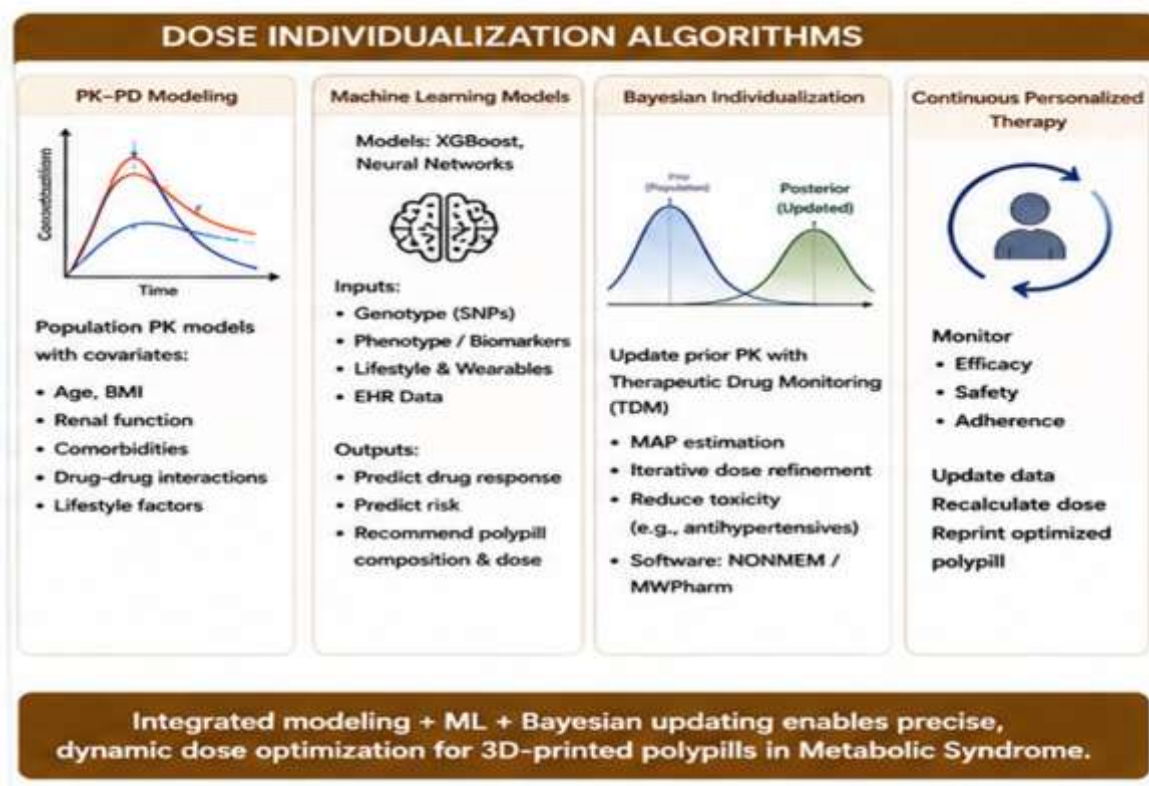


Fig. 05 Dose Individualization Algorithms

6. Regulatory Landscape

6.1 FDA Guidance on 3D-Printed Drug Products (2017)

This 2017 FDA “Technical Considerations for Additive Manufacturing for Medical Devices” guidance (and related thinking for drug products) sets a basis for how 3D-printed (additively manufactured, AM) device-drug products should be developed and controlled under CDER/CBER oversight, it boosts manufacturers to treat AM as a process-driven quality system as compare to new manufacturing tool, require explicit controls over design, materials, software, and testing [30]. The guidance efforts on devices (e.g., implants, surgical tools) cover AM process classification, plan considerations, material properties, and post-processing validation. Design and testing highlight process validation, critical quality attributes (CQAs) like drug content uniformity, and mechanical properties of printed structures. Patient-Specific Products: showing personalized dose falls under the 21st Century Cures Act, permitting point-of-care printing with risk-based control rather than full batch GMP. It supports on-demand production for pediatrics or polypharmacy via polypills [31].

6.2 EMA and EU Perspectives

EMA and EU authorities are developing and designing for 3D-printed medicinal products, strengthening patient-specific manufacturing. Current documents like the EMA's Q&A on 3D printing technology provide practical guidance for solid oral dosage forms. EMA issued a reflection paper on additive manufacturing applications in medical terms around 2020, with constant developments, including a 2026 Q&A document on 3DP implementation. It all covers process validation, quality controls like NIR/Raman for small batches, and patient-centric designs like polypills. Magistral Preparation: 3D printing sets magistral intensifying bases for customized, patient-specific forms in community pharmacies, providing automation for polypills and low-dose APIs under standard quality rules. Tasks include validating printers, stability testing, and controls for feedstocks like prefilled cartridges [32].

6.3 ICH Q8 / Q9 / Q10 / Q12 Application to 3D-Printed Polypills

These ICH Q8, Q9, Q10, and Q12 guidelines provide the foundational framework for applying Quality by Design values to 3D-printed polypills, enabling robust control of multi-drug printing processes. ICH Q8: Development: ICH Q8 encourages QbD by defining design space for critical print parameters such as extrusion temperature, nozzle speed, layer height, and infill density. For polypills, this involves multi-material compatibility studies and DoE to link CMAs/CPPs to drug release uniformity across multiple APIs in the formulation. ICH Q9: Risk Management: Quality risk management uses tools like FMEA or FMECA to analyse failures in multi-drug AM, such as cross-contamination between inks, print bed adhesion issues, or dimensional variability [33]. ICH Q10: Quality System: ICH Q10 establishes a PQS for lifecycle oversight of digital print files, including CAD/STL version control, change management, and knowledge management from print runs. ICH Q12: Post-Approval Changes: ICH Q12 manages print parameter adjustments via established conditions (ECs) and PACMPs, classifying changes (e.g., nozzle diameter tweaks) by risk for prior approval, notification, or post-implementation notification [34].

6.4 Gaps in Current Regulatory Frameworks

No harmonised international standard exists for national regulations (e.g., FDA, EMA), which largely treat 3D-printed dosage forms under the same general rules as conventional solid-dose products. Digital file security and prescription-to-print data integrity: The transition from e-prescription to a 3D-print file introduces new data-integrity risks. Regulatory obligation for certifying end-to-end integrity of digital files from prescriber to pharmacy, hospital printer is not clearly well-defined, raising questions about who is accountable for audit trails, electronic signatures, and secure file transfer. Scales-Up and Manufacturing Considerations [35].

7. From Bench to Clinical/Commercial Production

Traditional high-speed tablet presses achieve 100,000- 240,000 tablets per hour per head, in contrast to pharmaceutical 3D printers, which manage just 100-500 units per hour per head and reveal a significant throughput shortfall. To close this throughput gap, several reviews from 2022-2024 suggest farm-based or multi-printer 3D printing approaches, which offer a viable route for clinical trials, small-scale production, or on-demand decentralized manufacturing [36]. The infill percentage in FDM printed tablets tightly modulates weight, strength, porosity, and print duration, with low infill cuts time and material use but risks weakening mechanical properties and drug elution. Trade-offs in layer height and print speed are equally stark; diminutive layers and modest speeds deliver refined resolution and texture but inflate time, whereas larger heights and quicker rates shorten cycles but degrade dimensional accuracy and aesthetics [37, 38].

7.1 Process Analytical Technology (PAT) Integration

Process Analytical Technology (PAT) enhances quality control in 3D printed polypill manufacturing by enabling real-time monitoring of critical quality attributes like drug content, layer uniformity, and structural integrity [39]. Inline NIR Spectroscopy: near-infrared (NIR) spectroscopy delivers non-destructive, real-time analysis of drug content during filament extrusion in (FDM). Low-cost, compact NIR reviews integrated into the extruder die monitor active pharmaceutical ingredient (API). Raman Spectroscopy: Raman spectroscopy plots a drug distribution layer-by-layer without destroying the printed structure, using univariate or multivariate analysis to detect API uniformity in tablets and controlled-release devices [40, 41].

7.2 Cost-Benefit Analysis

Capital Expenditure (CAPEX): Pharmaceutical-3D grade printers are equipped with PAT tackles and cleanroom compatibility, ranging from USD 50,000 for entry-level FDM/SLA systems to over USD 500,000 for high-precision multi-material systems certified with GMP standards. These cost covers extruder, controlled environment, and software for dose customization. Operating Expenditure (OPEX): OPEX remains in small batches (e.g., €1.58–3.11 per tablet for sustained-release formulations), driven by cheap filaments (~USD 50–200/kg) and minimal waste versus large-scale tableting tooling and validation costs [42-44]. Break-Even Analysis: 3D printing costs turn competitive at batch sizes below 10,000 units, where per-unit costs drop below USD 0.20–0.50 compared to conventional manufacturing's USD 0.05–0.10 for mass production [45].

8. Current Challenges

8.1 Physicochemical Challenges

In FDM and other 3D printing methods, the key physicochemical barriers that affect drug stability and

effectiveness are drug polymer thermal incompatibility, moisture uptake issues in ambient printing, and interface reactions in layered designs. FDM's thermal incompatibility develops from poor drug polymer miscibility at extrusion temperatures above 150°C, breaking down status for causing API recrystallization [46]. The intense heat from hot melt extrusion (HME) and printing destabilizes thermolabile statins, leading to instability and unpredictable release [47]. Low-Tg polymers like PLA or plasticizers help, but always test miscibility with DSC upfront.

8.2 Formulation Challenges

Developing advanced multi-drug delivery systems remains challenging due to difficulties in achieving Spatial separation of drug release, accommodating high-dose compounds such as metformin, and ensuring the stability of amorphous forms [48]. The challenge of achieving spatially separated and concurrent multi-drug release profiles due to nanotechnology constraints, driving the need for sophisticated ratiometric and sequential release mechanisms to enhance spatiotemporal targeting of cancer cells. However, ensuring long-term stability of amorphous drugs in solid dispersions throughout their shelf life is challenging, as factors such as humidity, temperature fluctuations, and physical stress may lead to recrystallization [49]. Emerging research focuses on polymeric systems and proper storage conditions for preserving supersaturation and long-term bioavailability [50].

8.3 Clinical & Patient Acceptance Challenges

3D-printed polypills need to pass clinical and patient acceptance, such as unfamiliar looks, size-related, and swallowability issues, though studies show talent to pass them out. Non-Standard Appearance: Patients repeatedly prefer aware tablet shapes and colours over novel 3D-printed designs, which can erase trust in the technology [51]. The study of polypharmacy patients found heart or in almond shape, which is most suitable for taking and managing, Visual appeal, recognizability, and perceived reliability deeply influence uptake, with customizable designs boosting obedience if trust builds. Swallowability Issues: Polypills combine multiple drugs, so they increase in size, which can create complications for dysphagia patients, though pediatric trials report show high success rates [52]. In a possibility study of 30 children aged 4-12, 87% swallowed FDM 3D-printed tablets (6-10 mm), with 80% rating swallowability acceptable; smaller 6 mm sizes scored 100% success against 67% for 10 mm [53].

9.Future Perspectives

9.1 AI and Machine Learning in Formulation Design

ML models predicting drug release profiles: Machine-learning mock-ups (e.g., random forest, gradient boosting, neural networks) can forecast broad in-vitro dissolution or release profiles from formulation signifiers such as excipient type, API attentiveness, polymer grade, and even process variables [54]. These models are qualified on dynamic dissolution data to also forecast the full release profile at multiple time points for estimating kinetic parameters, effectively swapping much of the trial-and-error showing in controlled-release and polymeric systems. Generative AI for polypill geometry optimization: Generative AI and analysis situs optimization-founded outlines can routinely design polypill geometries and inner excipient deliveries to match needed pharmacokinetic (PK) profiles [55-57]. These tactics characterize each pill as a 3-D sphere where neuronal networks or understood functions encrypt material distribution, while fixed diffusion and phase-field calculations oversee dissolution [58].

9.2 Nanotechnology Integration

Nanotechnology integration tries 3D-printed polypills into high-performance, “nano-engineered” dosage forms that can increase bioavailability, control release, and respond to complex biological environments [59]. Nanoparticle-embedded nanocrystals, lipid nanoparticles, or polymeric nanocarriers can be incorporated or in a suitable form within 3D-printed polymer mediums, creating hybrid “nano-particles” that significantly increase surface area and dissolution amount of poorly soluble drugs [60]. SEDDS incorporated into 3D-printed compartments: Solid self-emulsifying drug delivery systems (SEDDS or SNEDDS) can be captured into definite 3D-printed sections converting liquid-built SEDDS into personalized solid oral forms. Electrospun nanofiber layers as rate-controlling membranes: Electrospun nanofiber films can be combined as a thin, porous coating or inter-compartmental barrier with printed polypills, behaving like rate-controlling films that modify diffusion and release [61].

9.3 Integration with Digital Therapeutics and Precision Nutrition

Integration with digital therapeutics and precision nutrition forms an adaptive, data-driven polypill ecosystem for

chronic diseases like metabolic syndrome. Closed-Loop Systems: Closed-loop stands for continuous glucose monitors (CGM) to 3D printers for on-demand polypill changes, permitting dose jerks based on glycemic trends [62]. AI algorithms capture CGM data to modify fixed-dose combinations with flexible release shapes. Precision Nutrition Data: Microbiome and metabolomics reporting guide polypill preparation by expecting separate responses to multi-drug effects. Deep learning replicas like McMLP predict metabolite moves from gut data, informing drug selection and ratios [63].

10. Conclusion

Managing a condition like metabolic syndrome is hard enough without having to swallow a handful of pills every single day. That is exactly the problem 3D-printed polypills are trying to solve — combining multiple medications into one carefully designed tablet, where each drug does its job at the right time and in the right amount. It sounds simple, but the science behind it is anything but. One of the more important things this review makes clear is that choosing a printing method is not a minor technical detail — it actually determines whether the whole thing works. FDM is accessible and widely available, but it is not always the most precise. SLA and DLP do better on that front. If a drug breaks down under heat, semisolid extrusion becomes the only real option. Inkjet and binder jetting shine when a fast release is needed. In short, the drug's needs come first, and the technology has to follow. The equipment is still expensive. And the question of who controls a patient's genetic data and how safely it is stored — is one that nobody has fully answered yet. Still, there is a real reason to be optimistic. AI tools are already helping researchers design better formulations in less time, reducing a process that used to take years of trial and error. 3D-printed polypills ultimately represent is a different way of thinking about medicine altogether. Not one formula for millions of people, but a tailored treatment for one person at a time. That vision will not become reality through science alone — it needs regulators to get on the same page, healthcare systems to invest, and policymakers to actually prioritize it. The foundation is solid. What happens next depends on whether everyone involved is willing to move together.

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Conflict of interest

No Conflict of interest was declared by the authors.

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