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A REVIEW ON PREFORMULATION STUDIES AND FORMULATION OF 3D PRINTED POLYPILL

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ABSTRACT

Three-dimensional (3D) printing is becoming an important technology in modern pharmaceutical manufacturing because it allows the creation of customized medicines whenever needed. A major innovation from this technology is the polypill, a single tablet that carries several drugs with different and adjustable release patterns. Such dosage forms are especially helpful for patients who take many medicines daily, such as those with long-term conditions like hypertension, diabetes, cardiovascular disorders, or age-related diseases.

To successfully produce a 3D-printed polypill, detailed preformulation studies are essential. These investigations include examining the physical and chemical properties of the drugs, checking the compatibility of drug–excipient combinations, assessing thermal stability, and evaluating flow and rheological characteristics. These parameters ensure that the material can be printed properly and that the drugs remain stable throughout the process.

This review outlines the key preformulation requirements and formulation approaches used in polypill development through various 3D-printing techniques such as fused deposition modeling (FDM), selective laser sintering (SLS), inkjet printing, and stereolithography (SLA). It also highlights the advantages and drawbacks of each method, regulatory considerations for 3D-printed medicines, and future research opportunities in this fast-growing field.

KEYWORDS

Fused deposition modelling (FDM); selective laser sintering (SLS); inkjet printing; stereolithography (SLA); controlled drug release; multi-drug dosage form; pharmaceutical innovation.

INTRODUCTION

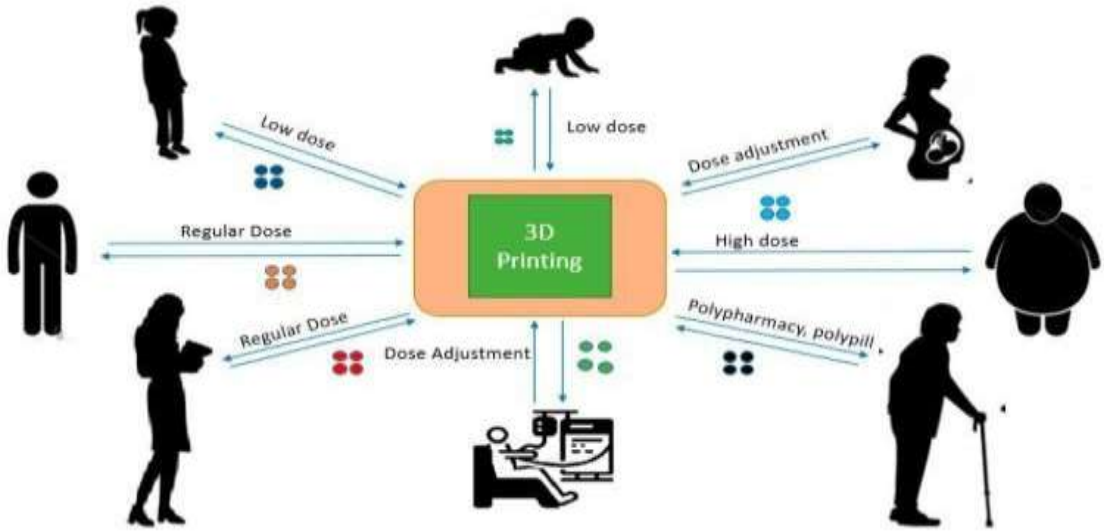

Fig. no. 1: Fabrication of Polypills

Polypharmacy is frequently observed in patients managing chronic conditions such as hypertension, diabetes, cardiovascular disorders, and age-related illnesses. Taking several medications each day often lowers patient adherence and increases the chances of missed or incorrect doses. The concept of a polypill, which incorporates multiple active drugs into one oral dosage form, offers an effective way to reduce pill burden, simplify therapy, and improve overall treatment outcomes.

Before developing such combination products—especially those produced through 3D printing-preformulation studies play a crucial role. These investigations evaluate the physicochemical, thermal, and mechanical characteristics of active pharmaceutical ingredients (APIs). In 3D-printed polypills, preformulation becomes even more important because several drugs are embedded within a single printed structure that undergoes heating, melting, laser exposure, or deposition during manufacturing. Without adequate preformulation work, problems such as drug degradation, incompatibility between components, non-uniform dosing, printing defects, or unstable release profiles may occur. Hence, preformulation data informs the choice of excipients, polymers, printing parameters, processing temperatures, and desired drug release patterns. [1]

As a manufacturing approach, 3D printing offers several advantages: it uses compact equipment, involves fewer processing steps, and allows rapid, on-demand production tailored to individual patients. Interest in pharmaceutical 3D printing grew substantially after the first FDA-approved 3D-printed drug, Spritam® (levetiracetam), developed by Aprecia Pharmaceuticals using a modified fused deposition modelling (FDM)-based technology. Since then, research has expanded rapidly, highlighting the potential of 3D printing to create innovative dosage forms—including flexible, patient-specific polypills. [2]

LITERATURE REVIEW

1. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ study used extrusionbased 3D printing to create a single tablet containing five different drugs arranged into compartments with two distinct release behaviours (immediate and sustained). The authors demonstrated that spatial separation inside one printlet can achieve independent release for each drug and that design (geometry/compartmentalisation) is a powerful tool to tune release. It's a practical proof-of-concept showing how preformulation (drug thermal/chemical stability and choice of printable excipient) and CAD design together determine whether a multi-drug printlet will succeed. [3]

2. Goyanes A., Wang J., Buanz A., Martínez-Pacheco R., Telford R., Gaisford S., Basit A.W. describes making drug-loaded PVA filaments for FDM printing and shows how filament composition and tablet geometry affect mechanical properties and dissolution. It provides stepwise details on filament preparation, printing parameters and postprinting testing. It links preformulation variables (polymer

choice, plasticiser level, drug load) to filament printability and the final tablet's content uniformity and release essential when planning hot-melt/extrusion routes. [4]

3. Robles-Martínez P., Xu X., Trenfield SJ., Awad A., Goyanes A., Telford R., Basit AW., Gaisford S. developed an SLA approach that can print multi-layered tablets containing six different actives, used Raman mapping to verify spatial distribution, and reported how resin choice influences drug release and mechanical integrity. Why it matters: Shows SLA is a viable route for polypills when heat sensitivity is a concern but photostability and resin-API compatibility become critical preformulation checkpoints. [5]

4. Trenfield SJ., Awad A., Goyanes A., Gaisford S., Basit AW. discusses the state of 3D printing in pharma, compares printing modalities (FDM, SSE, SLA, inkjet) and analyses regulatory, scale-up and clinical translation challenges. It offers a broad framework you can use to justify the study's need and to discuss regulatory considerations and method choice in your report. [6]

5. Wang S., et al. reported that multi-technology review comparing mechanisms, material needs, and the pros/cons for each printing approach; includes up-to-date practical guidance on preformulation testing (thermal screening, rheology, flow).
Why it matters: Use this as a modern reference for method selection and for detailed preformulation tests (e.g., DSC/TGA, rheology) you should include before printing. [7] 6. Azad MA., et al. examines polymer families used in FDM and direct extrusion, highlights how polymer molecular weight, melting point and viscosity affect filament formation and printability, and stresses the importance of rheological characterization. Important for preformulation decisions - polymer selection controls processing window (HME/FDM) and eventual release; the review also lists common plasticisers and testing workflows. [8]

7. Xu X., et al. present SLA printing of oral dose forms and multi-layer tablets; they point out advantages for heat-labile APIs and show how photopolymer chemistry, curing dose, and layer adhesion alter release and mechanical properties. Highlights preformulation tasks unique to SLA: photostability, API-photopolymer compatibility, and residual monomer testing - all vital for selection of printing route when APIs degrade with heat. [9]

8. Aguilar-de-Leyva Á. et al. focused on Direct Powder Extrusion (DPE)/Direct Powder Printing approaches, summarising formulation strategies, flowability, and solid-state issues encountered in DPE works and giving practical recommendations. DPE avoids HME for heat-sensitive APIs but requires excellent powder flow and specific excipient choices. Preformulation must therefore emphasise particle size distribution, bulk/tapped density and flow testing. [10]

9. Bácskay I., et al. traces technological advances and classifies studies by printing technique and dosage form; it summarizes mechanical testing, dissolution strategies and early clinical/translational examples. Good source for your literature review to show the evolutionary timeline and to justify why preformulation studies (thermal, solid-state, compatibility, mechanical testing) have become routine in 3D-printing
research. [11]

10. Crișan AG., et al. investigates how PVA particle/filament properties (particle size, polymer grade) affect extrusion residence time and drug release; it demonstrates that small changes in carrier properties can alter drug release and printability. Reinforces that preformulation must include careful polymer characterization (grade, Mw, particle size) because these affect HME processability and content uniformity in printed tablets.[12]

11. Yasin H., et al., creating multi-compartment printlets loaded with self-Nano emulsified drug formulations and demonstrating improved dissolution for poorly soluble drugs. The study discusses formulation tactics (lipid-based systems) to overcome solubility limitations in printlets. It shows a way to address poorly soluble APIs in polypills a preformulation strategy where you create drug-loaded Nano emulsions or SEDDS that are then incorporated into printable matrices. [13]

12. Henry S., et al., explores how material properties, extrusion settings and printer hardware interact; the paper compiles best practices for rheology testing, screw speeds, nozzle diameters and post-processing that affect final tablet quality. Practical checklist for your plan of work it helps translate preformulation data (e.g., melt viscosity, yield stress) into concrete printing parameters and troubleshooting
steps.[14]

1. Fused Deposition Modeling (FDM)

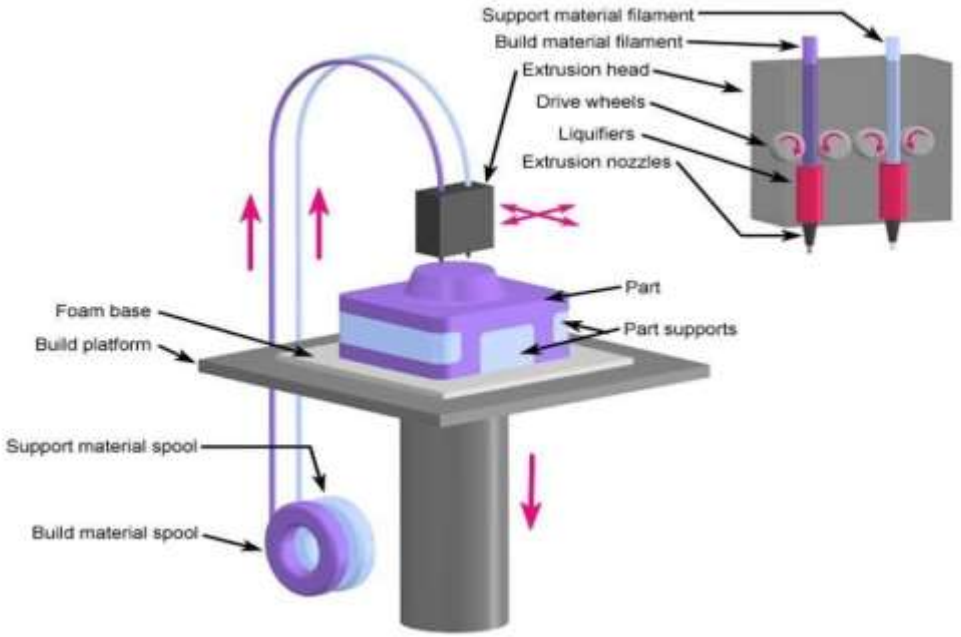

Fig. no. 2: Fused Deposition Modelling

Fused Deposition Modeling is currently one of the most commonly used 3D-printing techniques for preparing oral solid dosage forms. In this method, drug-loaded thermoplastic polymers are processed into filaments, which are then heated and extruded through a nozzle to build the dosage form layer by layer. Before printing begins, a digital model of the dosage form must be generated. This design can be created using computer-aided design (CAD) software or obtained from imaging techniques such as MRI or CT scans. The model is saved in the standard STL file format, which is interpreted by the printing software. The software then converts the design into thin, printable layers by applying slicing parameters and manufacturing settings. Once these parameters are finalized, the printer constructs the object sequentially, depositing one layer after another until the final structure is formed.
Commonly used polymers for FDM in pharmaceuticals include:

- Polylactic Acid (PLA)
- Polyvinyl Alcohol (PVA)
- Polyvinylpyrrolidone (PVP)
- Hydroxypropyl Methylcellulose (HPMC)

Advantages of FDM:

- Cost-effective technique.
- Allows easy dose customization and design flexibility.
- Suitable for producing sustained-release and modified-release formulations.

Limitations:

- Not ideal for drugs sensitive to heat, as processing involves high temperatures •

Choice of acceptable pharmaceutical-grade polymers is still limited. [15]

2. **Selective Laser Sintering (SLS)**

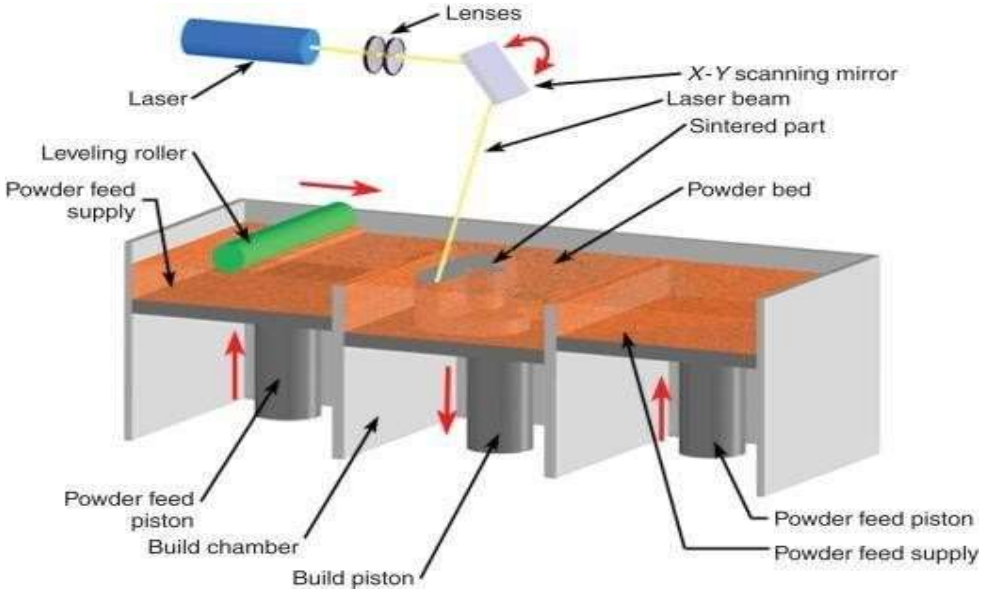

Fig. no. 3: Selective Laser Sintering

Selective Laser Sintering is a 3D-printing technique in which a focused laser beam fuses powder particles together to form solid dosage forms. This method does not require solvents or additional binding agents, making it suitable for moisture-sensitive and solvent-incompatible drugs. The process enables the production of tablets with controllable porosity, which can be adjusted to achieve rapid disintegration and immediate-release profiles.

SLS also supports the incorporation of multiple active ingredients within a single powder blend, allowing simultaneous printing of combination products. Although highly precise, the technique is relatively costly and may produce structures that are somewhat opaque or abrasive due to the nature of sintered powders. [16]

Inkjet Printing / Binder Jetting

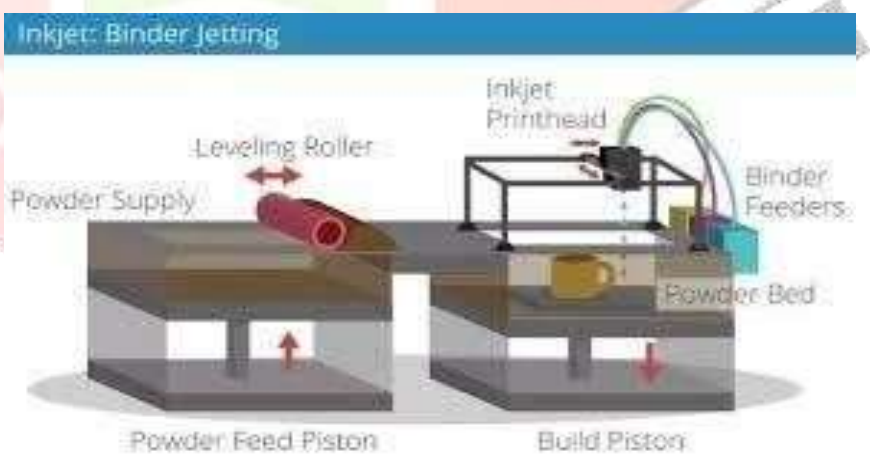

Fig. no. 4: Inkjet Printing / Binder Jetting

In inkjet or binder-jet 3D printing, a liquid binding solution is selectively deposited onto layers of powder, causing the particles to adhere and build the final structure. Since the method operates at low temperatures, it is particularly useful for heatsensitive APIs that cannot undergo thermal processing.

This technology supports the creation of multi-layered constructs and complex dosage geometries, making it suitable for polypills and personalized-release systems. Inkjet printing gained major recognition with the development of Spritam® (levetiracetam), the first FDA-approved 3D-printed drug, manufactured using a variation of this approach. [17]

3. **Stereolithography (SLA)**

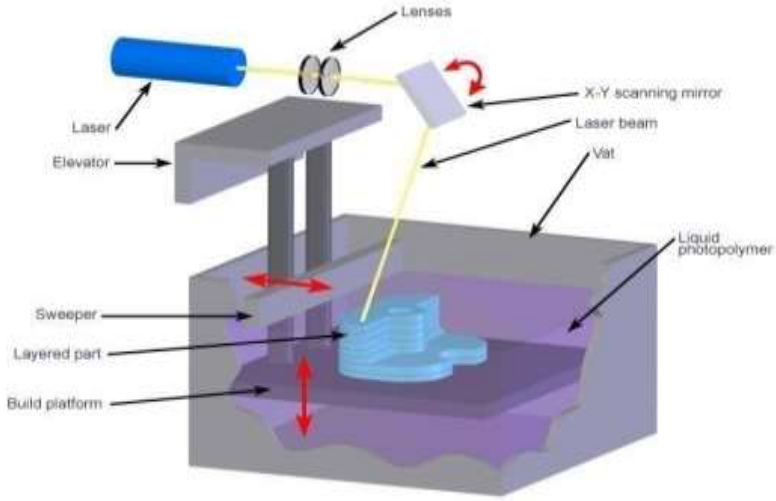

Fig. no. 5: Stereolithography

Stereolithography relies on photopolymerization, where a UV laser or light source cures and solidifies a photosensitive resin layer by layer. SLA offers high-dimensional accuracy, smooth surface finishes, and the ability to fabricate internal structures that support modified or programmed drug release.
This method is particularly useful for creating dosage forms with complex internal channels, delayed-release profiles, or intricate designs. However, its main drawback is the limited availability of biocompatible and orally safe photopolymers, which restricts the range of pharmaceutical applications. [18]

IMPORTANCE OF PREFORMULATION IN 3D-PRINTED POLYPILLS

Preformulation plays a central role in the development of 3D-printed polypills because it determines whether the selected drugs and excipients can withstand the printing process and still deliver consistent quality. Since a single polypill may contain several active ingredients - each with its own solubility behaviour, melting point, and degradation pattern - comprehensive preformulation studies are essential to ensure stability, printability, and predictable drug release.

1. Physicochemical Characterization

1.1 Solubility and pH–Solubility Profile

Understanding drug solubility across different pH values helps predict how the drug will dissolve in the gastrointestinal tract.

- Drugs with poor solubility may need conversion into an amorphous state or require solubilizing agents.
- Drugs with pH-dependent solubility can be strategically placed within pH-responsive polymer layers to control release at specific GI regions.

1.2 Partition Coefficient (Log P / Log D)

Log P and Log D values describe the lipophilicity and permeability of a drug.

- These parameters guide the choice of polymers for immediate-release or sustained release segments.
- Highly lipophilic drugs may benefit from matrix systems that slow diffusion, whereas hydrophilic drugs may require faster-eroding polymers.

1.3 p Ka and Ionization Behavior

The ionization state of a drug changes with pH and directly affects solubility, permeability, and chemical stability.

- Knowledge of pKa supports decisions regarding salt formation, enteric coating, or pH-dependent release mechanisms.

1.4 Polymorphism and Crystallinity

Drugs can exist in different crystalline forms, each with unique stability and solubility characteristics.

- Crystalline forms offer better long-term stability but typically dissolve slowly.
- Amorphous forms dissolve faster but may revert to a crystalline state during storage or during the printing process.

2. Thermal Analysis

Many 3D-printing techniques especially FDM and SLS expose materials to elevated temperatures. Therefore, assessing thermal behavior is vital.
Differential Scanning Calorimetry (DSC): Identifies melting point, glass transition temperature (Tg), and crystalline-to-amorphous transitions.

Thermogravimetric Analysis (TGA): Indicates the temperature at which the drug begins to degrade.

Hot-stage microscopy: Provides direct visual observation of melting, deformation, or degradation during heating.

If thermal studies show that a drug degrades at typical FDM or SLS temperatures, lower-temperature techniques-such as inkjet printing or semi-solid extrusion—or alternative polymer systems must be used.

3. Drug-Excipient Compatibility

In a polypill, all drugs and excipients coexist in a single structure, making compatibility evaluation essential.
Techniques such as FTIR, DSC, HPLC, and XRD help detect interactions, chemical instability, or degradation products.

If incompatibility is detected between specific APIs (e.g., aspirin and ranitidine), physical separation within the polypill-such as barrier layers or isolated compartments be required.

4. Rheology and Printability

For 3D-printing methods using semi-solid materials or inks, rheological properties determine whether a formulation can be printed accurately.
Formulations should show shear-thinning behaviour, meaning viscosity decreases under pressure, enabling smooth extrusion.

Poor rheology may cause nozzle clogging, inconsistent dosing, or defects in the final structure.

5. Solid-State Characterization

The printing process can alter the physical state of a drug-especially when heat is involved.
X-ray diffraction (XRD): Confirms whether the drug remains crystalline or becomes amorphous after printing.

Scanning Electron Microscopy (SEM): Visualizes the printed layers, surface texture, and porosity.

Dissolution testing: Ensures that the release profile remains consistent with the intended therapeutic design. [19]

FORMULATION STRATEGIES FOR POLYPILLS

1. Single-Layer Polypills

In this approach, all active ingredients are uniformly dispersed within a single polymeric matrix.
Works best when the incorporated drugs have similar physicochemical and stability profiles.

This method is simple to design and print, but it provides only minimal control over the independent release behavior of each drug.

Therefore, it is suitable mainly for combination therapies where simultaneous drug release is acceptable.

2. Multi-Layer Polypills

Multi-layer designs divide the dosage form into distinct segments, with each layer containing a specific drug or tailored release kinetics.

- For example, an upper layer may provide immediate release, while middle or lower layers deliver sustained or controlled release.
- This structure helps maintain separation between incompatible drugs and allows the design of sequential or time-dependent drug release.
- It is particularly useful for combinations requiring staged absorption.

3.Compartmentalized or Modular Polypills

These systems incorporate separate compartments within a single dosage form, offering a high degree of customization. Designs may include:

- Mini-tablets embedded within a larger tablet
- Capsules enclosed inside another tablet
- Reservoir-type structures containing multiple internal chambers

Such modular layouts are ideal for drugs that differ significantly in solubility, pH sensitivity, or chemical stability, enabling strict separation while delivering personalized release behavior.

4.Immediate, Sustained, and Pulsatile Release Systems Immediate Release:

- Achieved through highly porous structures such as those produced by SLS
- Can also use disintegrate-rich matrices to promote rapid drug release

Sustained Release:

- Uses hydrophilic swelling polymers like HPMC and PVA
- May include enteric or pH-dependent coatings such as Eudragit to prolong drug release

Pulsatile/Delayed Release:

- Designed to release the drug after a programmed lag time
- Beneficial for chronotherapy applications, such as managing early-morning surges in hypertension or asthma symptoms.

5. Role of Tablet Geometry in Drug Release

A major advantage of 3D printing is the ability to fabricate non-conventional geometries, including:

- Ring-shaped tablets
- Honeycomb and lattice structures
- Gyroid or porous architectures

These shapes increase the surface area-to-volume ratio, which can significantly enhance dissolution rate and allow fine control over drug release patterns. Geometry can therefore be used as a deliberate design tool to optimize therapeutic performance. [20]

QUALITY CONTROL AND EVALUATION OF 3D-PRINTED POLYPILLS

Quality evaluation of 3D-printed polypills requires a blend of traditional pharmacopeial testing and modern analytical techniques. Because additive manufacturing builds dosage forms layer by layer and often uses multiple materials or heat/light exposure, specialized tools are needed to verify uniformity, stability, and structural precision.

Key Quality Attributes (CQAs)

- Accurate assay and content uniformity for each incorporated drug
- Individual dissolution and release profiles
- Mechanical strength, including hardness and friability
- Microstructural characteristics and porosity
- Spatial distribution of APIs within the printed structure
- Solid-state stability, including polymorphism and degradation behavior.

Essential Quality Control Tests

- Assay & uniformity: HPLC or LC–MS methods
- Dissolution tests: USP apparatus using drug-specific protocols
- Mechanical strength: hardness, friability, and tensile testing
- Microstructure: X-ray micro-CT to visualize internal architecture
- Chemical mapping: Raman or NIR imaging to confirm API distribution
- Solid-state analysis: DSC, TGA, and XRD
- Residual solvent/photopolymer safety: GC and extractables analysis.

Non-Destructive & In-Process Monitoring (PAT Tools)

- NIR and Raman spectroscopy: rapid, real-time confirmation of drug loading
- Micro-CT: assessment of structural integrity and porosity
- Machine-vision tools: detection of dimensional errors and layer defects

These techniques support real-time release testing and enable more frequent quality checks during production.

QbD-Oriented Control Strategy

A structured Quality-by-Design workflow includes:

1. Identifying critical quality attributes.
2. Performing risk assessment.
3. Optimizing critical process parameters (e.g., nozzle temperature, layer height, infill density).
4. Validating PAT-based monitoring models.

5. Establishing acceptance limits.

6. Implementing continuous, data-driven process control. [21]

ADVANTAGES AND DISADVANTAGES OF 3D-PRINTED POLYPILLS

Advantages Of 3d-Printed Polypills

1. Customized dosing: Additive manufacturing enables precise control over drug quantity, tablet geometry, and release behaviour, allowing fully individualized therapy for chronic and multi-drug conditions.
2. Lower pill burden: Several active ingredients can be delivered in a single unit, improving convenience and boosting adherence, especially in elderly and polypharmacy patients.

Tailored release patterns: Different zones of the polypill can be engineered for immediate, sustained, delayed, or pulsatile release within the same dosage form.

3. Complex architectures: 3D printing supports intricate internal designs—lattices, gyroids, multilayer chambers, reservoirs that cannot be achieved using conventional manufacturing.

On-demand production: Units can be fabricated quickly at hospitals or pharmacies, reducing dependence on large-scale manufacturing, warehousing, and distribution chains.

4. Safe separation of incompatible APIs: Physically isolated compartments prevent chemical interaction between unstable or reactive drugs while still providing combination therapy.

Enhanced dissolution: High-surface-area structures and controlled porosity can improve the dissolution of drugs with poor solubility.

5.Efficient material usage: Additive processes minimize raw material wastage compared to compression or subtractive methods. [22]

Disadvantages Of 3d-Printed Polypills

1. Limited pharmaceutical-grade materials:

Only a small range of polymers, resins, and binders are approved and suitable for printing oral medicines.

2. Risk of drug degradation:

Heat (FDM/SLS) and light (SLA) used during printing may degrade thermolabile or photosensitive APIs.

3. Regulatory uncertainty:

Clear standards for batch consistency, QC testing, printer validation, and long-term stability are still evolving.

4. High cost:

Advanced printers, calibration tools, and maintenance increase the operational cost compared to conventional manufacturing.

5. Slower throughput:

Layer-by-layer fabrication is ideal for small batches but much slower than industrial tablet presses for mass production.

CHALLENGES AND LIMITATIONS OF 3D-PRINTED POLYPILLS

Although 3D printing offers a transformative path toward personalized combination therapy, several scientific, technical, and regulatory hurdles still limit its widespread adoption.

1. Material Constraints

- Only a limited range of pharmaceutically acceptable polymers, binders, and photopolymers are currently approved for oral use.
- Many 3D printing methods require materials with specific thermal, photochemical, or flow properties that are not compatible with all active pharmaceutical ingredients.

- Ensuring safety of new printable excipients requires extensive toxicological evaluation. [24]

2. API Stability Issues

- Heat-based processes (FDM, SLS) may degrade thermolabile drugs.
- Light-dependent techniques (SLA) risk photodegradation and generation of impurities.
- Moisture sensitivity during printing or storage may affect drug crystallinity and stability.

3. Complexity of Multi-Drug Compatibility

- Formulating multiple APIs in one dosage form requires careful control of interactions, pH incompatibilities, and cross-diffusion between layers/compartments.
- Achieving uniform distribution of each API within complex geometries is challenging. [25]

4. Process Variability and Reproducibility

- Layer-by-layer fabrication introduces inherent variability in porosity, density, and drug release pathways.
- Minor changes in printing temperature, layer thickness, or feed rate may alter critical quality attributes (CQAs).
- Reproducibility across different printers or batches remains a major barrier.

5. Mechanical Strength and Handling

- Printed structures may be more fragile than conventionally compressed tablets.
- Brittle or porous prints can break during packaging, transport, or patient handling.
- Designing robust yet modifiable geometries requires additional optimization. [26]

6. Limited Production Speed and Scale-Up Issues

- Most 3D printing platforms have slow printing times, unsuitable for mass manufacturing.
- Scaling from personalized single units to industrial batch production requires major technological upgrades.
- High equipment and material costs make routine use economically challenging.

7. Regulatory and Quality Assurance Barriers

- Regulatory pathways for multi-API, customized, on-demand printed medicines are still evolving.
- Lack of harmonized standards complicates global approval.

8. Need for Advanced Analytical and PAT Tools

- Real-time monitoring of multi-material prints requires sophisticated tools such as Raman mapping, NIR spectroscopy, and micro-CT.
- These instruments add high cost and require skilled personnel.
- In-process control models (QbD/PAT) for complex geometries are still under development.

9. Patient-Specific Data and Cybersecurity Considerations

- Personalized therapy depends on digital designs generated from patient data (dose, pharmacogenomics, clinical history).
- Protecting these digital files from tampering or unauthorized access is essential.

10. Storage, Stability, and Packaging Challenges

• Printed polypills with high porosity or novel shapes may have poor moisture resistance.

• Layer interfaces may weaken over time, affecting dissolution and mechanical integrity. • Packaging systems must be adapted to protect fragile designs. [27]

REGULATORY AND INDUSTRIAL PERSPECTIVE

The integration of 3D printing into pharmaceutical manufacturing offers significant opportunities for personalized therapy, but it also introduces new regulatory, economic, and operational challenges. As a result, both regulators and industry stakeholders are cautiously advancing toward standardized frameworks.

1. Evolving Regulatory Frameworks

• Regulatory bodies such as the FDA, EMA, and MHRA are still developing specific guidelines for 3D-printed oral dosage forms.

• Existing regulations focus primarily on traditional batch manufacturing, making their application to patient-specific, on-demand printing difficult.

• Issues requiring regulatory clarity include:

- Approval pathways for multi-API, customized tablets

- Validation of digital design files

- Acceptable ranges for layer thickness, geometry, and porosity

- Stability requirements for printed units

• Spritam®, the first FDA-approved 3D-printed drug, serves as a reference point, but guidelines for polypills with multiple APIs are still lacking. [28]

2. Quality Assurance and GMP Adaptation

• Additive manufacturing requires redefinition of Good Manufacturing Practices (GMP) to include:

- Control of printers as critical equipment

- Software verification and cybersecurity

- In-process controls for dimensional accuracy and API distribution

• The industry must adopt Quality by Design (QbD) and Process Analytical Technology (PAT) frameworks to maintain consistent quality across diverse geometries and materials. [29]

3. Challenges in Validation and Documentation

• Validating highly customizable dosage forms is more complex than validating uniform batches.

• Each patient-specific design may require:

- Separate risk assessment

- Verification of drug release profile

- Documentation of design parameters (CAD files, G-code, material lot numbers). [30]

4. Economic and Industrial Feasibility

• Current 3D printers for pharmaceuticals are expensive and have low throughput, limiting large-scale commercialization.

• Material costs are high compared with traditional tableting methods.

• Industries must justify:

- Cost–benefit for personalized medicine

- Scalability of decentralized or point-of-care printing units

- Workforce training for digital manufacturing skills. [31]

5. Decentralized Manufacturing and Point-of-Care Models

• The future may involve hospital-based or pharmacy-based 3D printing units, enabling personalized dosing.

• However, this raises regulatory questions regarding:

- Who is responsible for product quality—manufacturer, pharmacist, or printer system?

- How to maintain GMP-level control in non-industrial settings

- Standardization of printing software and materials across facilities. [32]

6. Data Integrity and Cybersecurity

• Digital designs and printer instructions (G-code) represent a new category of "digital drug product" information.

• Risks include:

- Unauthorized modification of dose or structure

- Hacking of design files

- Loss of patient-specific data

• Regulatory agencies emphasize the need for secure digital workflow systems and validated software.[33]

7. Lack of Global Harmonization

• Different countries are progressing at different speeds in drafting guidelines.

• Without harmonized standards:

- Global distribution of printed dosage forms is difficult

- Manufacturers face inconsistent requirements for validation and approval

•International regulatory collaboration is needed for future adoption. [34]

FUTURE SCOPE OF 3D-PRINTED POLYPILLS

The field of 3D-printed polypills is still emerging, but rapid advancements in materials science, digital design, and pharmaceutical engineering indicate significant future potential. Key future directions include:

1. Personalized and Precision Medicine

3D printing will enable on-demand fabrication of polypills tailored to an individual's:

- Age, weight, and pharmacokinetic profile
- Genetic markers influencing drug metabolism
- Disease progression or multi-drug requirements This approach could transform therapy for chronic diseases such as hypertension, diabetes, epilepsy, and cancer. [35]

2. Point-of-Care Manufacturing

Hospitals, clinics, and community pharmacies may eventually install compact 3D printing units to produce patient-specific polypills on-site.

- Reduce dependency on large-scale manufacturing
- Allow same-day dispensing
- Enable rapid dose adjustments for pediatric, geriatric, and critical-care patients. [36]

3. Development of New Printable Materials. Future research will focus on:

- Advanced biopolymers with tailored degradation rates
- Smart polymers responsive to pH, enzymes, or temperature
- Safer photopolymers for SLA and improved powder blends for SLS

These innovations will expand the types of drugs that can be incorporated and enhance release modulation. [37]

4. Multi-API Spatial Programming

New software tools and high-resolution printers will allow:

- Precise positioning of each drug within micro-compartments
- Integration of contrasting release mechanisms (immediate + sustained + delayed) in same pill
- Layer-wise digital verification of API placement

This will significantly improve dose accuracy and reproducibility. [38]

5. Integration of Digital Health Technologies Future polypills may incorporate:

- Embedded sensors for adherence monitoring
- Microchips providing controlled pulsatile release
- QR-coded drug signatures linked to patient electronic records

Such innovations could support real-time therapy tracking and intervention.

6. Expansion to Biologics and Heat-Sensitive APIs

Modified printing technologies (semi-solid extrusion, inkjet, cold extrusion) are expected to support:

- Peptides and proteins
- Vaccines
- Probiotics
- RNA-based therapeutics

This will broaden the range of conditions treatable with 3D-printed polypills. [39]

7. AI-Driven Design and Predictive Modelling. Artificial intelligence can optimize:

- Tablet geometry
- Internal architecture
- Polymer selection
- Release kinetics

Machine learning models will also predict drug–excipient compatibility and reduce formulation development time.

8. Sustainable and Cost-Efficient Manufacturing

Future improvements may decrease material waste and energy consumption, making 3D printing more economical for large-scale use.
Recyclable or bio-based polymers will support eco-friendly production.

9. Strengthened Regulatory Framework

As the technology matures, regulators like FDA and EMA will:

- Establish standardized guidelines for digital design files.
- Define quality metrics for layer-wise printing.
- Allow decentralized manufacturing under validated workflows.

This will speed up clinical adoption and industrial implementation. [40]

CONCLUSION

3D printing has emerged as a transformative technology in pharmaceutical manufacturing, offering unprecedented flexibility in designing personalized and multidrug dosage forms. Polypills produced through additive manufacturing can integrate multiple APIs, customized release profiles, and complex geometries within a single tablet—addressing long-standing challenges associated with polypharmacy, patient adherence, and fixed-dose limitations of traditional formulations.
Preformulation studies remain the foundation of successful 3D-printed polypill development, ensuring drug stability, compatibility, and printability. Advances in FDM, SLS, SLA, and binder jetting continue to expand the range of drugs and polymers suitable for printing, while quality control approaches such as micro-CT, PAT tools, and solid-state analysis ensure product consistency and regulatory compliance. Despite challenges related to material limitations, temperature sensitivity, regulatory uncertainty, and scale-up feasibility, ongoing research in smart polymers, AI-driven formulation design, and point-of-care manufacturing is rapidly overcoming these barriers.
Overall, 3D-printed polypills represent a promising step toward personalized, efficient, and patient-centric therapy. As the technology matures, it has the potential to revolutionize drug delivery, enhance treatment outcomes, and contribute to the future of precision medicine.

REFERENCES

1. Hull, C. W. (1986). Apparatus for production of three-dimensional objects by stereolithography (U.S. Patent No. 4,575,330). U.S. Patent and Trademark Office.
2. Martinez, R., Patel, S., Kumar, V., & Wong, S. Y. (2023). Floating 3D printed polypill formulation for the coadministration and sustained release of antihypertensive drugs. International Journal of Pharmaceutics, 655, 12-34.
3. Khaled, S. A., Burley, J. C., Alexander, M. R., Yang, J., & Roberts, C. J. (2015). 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. Journal of Controlled Release, 217, 308–314.
4. Goyanes, A., Wang, J., Buanz, A., Martínez-Pacheco, R., Telford, R., Gaisford, S., & Basit, A. W. (2015). 3D printing of medicines: Engineering novel oral devices with unique design and drug release characteristics. Molecular Pharmaceutics, 12(11), 4077–4084.
5. Robles-Martínez, P., Xu, X., Trenfield, S. J., Awad, A., Goyanes, A., Telford, R., Basit, A. W., & Gaisford, S. (2019). 3D printing of a multi-layered polypill containing six drugs using a novel stereolithographic method. Pharmaceutics, 11, Article 274.
6. Trenfield, S. J., Awad, A., Goyanes, A., Gaisford, S., & Basit, A. W. (2018). 3D printing pharmaceuticals: Drug development to frontline care. Drug Discovery Today, 23(8), 1547–1555.
7. Wang, S., et al. (2023). A review of 3D printing technology in pharmaceutics. Pharmaceutics, 15(2), 416.
8. Azad, M. A., et al. (2023). Polymers for extrusion-based 3D printing of pharmaceuticals.
9. Xu, X., et al. (2019–2020). Stereolithography (SLA) 3D printing of oral dosage forms / polyprintlets.
10. Aguilar-de-Leyva, Á., et al. (2024). 3D printing by direct powder extrusion in drug delivery system production: A systematic review.
11. Bácskay, I., et al. (2022). The evolution of 3D-printed drug delivery systems. [Journal], PMC.
12. Crișan, A. G., et al. (2021). Polyvinyl alcohol-based 3D printed tablets: Novel insight. Pharmaceutics, 14(5), 418.
13. Yasin, H., et al. (2024). Fabrication of polypill pharmaceutical dosage forms loaded with self-nanoemulsified formulations. Pharmaceutics, 16, 1285.
14. Henry, S., et al. (2021). Extrusion-based 3D printing of oral solid dosage forms. International Journal of Pharmaceutics.
15. International Organization for Standardization. (2015). ISO/ASTM 52900:2015—Standard terminology for additive manufacturing – General principles – Terminology.
16. Goh, J. L., Toh, Y. C., & Ng, W. Y. (2020). Fused deposition modeling in pharmaceutical dosage form manufacturing: Advantages and challenges. International Journal of Polymeric Materials and Polymeric Biomaterials, 69(4), 234–248.
17. Scoutaris, N., Alexander, M. R., Gellert, P. R., & Roberts, C. J. (2011). Inkjet printing as a novel medicine formulation technique: The potential to print directly onto medical devices. Journal of Pharmaceutical and Biomedical Analysis, 55(4), 626–633.
18. Douroumis, D. (2012). Hot-melt extrusion: Innovative application in drug delivery and beyond. Woodhead Publishing.
19. Maheshwari, A., Cheung, H. S., Chugh, H., Egorov, A. A., Mateti, S., Desai, N., et al. (2018). 3D printed pharmaceutical tablets by binder jetting technology: Effects of formulation parameters on tablet properties. Pharmaceutical Research, 35(7), 130.
20. Kempin, W., Haffner, N., Grawe, J., Bogdahn, M., Weitschies, W., & Semmling, B. (2018). Immediate release 3D-printed tablets prepared by fused deposition modeling of a thermo-sensitive drug. Pharmaceutical Research, 35(8), 124.
21. Ligon, S. C., Liska, R., Stampfl, J., Gurr, M., & Mülhaupt, R. (2017). Polymers for 3D printing and customized additive manufacturing. Chemical Reviews, 117(15), 10212–10290.
22. Norman, J., Madurawe, R. D., Moore, C. M., Khan, M. A., & Khairuzzaman, A. (2017). A new chapter in pharmaceutical manufacturing: 3D-printed drug products. Advanced Drug Delivery Reviews, 108, 39–50.
23. Desai, D. S., Ewing, G. J., Puri, V., & Dinh, Q. N. (2019). Assessment of mechanical properties and drug release characteristics of 3D-printed polypills.
    Journal of Pharmaceutical Sciences, 108(2), 789–798.
24. Pereira, G. G., Ryckaert, A., Grymonpré, W., Chalus, P., Laure, P., Leclercq, L., et al. (2019). Formulation development methodology for 3D-printed oral dosage forms with modified release. European Journal of Pharmaceutical Sciences, 130, 234–243.

25. Alomari, M., Vuddanda, P. R., Trenfield, S. N., Parsonage, D., Murdan, S., & Basit, A. W. (2016). Selective laser sintering 3D printing of anhydrous and hydrated calcium carbonate-containing formulations for the oral delivery of indomethacin. International Journal of Pharmaceutics, 503(1–2), 91–99.
26. Berman, B., & Marshall, D. (2012). 3-D printing: The new industrial revolution. Business Horizons, 55(2), 155–162.
27. Gupta, V. K., Khurana, J., & Sharma, H. (2021). Preformulation studies for optimization of 3D printing parameters in pharmaceutical formulation development. Journal of Applied Pharmaceutical Research, 9(4), 45–58.
28. Okwuosa, T. C., Soares, C., Goyanes, A., Nair, G., Stefanidis, D., Khorsandi, D., et al. (2018). 3D printing enables individualization of polypharmaceutical dosage forms: An investigation into the fabrication of polypills using fused deposition modeling. Journal of Pharmaceutical Sciences, 107(1), 290–295.
29. Muwaffak, Z., Goyanes, A., Clark, V., Basit, A. W., Hilton, S. T., & Gaisford, S. (2017). Patient-specific 3D scanned and 3D printed medication carriers with high drug loading. International Journal of Pharmaceutics, 528(1–2), 268–279. 30. Goyanes, A., Alleso, M., Soares, C., Nair, G. K., Miri, A. J., Tapia, A. S., et al. (2015). Fabrication of polymeric-based reconfigurable composite materials by 3D printing. International Journal of Pharmaceutics, 494(2), 657–663.
31. Mota, C., Puppi, D., Chiellini, F., & Chiellini, E. (2015). Additive manufacturing techniques for the production of tissue engineering constructs. Journal of Tissue Engineering and Regenerative Medicine, 9(3), 174–190.
32. Ding, Z., Khorsandi, D., du Toit, L. C., Gonzalez, R., Du Plessis, A., Tapia Martinez, M. C., et al. (2018). 3D printed pharmaceutical systems: Design considerations and practical solutions. Advanced Therapeutic Applications of Polymeric Nanomedicines, 35, 89–103.
33. Ashour, E. A., El-Kamel, A. H., Abd-Allah, F. I., & Ahmed, M. A. (2018). Preformulation studies and development of an improved dosage form. Journal of Pharmaceutical and Biomedical Analysis, 152, 155–165.
34. Khorsandi, D., Fahimipour, F., Abasian, P., Sideris, A., Tapia Martinez, M. C., Vashaee, D., et al. (2017). 3D bioprinting of a nucleus pulposus-mimetic intervertebral disc to provide long-term chemoprotection and mechanical support. Advanced Healthcare Materials, 6(10), 1601514.
35. Solanki, N. G., Tahsin, M., Senadheera, B., Shan, W., & Liao, I. C. (2018). Formulation of 3D-printed orodispersible films for preclinical pharmacokinetic studies. Journal of Controlled Release, 288, 68–78.
36. Goyanes, A., Scarpa, M., Kamble, H., Krampa, A., Nair, G., & Lim, S. H., et al. (2017). Patient-facing 3D printing of sacubitril/valsartan polypill. International Journal of Pharmaceutics, 544(2), 184–192.
37. Alomari, M., Sandler, N., & Preis, M. (2015). Perspectives on 3D printing for drug delivery. Current Pharmaceutical Design, 21(22), 3149–3165.
38. United States Pharmacopeial Convention. (2024). USP <905> Uniformity of Dosage Units,2123-2234.
39. United States Pharmacopeial Convention. (2024). USP <1216> Tablet Friability and USP <701> Disintegration,144-164.
40. International Conference on Harmonisation. (2000). ICH Q6A: Specifications— Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products,170-182.