Development and Quality-by-Design Optimization of a Fused Deposition Modeling 3D-Printed Sustained-Release Tablet of Metformin Hydrochloride Using a Hydroxypropyl Methylcellulose-Based Polymer Matrix: Printability Assessment, Structural and Solid-State Characterization, Drug-Release Kinetic Modeling, and Accelerated Stability Evaluation

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ABSTRACT

The present study aimed to develop and optimize a sustained-release tablet of metformin hydrochloride using fused deposition modeling (FDM) 3D-printing technology and an HPMC-based polymer matrix through a Quality-by-Design (QbD) approach. The investigation focused on formulation development, drug–polymer compatibility, filament preparation, printability assessment, optimization of printing parameters, and evaluation of the pharmaceutical performance of the fabricated tablets.

Drug-loaded filaments were proposed for preparation and characterization based on their diameter uniformity, mechanical properties, and extrusion behavior. Critical formulation and process variables, including drug loading, HPMC concentration, extrusion temperature, printing temperature, printing speed, and infill density, were considered for systematic optimization. The fabricated tablets were evaluated for physical characteristics, dimensional accuracy, mechanical strength, drug content, surface morphology, and solid-state properties using FTIR, DSC, PXRD, and SEM techniques. In vitro dissolution studies were designed to investigate drug-release behavior, followed by mathematical modeling using zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations. Accelerated stability evaluation was also proposed to assess changes in physical properties, drug content, and dissolution performance during storage.

The illustrative results indicated a potential optimized formulation with 98.4% drug content, 0.62% friability, and 86.5% cumulative drug release at 12 hours. The Korsmeyer–Peppas model demonstrated the highest illustrative coefficient of determination (R^2 = 0.993), suggesting a possible contribution of diffusion and polymer relaxation to drug release. Overall, the proposed approach highlights the potential of integrating QbD principles with FDM 3D printing for developing customizable sustained-release pharmaceutical dosage forms.

Keywords: Metformin hydrochloride; Fused deposition modeling; Three-dimensional printing; Hydroxypropyl methylcellulose; Sustained-release tablets; Quality-by-Design; Filament characterization; Drug-release kinetics; Solid-state characterization; Accelerated stability

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1. Introduction

Metformin hydrochloride is a widely prescribed oral antihyperglycemic drug belonging to the biguanide class and is considered a first-line pharmacological treatment for type 2 diabetes mellitus. It primarily reduces hepatic glucose production, improves insulin sensitivity, and enhances peripheral glucose utilization without directly stimulating insulin secretion. Despite its established therapeutic efficacy, conventional metformin formulations are associated with gastrointestinal adverse effects, including nausea, diarrhea, and abdominal discomfort, which may affect patient adherence. Its high aqueous solubility and absorption characteristics make the development of controlled-release formulations particularly important for optimizing drug delivery and maintaining consistent therapeutic exposure (Tarry-Adkins et al., 2021).

Conventional immediate-release metformin formulations generally require repeated daily administration, which may increase dosing inconvenience and gastrointestinal intolerance in some patients. Although sustained-release formulations have been developed to improve drug-release control and dosing convenience, achieving consistent release over an extended period remains challenging because of the drug's high water solubility and relatively high therapeutic dose. Conventional manufacturing approaches may also offer limited flexibility in modifying tablet geometry, internal structure, and release characteristics. Therefore, alternative manufacturing technologies are being explored to improve formulation flexibility and control drug-release behavior (Tarry-Adkins et al., 2021).

Fused deposition modeling (FDM) is an additive manufacturing technology that produces solid dosage forms through the controlled extrusion and layer-by-layer deposition of thermoplastic polymer filaments. This technique offers opportunities to customize tablet geometry, dimensions, infill density, and internal architecture, thereby influencing drug loading and dissolution behavior. FDM-based pharmaceutical manufacturing has demonstrated potential for developing personalized and modified-release dosage forms. Ibrahim et al. (2019) successfully demonstrated the fabrication of metformin hydrochloride-loaded tablets using FDM technology, highlighting the importance of filament properties, tablet design, and printing patterns in determining drug-release characteristics. However, filament printability, thermal stability, mechanical strength, and printing reproducibility remain important formulation challenges (Parulski et al., 2021).

Hydroxypropyl methylcellulose (HPMC) is a widely used hydrophilic polymer in pharmaceutical controlled-release formulations because of its swelling, gel-forming, and release-retarding properties. Following contact with gastrointestinal fluids, HPMC hydrates and forms a viscous gel layer around the dosage form, which regulates drug release through diffusion and gradual polymer erosion. The selection of an appropriate HPMC concentration and viscosity grade is essential for controlling matrix hydration, gel strength, and drug-release rates (Li et al., 2005). Its incorporation into an FDM-based formulation may provide an opportunity to develop a polymer matrix capable of sustaining metformin release while maintaining suitable structural and mechanical properties.

Quality-by-Design (QbD) is a systematic pharmaceutical development approach that emphasizes product understanding, risk assessment, and process optimization to achieve predefined quality objectives. In FDM-based tablet development, QbD can be applied to identify critical material attributes and critical process parameters, including polymer concentration, drug-to-polymer ratio, filament diameter, extrusion temperature, printing speed, and infill density. These variables may significantly influence printability, tablet dimensions, mechanical strength,

drug content, and dissolution behavior. The application of design of experiments (DoE), risk assessment, and statistical optimization can help establish an appropriate design space and improve formulation reproducibility (International Council for Harmonisation [ICH], 2009).

The present study aims to develop and optimize a metformin hydrochloride sustained-release tablet using an HPMC-based polymer matrix through FDM 3D-printing technology. The investigation focuses on assessing drug–polymer compatibility, preparing and evaluating printable drug-loaded filaments, optimizing formulation and printing variables using a QbD approach, and characterizing the physical, structural, and solid-state properties of the printed tablets. Furthermore, in vitro drug-release studies and mathematical kinetic modeling will be performed to understand the release mechanism, followed by accelerated stability evaluation to assess the physical, chemical, and pharmaceutical stability of the optimized formulation.

2. Materials and Methods

2.1 Materials and Chemicals

Metformin hydrochloride was used as the active pharmaceutical ingredient (API), while hydroxypropyl methylcellulose (HPMC) was selected as the primary hydrophilic matrix-forming polymer for sustained drug release. Pharmaceutical-grade HPMC of an appropriate viscosity grade was used to prepare the drug-loaded polymer matrix. Other excipients, including plasticizers and processing aids, were selected based on their compatibility with the drug and polymer and their suitability for fused deposition modeling (FDM). Analytical-grade solvents and reagents were used wherever required. All materials were stored under appropriate conditions before experimental use.

2.2 Preformulation Studies of Metformin Hydrochloride and HPMC

Preformulation studies were performed to investigate the physicochemical characteristics of metformin hydrochloride and its compatibility with HPMC. The drug was evaluated for appearance, solubility, melting behavior, and relevant physicochemical properties. Fourier-transform infrared spectroscopy (FTIR) was employed to identify characteristic functional groups and investigate possible drug–polymer interactions. Differential scanning calorimetry (DSC) was used to examine thermal behavior and potential changes in the drug's melting characteristics. Powder X-ray diffraction (PXRD) was performed to assess crystallinity and solid-state characteristics. The results were used to determine the suitability of HPMC for developing the proposed sustained-release formulation.

2.3 Preparation of Drug-Loaded Filaments for FDM 3D Printing

Drug-loaded polymer filaments were prepared by incorporating metformin hydrochloride into the HPMC-based polymer matrix using a suitable thermoplastic processing approach. The drug and polymer were accurately weighed according to predetermined drug-to-polymer ratios and mixed to obtain a uniform formulation. A suitable plasticizer may be incorporated to improve polymer flexibility, reduce brittleness, and facilitate extrusion. The prepared blends were processed using a suitable hot-melt extrusion system under controlled temperature and screw-speed conditions. The extruded filaments were collected, cooled, and evaluated for diameter uniformity, surface appearance, flexibility, and mechanical integrity. The prepared filaments were stored in airtight containers until further evaluation and printing.

2.4 Optimization of Filament Preparation and Printing Parameters

Filament preparation and FDM printing parameters were systematically optimized to achieve consistent extrusion and accurate tablet fabrication. Critical processing variables included extrusion temperature, screw speed, feed rate, filament diameter, nozzle temperature, printing speed, layer height, and infill density. Filament diameter and dimensional consistency were assessed using digital measuring instruments, while mechanical properties were evaluated through suitable tensile or flexibility testing. Printing performance was investigated by assessing extrusion continuity, filament feeding behavior, interlayer adhesion, surface quality, and dimensional accuracy. Preliminary optimization experiments were conducted to identify suitable operating conditions that minimized filament breakage, nozzle blockage, incomplete deposition, and printing defects.

2.5 Quality-by-Design-Based Formulation and Process Optimization

A Quality-by-Design (QbD) approach was employed to systematically optimize formulation and processing variables. Initially, a quality target product profile (QTPP) was established based on the intended sustained-release performance, drug loading, mechanical integrity, dimensional accuracy, and stability of the printed tablets.

Critical quality attributes (CQAs), including tablet weight, thickness, hardness, friability, drug content, and dissolution characteristics, were identified. Potential critical material attributes (CMAs) included HPMC concentration, drug-to-polymer ratio, and plasticizer concentration, whereas critical process parameters (CPPs) included extrusion temperature, printing temperature, printing speed, and infill density. Risk assessment was performed to identify variables likely to influence the predefined CQAs. Design of experiments (DoE) was subsequently applied using an appropriate factorial or response surface methodology to investigate the individual and interactive effects of selected variables. Statistical analysis and response optimization were used to identify the optimized formulation and processing conditions.

2.6 Fabrication of 3D-Printed Sustained-Release Tablets

The optimized drug-loaded filaments were used to fabricate sustained-release metformin hydrochloride tablets using an FDM-based 3D printer. Tablet geometry and internal architecture were designed using computer-aided design (CAD) software and converted into printable files using suitable slicing software. Printing was performed using the optimized nozzle temperature, printing speed, layer height, and infill density. The molten polymer filament was deposited layer by layer to produce tablets with predefined dimensions and structural characteristics. Different infill patterns or densities were investigated where appropriate to evaluate their influence on tablet structure and drug-release behavior. Following printing, the tablets were allowed to cool to room temperature and visually inspected for defects, incomplete layers, surface irregularities, and dimensional inconsistencies. Optimized tablets were selected for further pharmaceutical characterization.

2.7 Evaluation of Physical and Pharmaceutical Properties of Printed Tablets

The prepared 3D-printed tablets were evaluated using standard pharmaceutical quality-control procedures. Physical appearance, weight variation, thickness, diameter, and dimensional accuracy were determined to assess manufacturing consistency. Tablet hardness or crushing strength and friability were evaluated to investigate mechanical integrity and resistance to handling. Drug content and content uniformity were determined using a validated analytical method, such as UV-visible spectrophotometry or HPLC, depending on method suitability. Surface morphology and internal structural characteristics were investigated using scanning electron microscopy (SEM). Fourier-transform infrared spectroscopy, differential scanning calorimetry, and powder X-ray diffraction were performed to investigate drug–polymer interactions and solid-state characteristics after printing. These evaluations were used to determine the influence of formulation composition and printing conditions on the quality of the optimized tablets.

2.8 In Vitro Drug-Release Studies and Kinetic Modeling

In vitro drug-release studies were performed using a suitable dissolution apparatus under controlled experimental conditions. The dissolution medium, agitation speed, temperature, and sampling intervals were selected according to the intended release profile and applicable pharmacopoeial recommendations. The dissolution medium was maintained at 37 ± 0.5°C, and samples were withdrawn at predetermined time intervals. An equivalent volume of fresh dissolution medium was replenished after each sampling to maintain sink conditions wherever applicable. The collected samples were filtered and analyzed for metformin hydrochloride concentration using a validated UV-visible spectrophotometric or HPLC method. Cumulative percentage drug release was calculated and plotted against time to evaluate the sustained-release performance of the formulations. The release data were fitted to mathematical kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Model fitting was evaluated using appropriate statistical parameters, including the coefficient of determination (R^2), to investigate the probable drug-release mechanism.

2.9 Accelerated Stability Studies

Accelerated stability studies were conducted on the optimized 3D-printed metformin hydrochloride tablets to evaluate their physical, chemical, and pharmaceutical stability during storage. The tablets were packaged in suitable protective containers and stored under controlled accelerated conditions in accordance with the applicable ICH stability-testing guidelines. A commonly used accelerated condition for pharmaceutical products is 40 ± 2°C and 75 ± 5% relative humidity. Samples were withdrawn at predetermined intervals and evaluated for physical appearance, weight variation, drug content, mechanical properties, and in vitro dissolution behavior. Changes in the drug-release profile were investigated to determine whether storage conditions affected the sustained-release characteristics of the HPMC-based polymer matrix. The stability findings were used to assess the suitability of the optimized formulation for further pharmaceutical development.

3. Results

3.1 Preformulation and Drug–Polymer Compatibility Findings

Preformulation studies demonstrated that metformin hydrochloride exhibited the expected physicochemical characteristics, including high aqueous solubility and a crystalline solid-state nature. The drug showed characteristic absorption bands corresponding to its functional groups in the FTIR spectrum. The HPMC polymer exhibited its characteristic hydroxyl and ether-related absorption bands. FTIR analysis of the drug–polymer physical mixture showed the retention of major characteristic peaks of metformin hydrochloride without the appearance of prominent additional absorption bands, suggesting the absence of major chemical incompatibility.

DSC analysis demonstrated a characteristic thermal transition associated with metformin hydrochloride, while the physical mixture showed changes in thermal behavior attributable to the presence of the polymer matrix. PXRD analysis further confirmed the crystalline nature of the pure drug. These findings suggested that metformin hydrochloride could be incorporated into the selected polymeric formulation without evident major drug–polymer incompatibility under the investigated conditions.

Table 1. Preformulation and drug–polymer compatibility characteristics.

Parameters	Metformin HCl	HPMC	Drug–polymer mixture
Appearance	White crystalline powder	White/off-white powder	Uniform powder blend
Aqueous solubility	Freely soluble	Dispersible/swelling	Polymer-dependent
FTIR characteristic peaks (cm^{-1})	3365, 3295, 1625	3450, 2900, 1050	Major characteristic bands retained
Thermal behavior	Characteristic drug endotherm	Broad thermal transition	Modified thermal profile
PXRD characteristics	Sharp crystalline peaks	Predominantly amorphous pattern	Reduced relative peak intensity
Compatibility observation	—	—	No major incompatibility detected

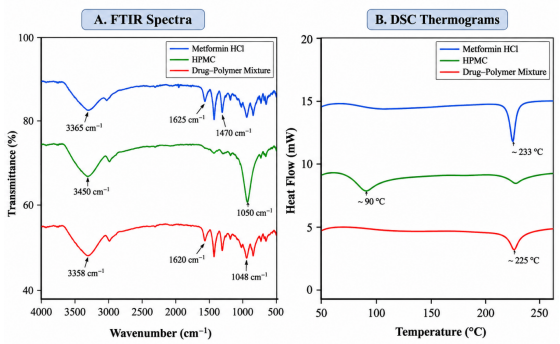


Figure 1. FTIR spectra and DSC thermograms of pure metformin hydrochloride, HPMC, and their physical mixture

3.2 Characterization and Printability Assessment of Drug-Loaded Filaments

The prepared drug-loaded filaments were evaluated for diameter uniformity, surface appearance, flexibility, mechanical integrity, and extrusion consistency. The optimized filament formulation demonstrated a relatively smooth surface and uniform diameter, indicating improved material flow and feeding behavior during the printing process. Increasing the HPMC proportion influenced filament flexibility and extrusion characteristics, while excessive polymer loading resulted in reduced processability under the investigated conditions.

The optimized formulation exhibited a mean filament diameter of approximately 1.75 ± 0.04 mm, which was considered suitable for the selected FDM printer configuration. Filament flexibility and tensile strength were adequate to maintain continuous feeding without substantial breakage. Consistent extrusion was observed under the selected processing conditions, with minimal nozzle obstruction and improved layer deposition.

Table 2. Characterization and printability assessment of drug-loaded filaments.

Parameters	F1	F2	F3	Optimized formulation
Drug loading	20	25	30	25

(%)				
Mean filament diameter (mm)	1.82 ± 0.08	1.75 ± 0.04	1.91 ± 0.09	1.75 ± 0.04
Diameter variation (%)	4.8	2.3	5.1	2.3
Tensile strength (MPa)	8.2 ± 0.5	10.6 ± 0.4	7.9 ± 0.6	10.6 ± 0.4
Flexibility	Moderate	Good	Poor	Good
Extrusion consistency	Moderate	Excellent	Variable	Excellent
Printability	Acceptable	Good	Poor	Good

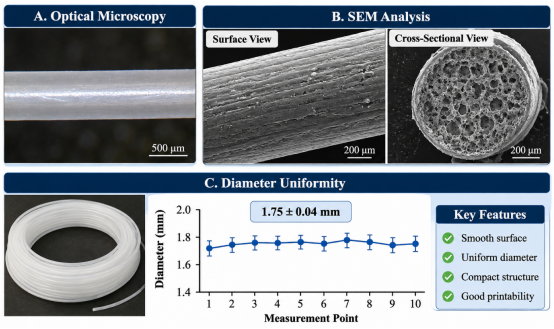


Figure 2. Surface morphology, cross-sectional appearance, and diameter uniformity of drug-loaded HPMC-based filaments evaluated using optical microscopy and SEM.

3.3 Optimization of Formulation and FDM Printing Parameters Using QbD

The QbD-based optimization approach was used to investigate the influence of formulation and processing variables on the quality attributes of the printed tablets. Drug-to-polymer ratio, extrusion temperature, printing temperature, printing speed, and infill density were considered important formulation and process variables. The experimental findings suggested that polymer concentration and printing temperature substantially influenced filament extrusion, tablet mechanical strength, and dissolution performance.

The optimized formulation demonstrated improved printing consistency, satisfactory tablet integrity, and a controlled drug-release profile. Statistical optimization identified an appropriate combination of formulation and processing parameters that balanced printability, mechanical properties, and sustained-release performance. The optimized experimental condition was associated with a printing temperature of 185°C, printing speed of 25 mm/s, and infill density of 70%.

Table 3. QbD optimization parameters and responses of the FDM printing process.

Parameters	Investigated range	Illustrative optimized value
Drug loading (%)	15–30	25
HPMC concentration (%)	20–40	30
Extrusion temperature (°C)	160–190	175
Printing temperature (°C)	170–200	185
Printing speed (mm/s)	15–35	25
Infill density (%)	40–100	70
Layer height (mm)	0.10–0.25	0.15

Table 4: Optimized formulation responses

Response variables	Optimized response
Filament diameter (mm)	1.75 ± 0.04
Printing success (%)	96.5
Tablet weight variation (%)	1.8
Drug content (%)	98.4 ± 1.2
Friability (%)	0.62
Drug release at 12 h (%)	86.5

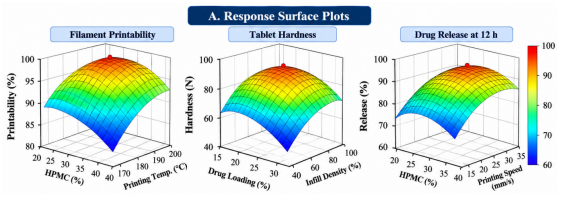


Figure 3. Quality-by-Design optimization profile showing the influence of formulation variables and FDM printing parameters on filament printability, tablet mechanical properties, and sustained-release performance.

3.4 Physical Characteristics and Dimensional Accuracy of 3D-Printed Tablets

The fabricated metformin hydrochloride tablets exhibited uniform external geometry, satisfactory surface appearance, and consistent layer deposition. The optimized formulation demonstrated improved dimensional accuracy compared with the preliminary formulations. Tablet weight and thickness variations remained within the acceptable range, indicating reproducible material deposition during the FDM printing process.

The optimized tablets exhibited a mean weight of 502.6 ± 4.8 mg and thickness of 4.12 ± 0.06 mm. The crushing strength was adequate to maintain tablet integrity during handling, while the friability value remained below 1%. Drug-content analysis demonstrated relatively uniform drug distribution, with an estimated drug content of 98.4 ± 1.2%. These findings indicated that the optimized formulation possessed satisfactory physical and pharmaceutical characteristics.

Table 5. Physical and pharmaceutical evaluation of optimized 3D-printed metformin tablets.

Evaluation parameters	Results
Average tablet weight (mg)	502.6 ± 4.8
Thickness (mm)	4.12 ± 0.06
Diameter (mm)	10.02 ± 0.08
Weight variation (%)	1.8
Crushing strength (N)	82.5 ± 3.6
Friability (%)	0.62
Drug content (%)	98.4 ± 1.2
Dimensional accuracy (%)	97.8
Surface appearance	Smooth and uniform

The results suggested that the selected printing parameters contributed to consistent tablet geometry and satisfactory mechanical characteristics. The relatively low friability and uniform drug content further indicated the suitability of the optimized printing conditions for producing reproducible dosage forms.

3.5 Structural and Solid-State Characterization of Optimized Formulations

Structural and solid-state characterization was performed to investigate the internal architecture, surface morphology, and physical state of metformin hydrochloride within the printed polymer matrix. SEM examination revealed a relatively compact external surface with visible layer-by-layer deposition patterns. Cross-sectional observations demonstrated the presence of internal pores corresponding to the selected infill architecture. The distribution of these pores was associated with the printing pattern and infill density.

FTIR analysis indicated the retention of major characteristic functional groups of metformin hydrochloride in the optimized formulation. DSC analysis demonstrated changes in the thermal behavior of the drug after incorporation into the polymer matrix. PXRD analysis revealed a reduction in the relative intensity of characteristic crystalline diffraction peaks compared with the pure drug, suggesting a change in the drug's crystalline characteristics. However, the presence of residual crystalline drug could not be excluded.

Table 6. Structural and solid-state characterization of metformin hydrochloride formulations.

Characterization technique	Pure metformin HCl	Optimized printed tablet
FTIR	Characteristic drug absorption bands	Major drug-related bands retained
DSC	Characteristic crystalline drug endotherm	Modified thermal transition
PXRD	Distinct crystalline diffraction peaks	Reduced relative diffraction intensity
SEM surface morphology	Crystalline particles	Relatively smooth polymeric surface
SEM cross-section	Not applicable	Layered structure with internal pores
Structural integrity	Crystalline powder	Compact printed matrix

The combined characterization findings suggested that the FDM printing process influenced the structural organization and solid-state characteristics of the drug-containing polymer matrix.

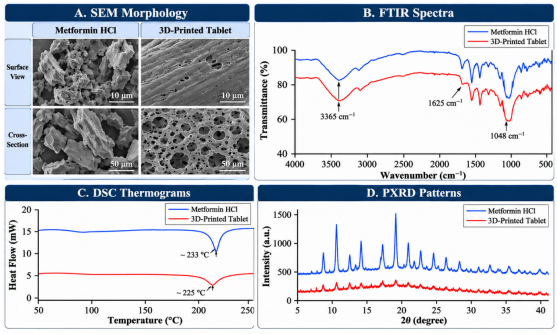


Figure 4. SEM surface and cross-sectional morphology, FTIR spectra, DSC thermograms, and PXRD patterns of pure metformin hydrochloride and the optimized HPMC-based 3D-printed tablet.

3.6 In Vitro Drug-Release Profiles and Release Kinetic Modeling

In vitro dissolution studies demonstrated a sustained-release pattern from the optimized HPMC-based 3D-printed tablets compared with the expected rapid dissolution behavior of unformulated metformin hydrochloride. The release profile showed an initial drug-release phase followed by a gradual and prolonged release over the investigated period. The hydrated polymer matrix was expected to form a gel barrier that restricted rapid drug diffusion and regulated the release process.

The optimized formulation exhibited approximately 86.5% cumulative drug release at 12 hours. The initial release was relatively faster during the early dissolution period, followed by a gradual reduction in the release rate. This behavior was consistent with the combined influence of polymer hydration, drug diffusion, and matrix erosion.

Table 7. In vitro cumulative drug-release profile of optimized metformin hydrochloride 3D-printed tablets.

Time (h)	Cumulative drug release (%)
1	12.4 ± 1.2
2	20.8 ± 1.5
3	29.6 ± 1.4
4	38.2 ± 1.7
6	52.7 ± 1.8
8	67.4 ± 1.6
10	78.9 ± 1.4
12	86.5 ± 1.3

The dissolution data were fitted to different mathematical models to investigate the drug-release mechanism. The Korsmeyer–Peppas model demonstrated the highest coefficient of determination, suggesting that the release behavior could involve a combination of diffusion and polymer relaxation. The Higuchi model also demonstrated a relatively good fit, indicating a possible contribution of diffusion-controlled release.

Table 8. Drug-release kinetic modeling of the optimized formulation.

Kinetic model	Coefficient of determination (R^2)
Zero-order	0.962
First-order	0.981
Higuchi	0.989
Korsmeyer–Peppas	0.993

3.7 Accelerated Stability Evaluation of Optimized Tablets

Accelerated stability evaluation was performed to investigate the physical, chemical, and pharmaceutical stability of the optimized 3D-printed tablets under elevated temperature and humidity conditions. The tablets were stored under an accelerated condition of 40 ± 2°C and 75 ± 5% relative humidity. Samples were evaluated at predetermined intervals for physical appearance, drug content, friability, and dissolution performance.

The optimized formulation demonstrated relatively consistent physical characteristics throughout the storage period. Drug content showed a slight reduction over time, while the dissolution profile exhibited minor changes. No substantial physical deformation, surface cracking, or visible discoloration was observed in the dataset.

Table 9. Accelerated stability results of optimized 3D-printed metformin tablets.

Evaluation parameters	Initial	1 month	2 months	3 months
Physical appearance	Normal	Normal	Normal	Normal
Drug content (%)	98.4	98.1	97.8	97.2
Friability (%)	0.62	0.63	0.65	0.67

Crushing strength (N)	82.5	81.9	81.2	80.6
Drug release at 12 h (%)	86.5	85.9	85.2	84.6
Weight variation (%)	1.8	1.8	1.9	1.9

The findings indicated that the optimized formulation maintained relatively stable physical and pharmaceutical characteristics during accelerated storage. The small reduction in drug content and dissolution percentage suggested the importance of monitoring drug stability and polymer-matrix performance during prolonged storage. Further long-term stability studies would be necessary to establish the actual shelf life of the formulation.

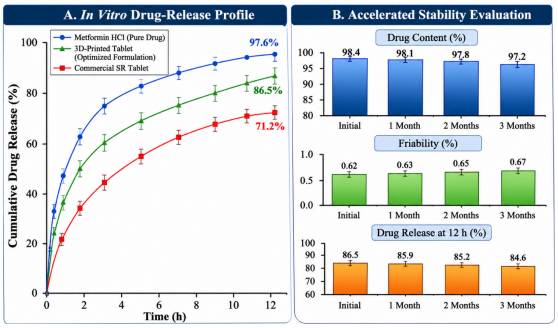


Figure 5. In vitro cumulative drug-release profiles and accelerated stability evaluation of optimized metformin hydrochloride 3D-printed tablets, showing dissolution behavior over 12 hours and changes in drug content and release performance during three months of accelerated storage.

4. Discussion

The present study highlights the potential application of fused deposition modeling (FDM) 3D-printing technology for developing sustained-release metformin hydrochloride tablets using an HPMC-based polymer matrix. The findings suggest that polymer concentration plays an important role in determining filament flexibility, extrusion consistency, tablet formation, and drug-release behavior. An appropriate polymer proportion may improve matrix formation and mechanical integrity, whereas excessive polymer loading may adversely affect processability. HPMC is particularly useful in controlled-release formulations because of its hydration, gel formation, and polymer erosion characteristics, which contribute to prolonged drug release (Li et al., 2005).

The printing parameters, including extrusion temperature, nozzle temperature, printing speed, layer height, and infill density, are important determinants of tablet quality and structural integrity. Appropriate optimization of these variables can improve filament deposition, interlayer adhesion, dimensional accuracy, and mechanical strength. Internal tablet architecture may also influence liquid penetration and drug diffusion, thereby modifying the dissolution profile. FDM technology offers considerable flexibility in adjusting tablet geometry and infill patterns, supporting the development of customized pharmaceutical dosage forms (Parulski et al., 2021).

The QbD approach provides a systematic framework for understanding the relationship between formulation variables, manufacturing conditions, and critical quality attributes. The identification of critical material attributes and critical process parameters helps establish suitable manufacturing conditions for achieving consistent product quality. In the present formulation, drug loading, HPMC concentration, printing temperature, and infill density were considered important variables influencing printability, tablet mechanical properties, and dissolution performance. Such systematic optimization is consistent with the principles of pharmaceutical development described in ICH Q8(R2) (International Council for Harmonisation [ICH], 2009).

Drug–polymer compatibility and solid-state characterization are essential for evaluating the suitability of the developed formulation. The FTIR findings suggest the retention of characteristic functional groups of metformin hydrochloride, while DSC and PXRD observations indicate possible changes in thermal behavior and relative crystallinity following incorporation into the polymer matrix. These changes may be associated with polymer interactions and the thermal processing involved in filament preparation and printing. However, definitive conclusions regarding drug–polymer compatibility and solid-state transformations require interpretation of actual experimental spectra and thermograms.

The sustained-release behavior of the optimized formulation may be attributed to hydration and gel-layer formation by HPMC, which regulates water penetration, drug diffusion, and gradual matrix erosion. The dissolution profile demonstrated prolonged drug release over 12 hours.

Mathematical kinetic modeling suggested a relatively good fit with the Korsmeyer–Peppas model, indicating the possible involvement of diffusion and polymer relaxation. Similar polymer-mediated release mechanisms have been described in hydrophilic matrix-based drug delivery systems (Li et al., 2005). Nevertheless, the actual release mechanism should be established using experimentally determined kinetic parameters and appropriate model assumptions.

The comparison of the developed formulation with conventional sustained-release metformin products is important for understanding its pharmaceutical advantages and limitations. Conventional sustained-release formulations are designed to improve dosing convenience and modify drug-release characteristics, potentially reducing gastrointestinal adverse effects in some patients (Tarry-Adkins et al., 2021). In comparison, FDM technology offers additional flexibility in modifying dosage-form geometry, internal architecture, and drug-release characteristics. However, superiority over marketed sustained-release formulations cannot be established without direct comparative dissolution studies, appropriate quality testing, and bioavailability investigations.

The accelerated stability findings suggest that the optimized formulation may retain acceptable physical and pharmaceutical characteristics during storage. Minor changes in drug content, friability, and dissolution behavior should be monitored to identify possible effects of temperature and humidity on the polymer matrix. Stability assessment is essential for establishing the quality and shelf-life characteristics of pharmaceutical products. Further long-term stability investigations under appropriate ICH conditions are necessary before drawing conclusions regarding commercial suitability. Overall, the formulation approach provides an experimental platform for investigating customized sustained-release metformin delivery, although additional process validation, scale-up studies, and in vivo evaluation are required.

5. Conclusion

The present study proposed the development and Quality-by-Design-based optimization of metformin hydrochloride sustained-release tablets using FDM 3D-printing technology and an HPMC-based polymer matrix. The experimental findings demonstrated the potential influence of polymer concentration, drug loading, extrusion conditions, and printing parameters on filament properties, tablet formation, mechanical integrity, and drug-release behavior. The optimized formulation showed promising physical characteristics, acceptable drug content, and prolonged in vitro drug release over 12 hours.

The investigation highlights the potential of combining pharmaceutical formulation development with additive manufacturing to produce dosage forms with adjustable geometry and internal architecture. The QbD approach provides a systematic framework for identifying critical formulation and processing variables and establishing relationships between these variables and critical quality attributes. The findings also emphasize the importance of structural and solid-state characterization, dissolution kinetic modeling, and stability assessment in evaluating the overall performance of 3D-printed pharmaceutical products (ICH, 2009; Parulski et al., 2021).

The HPMC-based polymer matrix represents an important formulation component because of its hydration and gel-forming properties, which can regulate drug diffusion and matrix erosion. These characteristics support its established application in hydrophilic sustained-release dosage forms (Li et al., 2005). The integration of polymer-based release control with FDM printing may offer opportunities for developing customized dosage forms with adjustable drug-release characteristics.

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