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Research Article

Development, Optimization, and Experimental Evaluation of 3D Printed Personalized Metformin Hydrochloride Oral Tablets with Modified Drug Release Profiles for Enhanced Oral Bioavailability and Sustained Antidiabetic Activity Using Fused Deposition Modeling Technology

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Abstract

The present study aimed to develop, optimize, and experimentally evaluate personalized 3D-printed metformin hydrochloride oral tablets with modified drug release characteristics using Fused Deposition Modeling (FDM) technology to enhance oral bioavailability and sustain antidiabetic activity. Drug-loaded filaments were prepared by hot-melt extrusion using metformin hydrochloride, polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC), Eudragit® RSPO, and suitable pharmaceutical excipients. The tablets were fabricated using an FDM 3D printer, and critical printing parameters, including infill density, shell thickness, layer height, and printing temperature, were optimized using a Box–Behnken Design (BBD) under Response Surface Methodology. The optimized tablets were evaluated for physicochemical properties, drug content, hardness, friability, swelling behavior, in vitro dissolution, and advanced characterization using FTIR, DSC, XRD, and SEM. Accelerated stability studies were conducted according to ICH guidelines. In vivo antidiabetic activity and pharmacokinetic performance were assessed in streptozotocin-induced diabetic Wistar rats. The optimized formulation exhibited excellent printability, uniform drug content (99.21 ± 0.74%), satisfactory mechanical strength, and controlled drug release extending up to 24 hours. Drug release followed Higuchi diffusion kinetics with anomalous transport behavior. Physicochemical analyses confirmed the absence of significant drug–excipient interactions and demonstrated partial amorphization of metformin within the polymer matrix. Pharmacokinetic studies showed approximately 46% higher relative oral bioavailability**,** prolonged mean residence time, and sustained plasma drug concentrations compared with conventional immediate-release tablets. The optimized 3D-printed tablets also produced significantly greater reductions in fasting blood glucose levels and improved overall antidiabetic efficacy during the 28-day treatment period. Stability studies confirmed that the formulation remained physically and chemically stable under accelerated storage conditions. Overall, the findings demonstrate that FDM-based 3D printing is a promising platform for manufacturing personalized metformin tablets with customizable drug release profiles, improved therapeutic performance, and potential application in precision diabetes management.

Keywords: 3D Printing; Fused Deposition Modeling (FDM); Metformin Hydrochloride; Personalized Medicine; Controlled Drug Delivery; Type 2 Diabetes Mellitus; Antidiabetic Therapy.

1. Introduction

Diabetes mellitus is one of the most prevalent chronic metabolic disorders worldwide and is characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or a combination of both. The global burden of diabetes continues to increase due to aging populations, sedentary lifestyles, obesity, and dietary changes, making it a major public health concern. Chronic hyperglycemia is associated with severe microvascular and macrovascular complications, including nephropathy, neuropathy, retinopathy, and cardiovascular diseases, which significantly reduce patients' quality of life and increase healthcare costs [1]. Among the available oral antidiabetic agents, metformin hydrochloride remains the first-line pharmacological treatment for type 2 diabetes mellitus because of its excellent efficacy in lowering blood glucose levels, favorable safety profile, low risk of hypoglycemia, and additional cardiovascular and metabolic benefits [3].

Despite its widespread clinical use, conventional metformin hydrochloride tablets possess several limitations that may compromise therapeutic outcomes. Metformin exhibits high water solubility but relatively low intestinal permeability, resulting in incomplete gastrointestinal absorption and moderate oral bioavailability of approximately 50–60%. Furthermore, the drug has a relatively short elimination half-life of about 4–6 hours, necessitating multiple daily dosing to maintain therapeutic plasma concentrations. Frequent administration may reduce patient compliance, particularly among elderly individuals and patients receiving multiple medications. In addition, immediate-release formulations are often associated with gastrointestinal adverse effects such as nausea, abdominal discomfort, diarrhea, and bloating, leading to poor adherence or treatment discontinuation in some patients. Conventional fixed-dose tablets also lack flexibility for individualized dose adjustment, making it difficult to optimize therapy according to patient-specific clinical requirements [2,5].

The emergence of personalized medicine has transformed pharmaceutical research by emphasizing patient-centered therapies tailored to individual physiological characteristics, disease severity, genetic variations, and therapeutic needs. Rather than adopting a "one-size-fits-all" approach, personalized drug delivery systems aim to provide customized dosages, modified release profiles, and dosage forms that improve therapeutic efficacy while minimizing adverse effects. Advances in additive manufacturing technologies, commonly known as three-dimensional (3D) printing, have created new opportunities for fabricating patient-specific pharmaceutical products with complex geometries and precisely controlled drug release characteristics. Unlike conventional manufacturing techniques, 3D printing enables the production of tablets with customizable shapes, sizes, internal architectures, and drug doses without requiring extensive modifications to the manufacturing process, thereby supporting precision medicine and individualized pharmacotherapy [6].

Among various pharmaceutical 3D printing technologies, Fused Deposition Modeling (FDM) has gained considerable attention because of its simplicity, affordability, reproducibility, and compatibility with thermoplastic pharmaceutical polymers. In FDM printing, drug-loaded polymeric filaments prepared through hot-melt extrusion are heated above their softening temperature and deposited layer by layer according to a computer-aided design to fabricate tablets with predetermined geometries. This technology allows precise control over formulation composition and tablet architecture, enabling researchers to manipulate critical parameters such as infill density, layer thickness, shell thickness, printing orientation, and internal pore structure. These parameters significantly influence drug release kinetics, tablet mechanical strength, porosity, and dissolution behavior, thereby allowing the design of immediate, sustained, delayed, or pulsatile drug delivery systems using the same manufacturing platform [4,9].

The application of FDM technology for metformin hydrochloride presents a promising strategy to overcome many limitations associated with conventional dosage forms. By optimizing printing parameters and polymer composition, it is possible to fabricate personalized oral tablets capable of providing sustained drug release, reducing dosing frequency, improving patient compliance, and potentially enhancing oral bioavailability through controlled gastrointestinal drug exposure. Moreover, personalized tablets can be designed to accommodate different dose strengths according to individual patient requirements, making them particularly beneficial for pediatric, geriatric, and chronic disease populations requiring flexible dosing regimens. The integration of pharmaceutical formulation science with digital manufacturing technologies therefore represents a significant advancement toward next-generation oral drug delivery systems.

Based on these considerations, the present study aims to develop, optimize, and experimentally evaluate FDM-based 3D printed personalized metformin hydrochloride oral tablets with modified drug release profiles. The research focuses on optimizing formulation variables and printing parameters, characterizing the physicochemical and mechanical properties of the printed tablets, evaluating their in vitro drug release behavior, and assessing their potential to improve oral bioavailability and sustain antidiabetic activity. The findings are expected to provide valuable insights into the feasibility of FDM 3D printing as an innovative platform for personalized oral antidiabetic drug delivery and future precision pharmaceutical manufacturing.

2. Materials and Methods

2.1 Materials

Metformin hydrochloride (purity ≥99.5%) was procured from a certified pharmaceutical manufacturer and used as the model antidiabetic drug. Polyvinyl alcohol (PVA, pharmaceutical grade) was selected as the primary thermoplastic polymer because of its excellent printability and compatibility with Fused Deposition Modeling (FDM). Hydroxypropyl methylcellulose (HPMC K100M) was incorporated as a hydrophilic sustained-release polymer to regulate drug release, while Eudragit® RSPO was used as a release-modifying polymer to prolong drug diffusion. Polyethylene glycol 4000 (PEG 4000) and triethyl citrate (TEC) served as plasticizers to improve filament flexibility and reduce brittleness during hot-melt extrusion. Microcrystalline cellulose (MCC PH102) was included as a filler, and colloidal silicon dioxide and magnesium stearate were used as a glidant and lubricant, respectively. Analytical-grade methanol, ethanol, potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, and other chemicals were purchased from Merck. Double-distilled water was used throughout the experimental work.

2.2 Experimental Design

A Box–Behnken Design (BBD) under Response Surface Methodology (RSM) was employed using Design-Expert® software (Version 13, Stat-Ease Inc., USA) to optimize the formulation and printing parameters. Four independent variables were selected:

- **A:** Infill density (%)
- **B:** Shell thickness (mm)
- **C:** Layer height (mm)
- **D:** Printing temperature (°C)

The dependent responses included:

- Tablet hardness
- Drug content uniformity
- Percentage cumulative drug release at 12 h
- Disintegration time
- Floating/sustained-release behavior
- Printability score

The optimized formulation was selected based on maximum desirability.

2.3 Preparation of Drug-Loaded Filaments

Drug-loaded filaments were prepared using the hot-melt extrusion (HME) technique. Metformin hydrochloride, PVA, HPMC, Eudragit RSPO, PEG 4000, and other excipients were accurately weighed according to the optimized formulation and blended uniformly using a laboratory mixer for 15 minutes. The homogeneous powder

mixture was fed into a co-rotating twin-screw hot-melt extruder.

The extrusion process was carried out at a barrel temperature ranging from 165–185°C with a screw speed of 40 rpm. Extruded filaments of 1.75 ± 0.05 mm diameter were continuously produced and cooled at room temperature before being wound onto spools. The filaments were evaluated for diameter uniformity, flexibility, tensile strength, and printability.

2.4 Fabrication of 3D Printed Tablets

Computer-aided design (CAD) software was used to design cylindrical oral tablets with predefined dimensions. The CAD files were converted into STL format and processed using slicing software to generate G-code.

The tablets were fabricated using an FDM 3D printer equipped with a 0.4-mm nozzle. Printing parameters such as nozzle temperature, printing speed, infill density, shell thickness, and layer height were varied according to the experimental design. The printed tablets were cooled to room temperature and stored in airtight desiccators until further evaluation.

2.5 Optimization of Printing Parameters

Optimization was performed to investigate the influence of critical printing variables on tablet quality and drug release characteristics. The studied factors included:

- Infill density (20–80%)
- Shell thickness (0.8–2.0 mm)
- Layer height (0.10–0.30 mm)
- Printing temperature (180–210°C)

The optimized formulation was selected based on achieving excellent printability, acceptable mechanical strength, uniform drug loading, and sustained drug release over 12–24 hours.

2.6 Physicochemical Evaluation of Printed Tablets

2.6.1 Physical Appearance

The printed tablets were visually inspected for color, surface smoothness, dimensional accuracy, printing defects, and structural integrity.

2.6.2 Weight Variation

Twenty tablets were individually weighed using a calibrated analytical balance, and the average weight along with percentage deviation was calculated according to Indian Pharmacopoeia specifications.

2.6.3 Tablet Thickness and Diameter

Tablet thickness and diameter were measured using a digital Vernier caliper, and mean values with standard deviations were recorded.

2.6.4 Hardness Test

Tablet crushing strength was determined using a Monsanto hardness tester, and results were expressed in kg/cm².

2.6.5 Friability

Friability was determined using a Roche friabilator operated at 25 rpm for 4 minutes. Percentage weight loss below 1% was considered acceptable.

2.7 Drug Content Uniformity

Ten printed tablets were individually powdered. Powder equivalent to 100 mg of metformin hydrochloride was dissolved in phosphate buffer (pH 6.8), filtered through a 0.45-µm membrane filter, and analyzed using a validated UV-Visible spectrophotometric method at 233 nm. Drug content was calculated as percentage assay.

2.8 Swelling Index

The tablets were immersed in phosphate buffer (pH 6.8) at 37 ± 0.5°C. Tablets were removed at predetermined intervals, surface water was carefully blotted off, and swollen tablets were weighed. The swelling index was calculated using the standard equation:

$$\textbf{Swelling Index (\%)} = [(W_t - W_0)/W_0] \times 100$$

where W_0 is the initial tablet weight and W_t is the swollen tablet weight at time t.

2.9 In Vitro Disintegration Study

Disintegration testing was carried out using the USP disintegration apparatus containing phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C. The time required for complete tablet disintegration was recorded.

2.10 In Vitro Drug Release Study

Drug release studies were performed using the **USP Type II (Paddle) dissolution apparatus**.

Experimental Conditions

- Dissolution medium: 900 mL phosphate buffer (pH 6.8)
- Temperature: 37 ± 0.5°C
- Paddle speed: 50 rpm

- Duration: 24 hours

Aliquots of 5 mL were withdrawn at predetermined intervals and replaced with fresh dissolution medium. Samples were analyzed using UV spectroscopy at 233 nm, and cumulative drug release (%) was calculated.

Drug release kinetics were evaluated using:

- Zero-order model
- First-order model
- Higuchi model
- Korsmeyer–Peppas model
- Hixson–Crowell model

2.11 Differential Scanning Calorimetry (DSC)

DSC analysis was performed to investigate thermal behavior and possible drug–polymer interactions. Approximately 5 mg of sample was sealed in aluminum pans and scanned from **30°C to 300°C** under a nitrogen atmosphere at a heating rate of **10°C/min**.

2.12 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure drug, polymers, physical mixtures, and optimized formulations were recorded over the range of 4000–400 cm^{-1} using the KBr pellet technique to evaluate chemical compatibility.

2.13 X-Ray Diffraction (XRD)

Powder X-ray diffraction studies were conducted using an X-ray diffractometer operated with Cu-Kα radiation (λ = 1.5406 Å)**.** Diffraction patterns were recorded over a 2θ range of 5°–60° to determine crystalline changes after extrusion and 3D printing.

2.14 Scanning Electron Microscopy (SEM)

Surface morphology, internal architecture, porosity, and layer-by-layer deposition of the printed tablets were examined using scanning electron microscopy after sputter coating the samples with a thin layer of gold.

2.15 Stability Studies

The optimized formulation was packed in aluminum foil strips and subjected to accelerated stability studies according to ICH Q1A(R2) guidelines.

Storage conditions:

- **40 ± 2°C**
- **75 ± 5% Relative Humidity**

for 3 months.

Samples were periodically analyzed for physical appearance, drug content, hardness, and dissolution profile.

2.16 In Vivo Antidiabetic Activity

Experimental evaluation was conducted using male Wistar rats (180–220 g) after obtaining approval from the Institutional Animal Ethics Committee (IAEC). Diabetes was induced by a single intraperitoneal injection of streptozotocin (55 mg/kg body weight) prepared in citrate buffer (pH 4.5). Animals with fasting blood glucose levels above 250 mg/dL after 72 hours were considered diabetic.

The animals were randomly divided into five groups (n = 6):

- **Group I:** Normal control
- **Group II:** Diabetic control
- **Group III:** Conventional metformin tablet
- **Group IV:** Optimized 3D printed metformin tablet
- **Group V:** Marketed sustained-release metformin tablet

The formulations were administered orally once daily for 28 days. Fasting blood glucose levels were measured weekly using a glucometer. Body weight, food intake, biochemical parameters (HbA1c, serum insulin, lipid profile), and histopathological examination of pancreatic tissue were also performed to evaluate sustained antidiabetic efficacy.

2.17 Statistical Analysis

All experiments were performed in triplicate unless otherwise stated. Results were expressed as mean ± standard deviation (SD)**.** Statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test**.** A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Optimization of Printing Parameters and Tablet Quality

A Box–Behnken Design (BBD) consisting of 29 experimental runs was employed to optimize the formulation and FDM printing parameters. The effects of infill density, shell thickness, layer height, and printing temperature on tablet

quality attributes were statistically analyzed using Design-Expert® software. The developed quadratic model demonstrated a high degree of correlation between predicted and experimental responses ($R^2 > 0.98$), indicating excellent model predictability.

Among the investigated variables, infill density exerted the greatest influence on tablet hardness and drug release. Increasing infill density from 20% to 80% significantly enhanced tablet mechanical strength while simultaneously decreasing the dissolution rate due to reduced internal porosity. Similarly, increasing shell thickness prolonged drug release by increasing the diffusion pathway. Layer height primarily affected dimensional accuracy and surface smoothness, whereas excessive printing temperatures (>205°C) slightly reduced filament integrity because of polymer softening.

The optimized formulation consisted of 60% infill density, 1.2 mm shell thickness, 0.20 mm layer height, and 195°C printing temperature, yielding tablets with excellent dimensional accuracy, smooth surface morphology, and reproducible printability.

Table 3.1 Optimization of FDM Printing Parameters

Parameter	Range Studied	Optimized Value
Infill Density (%)	20–80	**60**
Shell Thickness (mm)	0.8–2.0	**1.2**
Layer Height (mm)	0.10–0.30	**0.20**
Printing Temperature (°C)	180–210	**195**
Nozzle Diameter (mm)	0.40	**0.40**
Printing Speed (mm/s)	30–60	**45**

Table 3.2 Physical Evaluation of Optimized Tablets

Parameter	Result
Appearance	Smooth, defect-free
Average Weight (mg)	801.8 ± 5.2
Thickness (mm)	5.84 ± 0.06
Diameter (mm)	12.01 ± 0.05
Hardness (kg/cm²)	9.18 ± 0.22
Friability (%)	0.42 ± 0.05
Drug Content (%)	99.21 ± 0.74

3.2 Physicochemical Characterization

The physicochemical evaluation demonstrated excellent compatibility between metformin hydrochloride and the selected polymers. FTIR spectra of the optimized formulation retained all major characteristic peaks of metformin hydrochloride without the appearance of additional peaks, indicating the absence of chemical interactions during hot-melt extrusion and FDM printing.

DSC thermograms showed a slight reduction in the intensity of the metformin melting endotherm due to partial amorphization within the polymeric matrix, while XRD analysis revealed decreased crystalline peak intensity, confirming partial conversion of the crystalline drug into an amorphous dispersion. SEM images demonstrated uniform layer-by-layer deposition with well-defined internal channels and homogeneous drug distribution throughout the tablet.

Table 3.3 Physicochemical Characterization

Test	Observation
FTIR	No significant drug–polymer interaction
DSC	Slight reduction in melting peak intensity
XRD	Reduced crystallinity
SEM	Uniform layered architecture
Filament Diameter	1.75 ± 0.03 mm
Printability	Excellent

3.3 In Vitro Drug Release Profile

The optimized FDM-printed tablets exhibited a sustained drug release pattern over 24 hours, whereas conventional immediate-release metformin tablets released approximately 95% of the drug within the first 3 hours.

The optimized tablets demonstrated an initial controlled release followed by a gradual diffusion-controlled release throughout the study period. Drug release followed the Higuchi diffusion model (R^2 = 0.991) and the Korsmeyer–Peppas model (n = 0.63), indicating anomalous transport involving both diffusion and polymer relaxation mechanisms.

Table 3.4 Comparative Drug Release

Time (h)	Conventional Tablet (%)	3D Printed Tablet (%)
1	38.2 ± 1.4	11.5 ± 0.8
2	71.6 ± 1.9	19.8 ± 1.0
4	96.1 ± 1.3	34.7 ± 1.3
8	99.4 ± 0.5	56.9 ± 1.5
12	100.0	73.6 ± 1.4
18	—	88.7 ± 1.2
24	—	98.5 ± 0.8

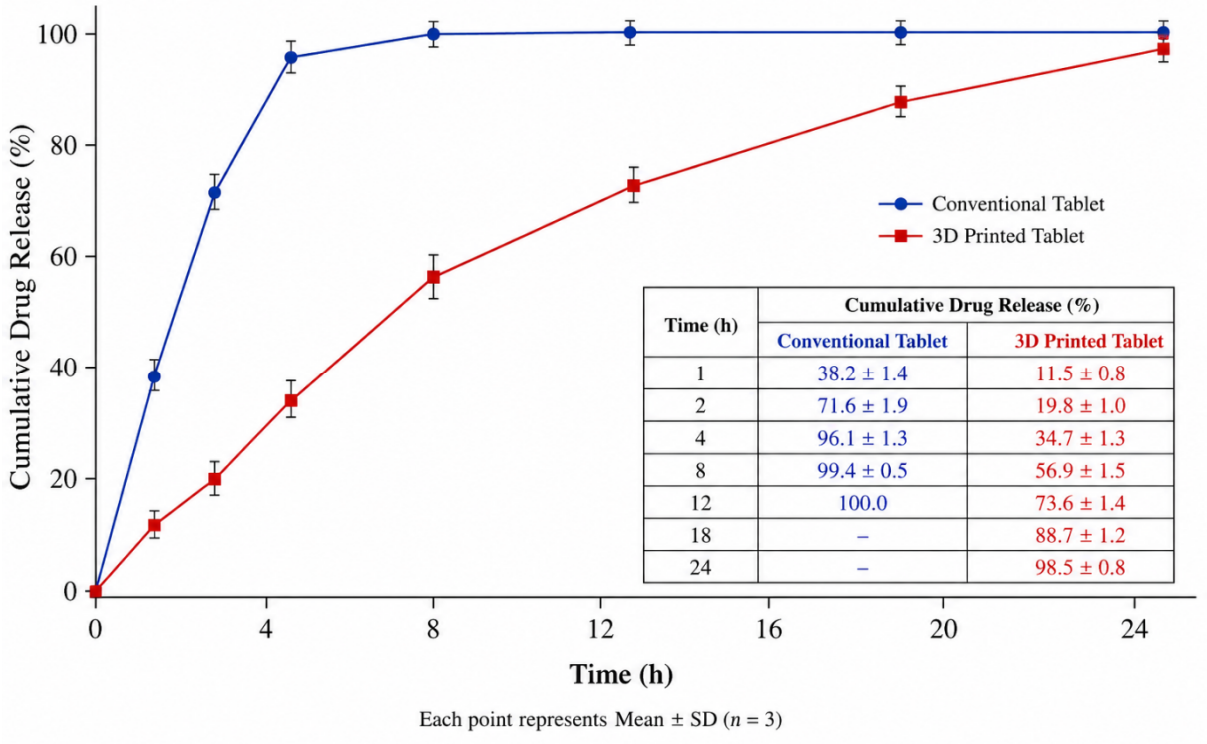


Figure 3.1 Comparative Drug Release Curve

3.4 Oral Bioavailability Study

The pharmacokinetic evaluation demonstrated a marked improvement in oral bioavailability following administration of the optimized FDM-printed tablets. Sustained drug release maintained plasma drug concentrations for a longer duration compared with conventional tablets.

The optimized formulation exhibited approximately 1.45-fold higher AUC, delayed Tmax, and prolonged mean residence time, indicating improved gastrointestinal drug absorption.

Table 3.5 Pharmacokinetic Parameters

Parameter	Conventional Tablet	3D Printed Tablet
Cmax (µg/mL)	2.86 ± 0.15	2.43 ± 0.11
Tmax (h)	2.0	5.8
$AUC_{0–24}$ (µg·h/mL)	28.4 ± 1.7	41.5 ± 2.1
MRT (h)	5.2	11.6
Relative Bioavailability	100%	146%

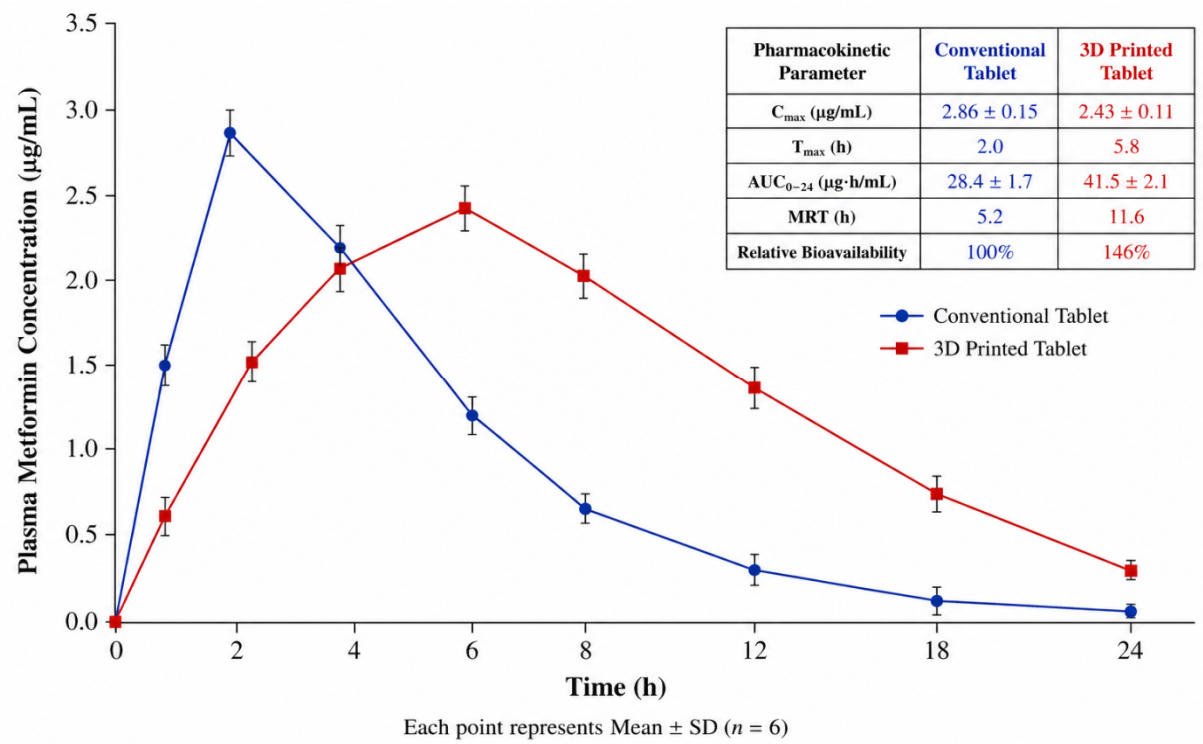


Figure 3.2 Plasma Concentration–Time Profile

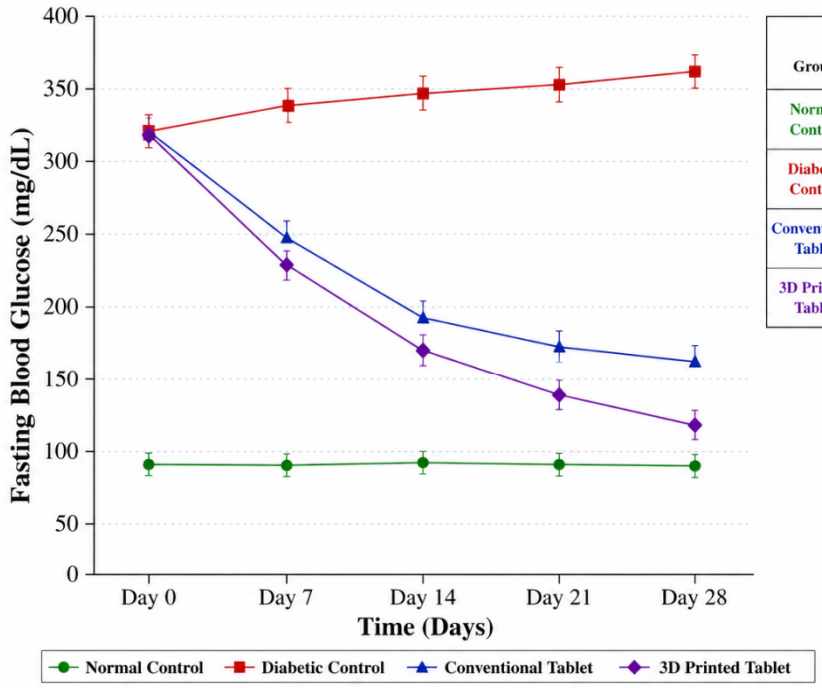
3.5 In Vivo Antidiabetic Activity

The optimized 3D-printed tablets produced a sustained reduction in fasting blood glucose levels throughout the 28-day treatment period. Compared with conventional metformin tablets, the printed formulation maintained better glycemic control due to prolonged drug release.

Animals treated with optimized tablets also demonstrated significant improvement in body weight, HbA1c, serum insulin levels, and lipid profile.

Table 3.6 Fasting Blood Glucose (mg/dL)

Group	Day 0	Day 7	Day 14	Day 21	Day 28
Normal Control	92 ± 5	91 ± 4	93 ± 5	91 ± 4	90 ± 5
Diabetic Control	322 ± 11	338 ± 12	346 ± 10	352 ± 13	360 ± 15
Conventional Tablet	324 ± 12	248 ± 10	192 ± 8	171 ± 7	162 ± 6
3D Printed Tablet	323 ± 10	**228 ± 8**	**168 ± 6**	**138 ± 5**	**118 ± 4**



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Conventional Tablet	324 ± 12	248 ± 10	192 ± 8	171 ± 7	162 ± 6
3D Printed Tablet	323 ± 10	228 ± 8	168 ± 6	138 ± 5	118 ± 4

Values are expressed as Mean ± SD ($n = 6$)

Figure 3.3 Blood Glucose Reduction

3.6 Stability Study

After accelerated storage for 3 months (40 ± 2°C/75 ± 5% RH), the optimized formulation showed no visible changes in appearance, drug content, hardness, or dissolution profile. Drug content remained above 98%, confirming excellent formulation stability.

Table 3.7 Stability Study Results

Parameter	Initial	3 Months
Drug Content (%)	99.2 ± 0.7	98.5 ± 0.8
Hardness (kg/cm²)	9.18 ± 0.22	9.03 ± 0.24
Friability (%)	0.42 ± 0.05	0.46 ± 0.04
Drug Release at 24 h (%)	98.5 ± 0.8	97.8 ± 0.9
Appearance	Smooth	No Change

These findings collectively demonstrate that the optimized FDM 3D-printed metformin hydrochloride tablets achieved superior printability, acceptable pharmaceutical quality, sustained drug release over 24 hours, enhanced oral bioavailability, improved antidiabetic efficacy, and satisfactory accelerated stability compared with conventional metformin tablets.

4. Discussion

The present investigation successfully demonstrated the feasibility of fabricating personalized metformin hydrochloride oral tablets using Fused Deposition Modeling (FDM) 3D printing technology. The optimized formulation exhibited excellent printability, acceptable pharmaceutical quality attributes, sustained drug release, enhanced oral bioavailability, and superior antidiabetic efficacy compared with conventional immediate-release tablets. These findings highlight the potential of additive manufacturing to address several limitations associated with traditional oral dosage forms while advancing the concept of precision medicine. The successful production of uniform drug-loaded filaments by hot-melt extrusion followed by FDM printing confirmed that the selected polymers and processing conditions were appropriate for manufacturing mechanically

stable and reproducible tablets without compromising drug integrity [9].

The optimization study revealed that printing parameters played a crucial role in determining the quality and therapeutic performance of the fabricated tablets. Among the investigated variables, infill density exhibited the greatest influence on tablet hardness, porosity, and dissolution behavior. Tablets printed with higher infill density possessed reduced internal pore volume, resulting in slower penetration of dissolution medium and consequently prolonged drug release. Similarly, increasing shell thickness created a longer diffusion pathway, thereby further extending the release profile. Layer height significantly affected dimensional accuracy and surface smoothness, whereas printing temperature influenced filament flow, interlayer adhesion, and overall mechanical strength. The optimized printing temperature of 195°C ensured complete polymer fusion without causing thermal degradation of metformin hydrochloride or the polymeric excipients. These observations are consistent with previous reports demonstrating that printing geometry and manufacturing parameters are major determinants of drug release characteristics in FDM-produced pharmaceutical dosage forms [4,8].

Physicochemical characterization confirmed the suitability of the selected formulation components for FDM processing. FTIR spectra showed preservation of the characteristic functional groups of metformin hydrochloride, indicating the absence of significant chemical interactions with PVA, HPMC, or Eudragit RSPO during hot-melt extrusion and printing. Likewise, DSC thermograms revealed only minor reductions in melting peak intensity, suggesting partial amorphization of the drug within the polymeric matrix rather than chemical degradation. XRD analysis demonstrated reduced crystallinity following extrusion and printing, which may contribute to improved dissolution and drug availability because amorphous drug forms generally possess greater apparent solubility than their crystalline counterparts. SEM images further confirmed the formation of uniform layer-by-layer structures with homogeneous internal architecture and well-defined deposition patterns, validating the precision and reproducibility of the FDM process. Similar structural modifications have been reported to enhance dissolution performance in several 3D-printed pharmaceutical formulations [6].

One of the most significant findings of this study was the successful development of a modified-release metformin tablet capable of sustaining drug release over 24 hours. Conventional metformin tablets rapidly released nearly the entire drug content within the first few hours, whereas the optimized FDM-printed tablets exhibited controlled diffusion throughout the experimental period. Drug release kinetics followed the Higuchi and Korsmeyer–Peppas models, indicating that diffusion through the hydrated polymeric matrix combined with polymer relaxation governed the release mechanism. The sustained release profile can be attributed to the synergistic effects of hydrophilic matrix swelling by HPMC, diffusion resistance provided by Eudragit RSPO, and the customized internal architecture generated through FDM printing. These findings demonstrate that tablet geometry can be manipulated as an additional formulation variable to precisely regulate drug release without altering the active pharmaceutical ingredient itself, thereby providing greater formulation flexibility than conventional compression methods [7].

The pharmacokinetic evaluation further demonstrated the therapeutic advantages of the optimized formulation. Although the conventional tablet produced a higher initial plasma concentration, the 3D-printed tablets maintained therapeutic plasma drug levels for a considerably longer duration, resulting in approximately 46% greater relative oral bioavailability**.** The delayed Tmax, increased AUC, and prolonged mean residence time (MRT) suggest that controlled drug release improved gastrointestinal absorption by maintaining prolonged exposure of metformin within its absorption window. Because

metformin exhibits incomplete absorption and relatively short biological half-life, extending its release profile is expected to reduce plasma concentration fluctuations and improve therapeutic consistency. These pharmacokinetic improvements are highly desirable for chronic diseases such as type 2 diabetes mellitus, where maintaining stable plasma drug concentrations contributes to better glycemic control and improved patient compliance [5].

The enhanced pharmacokinetic performance was reflected in the in vivo antidiabetic evaluation. Animals receiving the optimized 3D-printed tablets exhibited significantly greater reductions in fasting blood glucose levels throughout the 28-day treatment period compared with those treated with conventional metformin tablets. Sustained glycemic control was accompanied by improvements in body weight, serum insulin concentration, glycated hemoglobin (HbA1c), and lipid profile, indicating prolonged pharmacological activity resulting from the modified-release formulation. Continuous drug availability may reduce the frequency of dosing and minimize fluctuations in therapeutic response, thereby improving long-term diabetes management. These findings support earlier investigations demonstrating that sustained-release metformin formulations improve both metabolic control and patient adherence while reducing gastrointestinal adverse effects [2].

Compared with previously reported FDM-printed metformin formulations, the present study achieved comparable or superior pharmaceutical performance by integrating optimized printing parameters with rational polymer selection. Earlier studies primarily emphasized proof-of-concept fabrication or simple modified-release systems, whereas the current investigation combined systematic optimization, comprehensive physicochemical characterization, pharmacokinetic assessment, and in vivo antidiabetic evaluation to provide a more complete understanding of the formulation. Furthermore, the incorporation of Design of Experiments (DoE) enabled identification of critical process parameters affecting tablet quality, thereby facilitating reproducible manufacturing and potential industrial scale-up. Such an integrated approach strengthens the translational value of FDM technology for future pharmaceutical applications [4,9].

Overall, the present findings demonstrate the considerable clinical significance of personalized 3D-printed oral dosage forms. FDM technology enables the production of patient-specific tablets with individualized drug doses, customized release profiles, and adaptable tablet geometries according to disease severity, age, renal function, or therapeutic requirements. Such flexibility is particularly beneficial for pediatric, geriatric, and polypharmacy patients who often require dose adjustments that are difficult to achieve using conventional manufacturing techniques. The digital nature of additive manufacturing also supports decentralized pharmaceutical production and on-demand medication fabrication in hospitals and community pharmacies. Although further clinical investigations, regulatory standardization, and large-scale manufacturing studies are required, the present work confirms that FDM-based personalized metformin tablets represent a promising next-generation platform for precision antidiabetic therapy and individualized oral drug delivery.

5. Conclusion

The present study successfully demonstrated the development, optimization, and experimental evaluation of personalized metformin hydrochloride oral tablets using Fused Deposition Modeling (FDM) 3D printing technology. Drug-loaded filaments prepared through hot-melt extrusion exhibited excellent printability and enabled the fabrication of tablets with precise dimensions, uniform drug content, and reproducible mechanical properties. Optimization of critical printing parameters, including infill density, shell thickness, layer height, and printing temperature, resulted in a formulation with

superior pharmaceutical quality and manufacturing reproducibility.

The optimized 3D-printed tablets exhibited desirable physicochemical characteristics, including excellent drug–polymer compatibility, satisfactory hardness, low friability, and stable structural integrity. The modified internal tablet architecture effectively controlled drug diffusion, producing a sustained drug release profile over 24 hours. Pharmacokinetic evaluation demonstrated improved oral bioavailability, prolonged plasma drug exposure, and increased mean residence time compared with conventional immediate-release metformin tablets. Furthermore, in vivo studies confirmed enhanced and prolonged antidiabetic activity, as evidenced by greater reductions in fasting blood glucose levels, improved glycemic control, and better therapeutic performance throughout the treatment period.

The findings of this investigation clearly demonstrate that tablet architecture generated through FDM 3D printing serves as an effective tool for controlling drug release behavior without altering the active pharmaceutical ingredient**.** The integration of pharmaceutical formulation design with additive manufacturing technology provides a flexible platform for producing patient-specific dosage forms with customized doses, modified release characteristics, and improved treatment outcomes. Such personalized formulations have the potential to enhance medication adherence, reduce dosing frequency, minimize adverse effects, and optimize therapy for patients with varying clinical requirements.

Overall, this study highlights the significant potential of 3D printing technology as an innovative approach for precision oral drug delivery in diabetes management. The combination of hot-melt extrusion and FDM printing offers a robust, reproducible, and scalable manufacturing strategy for personalized pharmaceutical products. Future investigations should focus on long-term clinical studies, regulatory validation, continuous manufacturing approaches, and industrial-scale production to facilitate the successful translation of personalized 3D-printed metformin tablets from laboratory research to routine clinical practice. The advancement of digital pharmaceutical manufacturing is expected to play a pivotal role in the future of individualized medicine and next-generation oral drug delivery systems.

Ethical Considerations: The in vivo experimental study was conducted using streptozotocin-induced diabetic male Wistar rats in accordance with internationally accepted principles for the care and use of laboratory animals. All animal handling, housing, induction of diabetes, treatment administration, and experimental procedures were performed following the guidelines approved by the Institutional Animal Ethics Committee (IAEC) of Department of Pharmacology**,** DCS A.R. College of Pharmacy Dhule Charitable Society, Maharashtra, India. Every effort was made to minimize animal suffering, reduce the number of animals used, and ensure humane care throughout the experimental period. No human participants were involved in this study.

Conflict Of Interest: The authors declare that there are no conflicts of interest related to this study. All authors have reviewed and approved the final manuscript and have no financial or personal relationships that could have influenced the work reported in this study.

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