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Quality by Design (QbD)-Driven Development of Metformin HCl Sustained-Release Tablets via Fused Deposition Modeling 3D Printing

Vignesh Babu Sekar[1], Sreemoy Kanti Das[2]
School of Pharmacy, Lincoln University College, Malaysia

Abstract: ***This study explains how we used systematic Quality by Design (QbD) approach to develop slow-release metformin HCl tablets. We did this specifically using a 3D printing method called Fused Deposition Modeling (FDM). To find the best settings for printing, we employed a Box-Behnken design. This helped us identify the ideal temperature range (between 150 and 180°C), the best layer thickness (from 0.1 to 0.3 mm), and the optimal internal density (80-100%) for the tablets. We looked closely at the physical form of the metformin inside the tablets using techniques like XRPD, DSC, and TGA. Our findings confirmed that the drug formed an amorphous dispersion, meaning it was evenly spread throughout the tablet and remained stable even when heated. The specific recipe we created, which included a particular polymer known as High PVA Formulation (HPF), allowed the drug to release steadily over time. This achieved what's called zero-order release kinetics, and the tablet had a high dissolution efficiency of 71.25%. It successfully delivered 90% of the drug within 12 hours. Importantly, its release pattern was very similar to a commercially available product, Glucophage® XR, with a similarity factor (f2) of 68.41. When we analyzed the release data using the Korsmeyer-Peppas model, it suggested that the main way the drug left the tablet was through simple diffusion (n= 0.426). By applying this QbD-guided FDM printing method, we were able to precisely control the tablet's internal structure. This demonstrates that this 3D printing technique holds promise as a practical and scalable platform for creating personalized generic medicines, especially for treating type 2 diabetes.***

Keywords: Quality by Design, Metformin HCl, FDM 3D Printing, Sustained Release, Release Kinetics, Thermal Stability

I. INTRODUCTION

The oral route remains a basis of drug delivery, valued for its non-invasiveness, patient compliance, and cost-effectiveness. Among oral dosage forms, sustained release (SR) tablets are particularly useful for chronic conditions like type 2 diabetes, where maintaining steady plasma drug concentrations improves therapeutic results and reduces dosing frequency. Metformin Hydrochloride (HCl), a first-line therapy for type 2 diabetes, shows this need. However, its short biological half-life (~6.5 hours) and dose-dependent gastrointestinal side effects necessitate SR formulations to enhance patient adherence and minimize adverse effects. Despite its efficacy, developing SR formulations of Metformin HCl presents challenges, including achieving consistent drug release kinetics and ensuring bioavailability. Traditional manufacturing methods, such as wet granulation or compression, often struggle to precisely control matrix porosity and drug distribution—critical factors for sustained release. Quality by Design (QbD), a systematic framework endorsed by regulatory agencies like the FDA and ICH. QbD emphasizes *predefined product objectives, risk assessment*, and *process understanding* to ensure robust formulations. By identifying Critical Quality Attributes (CQAs)such as drug release kinetics, Degradation Products, and content uniformity —QbD guides the optimization of formulation and process parameters. This study integrates QbD with Fused Deposition Modeling (FDM) 3D printing, an innovative manufacturing technology. FDM enables layer-by-layer fabrication of tablets using thermoplastic polymers, offering unparalleled control over internal architecture (printing temperature, infill density, and layer height). This precision is pivotal for tailoring drug release kinetics in SR formulations. For instance, varying infill patterns (e.g., rectilinear vs. honeycomb) can modulate porosity, directly influencing diffusion rates(Ayyoubi, et al., 2021).

A Design of Experiments (DoE) approach, specifically a *three-factor,3-level Box-Behnken Design* is employed to optimize key variables:

1) Printing temperature (150^0C-180^0C): A hydrophilic polymer Tg temperature.
2) Layer height (0.1–0.3 mm): Impacts tablet density and dissolution.
3) Infill density (80–100%): Controls porosity and drug release rate.

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By correlating these factors with CQAs, this work aims to develop a bioequivalent SR Metformin HCl tablet that mirrors the release profile of Glucophage® XR while leveraging FDM's scalability and customization potential.

II. MATERIALS AND METHODS

A. Materials

Metformin HCl (purity > 97%) was obtained from Harman Finochem Pvt Ltd (Mumbai, Maharashtra, India). Triethyl citrate (purity > 99%) was sourced from Mamta Polycoats (Ahmedabad, Gujarat, India). Hydroxypropyl methyl cellulose (HPMC K4M, Methocel® K4M) was procured from Colorcon India Pvt Ltd (Verna, Goa, India). Polyvinyl alcohol (PVA) was obtained as finer PVA (Parteck® MXP, Mw ~ 31,000) from EMD Millipore Sigma (Burlington, MA, USA). Analytical grade solvents like tetrahydrofuran (THF), acetonitrile (HPLC grade), and dimethyl sulfoxide (DMSO) were used for preparation and analysis procedures. All other materials used were of pharmaceutical grade.

B. QbD Experimental Design

A Quality by Design (QbD) framework was employed to evaluate the influence of critical process parameters (CPPs) on the performance of 3D-printed metformin tablets, following ICH Q8 (R2) guidelines (ICH, 2009). A Box–Behnken Design (BBD) with three factors at three levels was selected for systematic experimentation, requiring 17 runs including center points (Ferreira et al., 2007).

The selected CPPs were:

- Printing temperature: 150°C, 165°C, 180°C (Ayyoubi et al., 2021)
- Layer height: 0.1 mm, 0.2 mm, 0.3 mm (Sadia et al., 2016)
- Infill density: 80%, 90%, 100% (Afsana et al., 2022)

The Critical Quality Attributes (CQAs) were:

- Dissolution efficiency (DE%) – widely used as a surrogate of release performance (Khan, 1975)
- Similarity factor (f_2) – recommended by FDA/EMA for dissolution profile comparison (FDA, 1997; EMA, 2010)
- Tablet integrity – critical for ensuring robustness of FDM-printed dosage forms (Goyanes et al., 2015a)

This experimental design enabled the development of a design space, ensuring robustness and reproducibility of 3D-printed sustained-release tablets.

C. Formulation Design

Three formulations were developed by varying polymer composition, while maintaining drug loading constant at 5.3% w/w metformin HCl (Awad et al., 2020). The polymers selected were HPMC K4M, a hydrophilic release-retardant, and PVA, a thermoplastic filament-former commonly used in FDM printing (Goyanes et al., 2015b). Triethyl citrate (TEC) was included as a plasticizer (9.1% v/w) to improve filament flexibility (Alhijjaj et al., 2016).

Table 2. Composition of 3D-printed formulations

Component	OF (% w/w)	HPF (% w/w)	BPF (% w/w)
Metformin HCl	5.3	5.3	5.3
HPMC K4M	36.8	31.6	47.4
PVA	57.9	63.2	47.4
TEC* (v/w)	9.1	9.1	9.1

TEC: Triethyl citrate used as a plasticizer.

This ratio variation facilitated tailoring of drug release, with PVA ensuring mechanical strength, and HPMC prolonging drug release through matrix swelling and gel layer formation (Siepmann & Peppas, 2001).

D. Filament Preparation and 3D Printing

Drug–polymer blends were homogenized by geometric dilution (15 min in mortar and pestle), ensuring uniform distribution (Patel et al., 2017). Blends were processed into filaments by hot-melt extrusion (HME) using Noztek® Pro extruder, operated at a temperature profile of 100°C → 120°C → 110°C and screw speed of 20 rpm (Goyanes et al., 2015a).

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Filaments were directly utilized in a Creality Ender-3 fused deposition modeling (FDM) 3D printer. The tablet design was 10 mm diameter × 4 mm thickness, created using Ultimaker Cura 5.0 slicing software (Afsana et al., 2022). Post-printing, tablets were conditioned at 40°C for 24 h, to reduce residual moisture and improve dimensional stability (Tagami et al., 2017).

E. Methodology: Box-Behnken Design of Experiments

Three key 3D printing parameters were selected for this study, each examined at low (−1), medium (0), and high (+1) levels. These parameters influence both the physical quality of the printed tablets and their drug release performance (Alhnan et al., 2016).

Printing temperature (A): Set at 150 °C, 165 °C, and 180 °C, this factor ensures proper polymer melting and interlayer adhesion, which are essential for tablet integrity. The range was chosen around the glass transition temperature of the polymer.

Layer height (B): Tested at 0.1 mm, 0.2 mm, and 0.3 mm, this parameter affects surface smoothness, density, and dissolution behavior. Lower values produce denser, smoother tablets, while higher values lead to more porous structures.

Infill density (C): Set at 80%, 90%, and 100%, infill determines internal porosity and mechanical strength. Higher densities yield stronger but slower-releasing tablets, while lower densities promote faster drug release (Kempin et al., 2017).

F. Experimental Design Matrix

A Box–Behnken design (BBD) was employed to evaluate the effects of three critical 3D printing parameters—printing temperature, layer height, and infill density—on tablet performance. This design is widely used in pharmaceutical formulation studies because it provides efficient estimation of linear, quadratic, and interaction effects with fewer experimental runs compared to full factorial designs (Ferreira et al., 2007).

In the BBD, experimental runs are positioned at the midpoints of the edges of the cubic design space and at center points. This setup enables systematic evaluation of how factor variations influence response outcomes such as drug release (Bezerra et al., 2008).

The design matrix and corresponding Q60 (% drug released at 60 minutes) results are summarized in **Table 1**.

Table 1. Box–Behnken Experimental Design Matrix

Run	Printing temperature (°C)	Layer height (mm)	Infill density (%)
1	150	0.1	90
2	180	0.1	90
3	150	0.3	90
4	180	0.3	90
5	150	0.2	80
6	180	0.2	100
7	150	0.2	80
8	180	0.2	100
9	165	0.1	80
10	165	0.3	80
11	165	0.1	100
12	165	0.3	100
13	165	0.2	90
14	165	0.2	90
15	165	0.2	90

G. Characterization of 3D-Printed Tablets

Solid-State Characterization

X-ray Powder Diffraction (XRPD): XRPD analysis was performed using a Bruker D8 Advance diffractometer, scanning over a 2θ range of 5–60° with a step size of 0.02°. This technique was used to evaluate the crystalline or amorphous nature of the drug, as well as possible drug–polymer interactions. Sharp, intense peaks in the diffractograms are indicative of crystalline domains, whereas broad halos suggest amorphous states or molecular dispersion within the polymer matrix. Such analysis provides crucial insights into changes in crystallinity following formulation processes (Alhijjaj et al., 2016). Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA): DSC studies were conducted using a TA Instruments Q2000 DSC, with samples heated at a

rate of 10 °C/min under nitrogen flow to evaluate glass transition temperature (Tg), melting behavior, and miscibility between the drug and polymer. Complementary TGA analysis was performed on a PerkinElmer STA 6000 system under identical conditions to assess the thermal stability and decomposition profile of the formulations. The combined use of DSC and TGA enables detection of physical transitions, interaction between excipients and drug, and degradation patterns, providing a comprehensive understanding of thermal properties and stability (Awad et al., 2020).

H. In vitro Drug Release Studies

Drug release studies were carried out using USP dissolution apparatus II (paddle type, Electrolab, Mumbai, India) at 50 rpm and 37 ± 0.5 °C. The dissolution medium consisted of 900 mL of 0.1 mol/L hydrochloric acid (HCl) for the first 2 hours, followed by phosphate buffer at pH 6.8 for the remaining 10 hours to simulate gastrointestinal transit. To avoid disturbance of the dosage form during the media change, each tablet was placed in a stainless-steel sinker at the start of the study. After 2 hours, approximately 750 mL of the acidic medium was withdrawn using a narrow cannula with minimal turbulence, and an equivalent volume of pre-warmed (37 ± 0.5 °C) phosphate buffer was gently replaced along the vessel wall. Sampling was performed at predetermined time intervals, filtered through a 0.45 µm membrane filter (Nunc, New Delhi, India), and analyzed at 233 nm using a UV-visible spectrophotometer (Shimadzu UV-1700, Shimadzu Corporation, Japan). The studies were performed in triplicate, and cumulative drug release was plotted against time to generate release profiles (Shah et al., 1998).

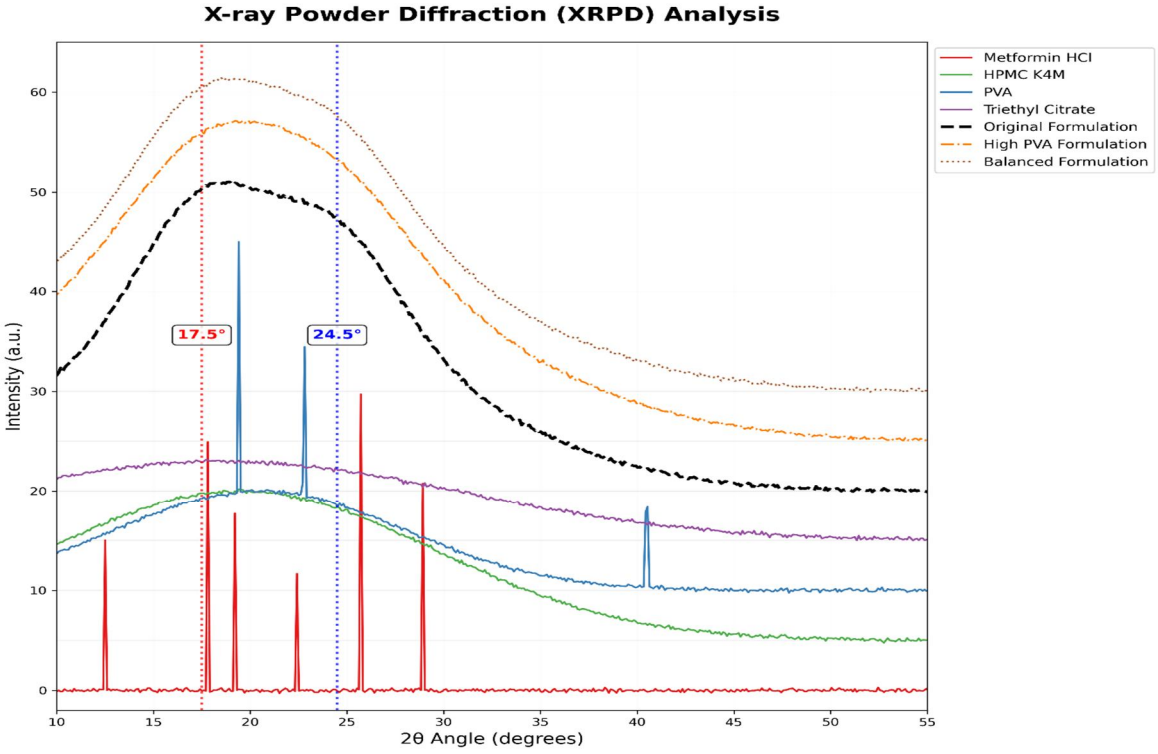
I. Data Analysis & Modeling

The dissolution profile was quantified using model-independent, integral metrics—particularly similarity factors f_1 (difference factor) and f_2 (similarity factor). Multi-response modeling approaches were employed, including multiple regression and multivariate optimization, to develop predictive models for quality outcomes.

III. RESULTS AND DISCUSSION

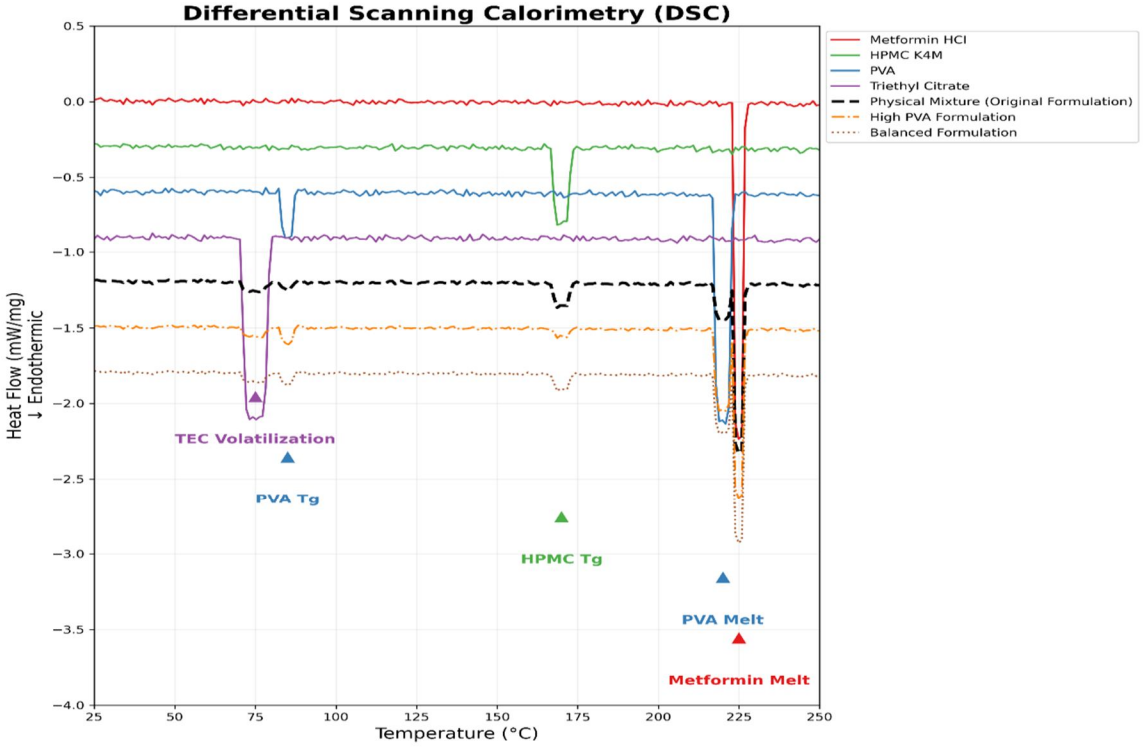
A. X-Ray Powder Diffraction (XRPD)

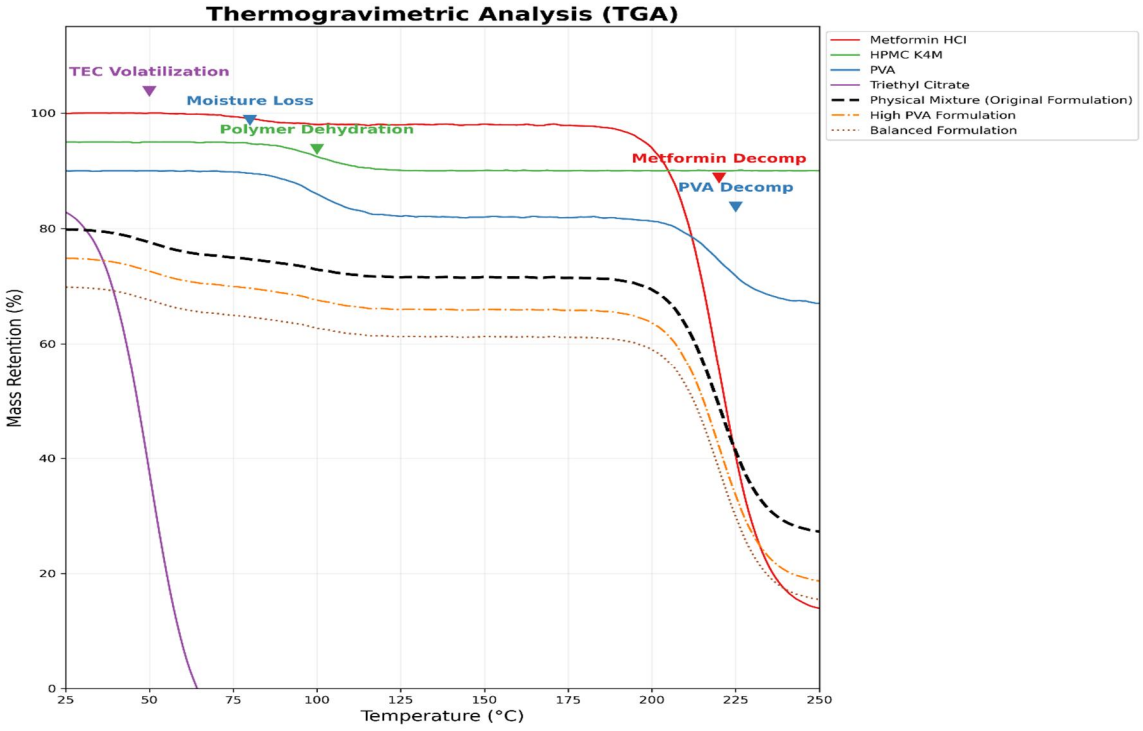
XRPD scans of pure metformin showed distinct diffraction peaks at 17.5° and 24.5°, indicative of its crystalline nature. In contrast, FDM-printed tablets displayed complete absence of these peaks, confirming **amorphization** of the drug during extrusion and printing. This transformation suggests the formation of a stable solid dispersion.



B. Thermal Analysis (DSC and TGA)

Thermogravimetric analysis (TGA) revealed that both pure metformin HCl and filaments exhibited minimal weight loss below 180 °C (3.0 ± 0.1% for metformin, 4.1 ± 0.3% for HPF filaments), confirming **thermal stability** of the system at the extrusion and printing temperature range. At 600 °C, residues of 5.2 ± 0.3% (drug) and 12.9 ± 0.4% (filaments) were observed, corresponding to polymeric decomposition (Table 1). Differential scanning calorimetry (DSC) further confirmed **molecular dispersion** of the drug within the polymer matrix, as the sharp endothermic melting peak of crystalline metformin HCl at 233 °C was absent in the DSC thermograms of the HPF .





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C. In Vitro Drug Release Studies

The prepared 3D printed sustained release tablets of Metformin were evaluated for drug content uniformity, infrared (IR) compatibility, and in-vitro dissolution profiles. The drug content was found to be in the range of 94–98%, confirming uniform distribution within acceptable pharmacopeial limits (±5%).

Drug release studies were conducted using USP dissolution apparatus II (paddle type, Electrolab, Mumbai, India) operated at 50 rpm and maintained at 37 ± 0.5 °C. The dissolution medium consisted of 900 mL of 0.1 mol/L hydrochloric acid (HCl) for the initial 2 hours, followed by phosphate buffer (pH 6.8) for the remaining 10 hours, thereby simulating gastrointestinal transit conditions. The cumulative drug release profiles are summarized in Table 1.

Table 1: Comparative Dissolution Profile (%)

Time (h)	Glucophage XR	Original Formulation	High PVA Formulation	Balanced Formulation
0	0.0	0.0	0.0	0.0
2	43.7	42.5	49.6	33.9
4	54.9	55.7	62.3	47.3
6	71.7	70.3	74.5	65.0
8	90.4	88.5	92.6	82.3
10	99.1	97.7	98.5	93.5
12	101.4	100.5	100.2	100.0

To further evaluate similarity, F1 (dissimilarity factor) and F2 (similarity factor) were calculated against Glucophage XR.

Table 2: F1 and F2 Similarity Factors

Formulation	F1 (%)	F2 Similarity	Conclusion
Original Formulation	1.65	89.07	Similar
High PVA Formulation	4.36	68.41	Similar
Balanced Formulation	8.50	57.40	Similar

The results confirmed that all three test formulations were similar to the reference (Glucophage XR), as the F2 values were >50. Among them, the Original Formulation (F2 = 89.07) demonstrated the closest match to the reference product, followed by the High PVA Formulation (F2 = 68.41) and the Balanced Formulation (F2 = 57.40).

D. Dissolution Efficiency (DE)

To further evaluate and compare the release performance of the formulations, Dissolution Efficiency (DE) was calculated. Dissolution efficiency is defined as the area under the dissolution curve (AUC) up to a specified time (t), expressed as a percentage of the area of a rectangle representing 100% dissolution over the same time period. It provides a single quantitative parameter that reflects both the rate and extent of drug release (Khan and Rhodes, 1972).

Mathematically, DE is expressed as:

$$\text{DE (\%)} = \int_0^t \frac{Q(t)dt}{Q100 * t} * 100$$

where:

- Q(t) = percentage of drug dissolved at time t,
- Q_{100}= 100% drug release,
- t = selected time point for calculation.

In the present study, DE values were computed over a 12-hour period for Glucophage XR (reference) and the three test formulations. The comparison is summarized below:

- High PVA Formulation: 71.25% → Highest DE, indicating the most efficient drug release.
- Glucophage XR: 68.26% → Second highest, confirming the robustness of the reference.
- Original Formulation: 67.45% → Slightly lower than Glucophage XR, but still comparable.
- Balanced Formulation: 62.00% → Lowest DE, suggesting slower and less efficient release.

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These results highlight that the High PVA Formulation provided the most efficient drug release, even exceeding that of the marketed reference, while the Balanced Formulation showed the least efficiency, consistent with its lower F2 similarity factor.

Drug Release Kinetics

To elucidate the release mechanisms of Glucophage XR and the test formulations, dissolution data were fitted to common kinetic models: Zero-order, First-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas. The mathematical models and their mechanistic interpretations are summarized in Table 1.

Table 1: Kinetic Models and Mechanisms

Model	Equation	Mechanism
Zero-order	$Q=k_0 \cdot t$	Constant release rate
First-order	$\ln(100-Q) = \ln(100) - k_1 \cdot t$	Concentration-dependent release
Higuchi	$Q=k_h \cdot \sqrt{t}$	Diffusion-controlled matrix release
Hixson-Crowell	$100^{1/3} - (100-Q)^{1/3} = k_{hc} \cdot t$	Erosion-controlled dissolution
Korsmeyer–Peppas	$Q=k_{kp} \cdot t^n$	Combined diffusion/erosion

The correlation coefficients (r^2) and kinetic constants obtained from model fitting are summarized in **Table 2**.

Table 2: Kinetic Model Parameters

Formulation	Zero-order r^2	Zero-order k	First-order r^2	First-order k	Higuchi r^2	Higuchi k	Hixson-Crowell r^2	Hixson-Crowell k	Korsmeyer–Peppas n	Korsmeyer–Peppas k
Glucophage XR	0.827	10.077	0.971	0.249	0.989	30.180	-0.550	0.083	0.520	28.939
Original Formulation	0.830	9.947	0.976	0.242	0.992	29.788	-0.525	0.083	0.520	28.569
High PVA Formulation	0.722	10.230	0.979	0.281	0.985	30.898	-0.837	0.083	0.426	35.986
Balanced Formulation	0.921	9.452	0.971	0.201	0.979	28.015	-0.168	0.083	0.643	20.782

Interpretation:

The highest correlation ($r^2 = 0.992$) was observed for the Original Formulation with the Higuchi model, indicating a diffusion-controlled release mechanism. Similar behavior was observed for Glucophage XR ($r^2 = 0.989$) and the High PVA Formulation ($r^2 = 0.985$).The Balanced Formulation also showed strong Higuchi fitting ($r^2 = 0.979$), but it exhibited a higher Zero-order correlation ($r^2 = 0.921$) compared to other formulations, suggesting a tendency towards constant release kinetics.The First-order model also fitted well across all formulations (r^2 ~0.97–0.98), supporting a concentration-dependent release component. The Korsmeyer–Peppas model provided additional mechanistic insights: For Glucophage XR and the Original Formulation, the release exponent $n \approx 0.52$ approx , suggesting anomalous (non-Fickian) transport, where both diffusion and erosion contribute.

The High PVA Formulation exhibited a lower n=0.426, consistent with Fickian diffusion being predominant.

The Balanced Formulation showed the highest n= 0.643, indicating a stronger contribution from erosion-controlled release.

Overall, the results suggest that Glucophage XR and the Original Formulation closely follow Higuchi kinetics with anomalous diffusion, whereas the High PVA Formulation is more diffusion-driven, and the Balanced Formulation shows a mixed profile with a stronger Zero-order and erosion component.

E. Box–Behnken Experimental Design DoE

The Box–Behnken design generated a total of 15 experimental runs, including three replicates at the center point, which are essential for estimating pure error and detecting curvature in the response surface. Each run corresponded to a unique combination of printing temperature, layer height, and infill density, with the resulting Q_{60} values (cumulative drug release at 60 minutes) summarized in Table 1. All observed Q_{60} values were within the target range of 45–75% drug release at 60 minutes, consistent with the requirements for sustained-release dosage forms.

Following fabrication, the 3D-printed tablets underwent a series of characterization tests, including in vitro dissolution studies to determine Q_{60} values. These experimental results served as response variables for subsequent statistical analysis.

Statistical modeling was performed using R software, where regression analysis was applied to construct quadratic response surface models. Analysis of Variance (ANOVA) was used to evaluate the significance of individual factors and their interactions on Q_{60}. Regression equations were derived to describe the quantitative relationships between process variables and drug release, enabling prediction of tablet performance under different printing conditions. In addition, contour plots and three-dimensional response surface plots were generated to visually illustrate factor effects and to identify optimal processing conditions for achieving the desired sustained-release profile, specifically targeting the 45–75% Q_{60} range.

Box–Behnken Experimental Design Matrix and Q60 results

Run	Printing temperature (°C)	Layer height (mm)	Infill density (%)	Q60 (%)
1	150	0.1	90	60.91
2	180	0.1	90	65.00
3	150	0.3	90	62.97
4	180	0.3	90	68.00
5	150	0.2	80	69.45
6	180	0.2	100	72.00
7	150	0.2	80	65.00
8	180	0.2	100	70.00
9	165	0.1	80	59.72
10	165	0.3	80	63.00
11	165	0.1	100	61.30
12	165	0.3	100	66.00
13	165	0.2	90	64.00
14	165	0.2	90	64.50
15	165	0.2	90	63.50

F. Statistical Modeling and ANOVA Summary

OLS Regression Results

Dep. Variable:	Q60	R-squared:	0.895
Model:	OLS	Adj. R-squared:	0.705
Method:	Least Squares	F-statistics:	4.711
Date:	Sat, 26 Jul 2025	Prob (F-statistics):	0.0513
Time:	10:38:09	Log-Likelihood:	-22.786
No. Observations:	15	AIC:	65.57
Df Residuals:	5	BIC:	72.65
Df Model:	9		
Covariance Type:	**no robust**		

	coef	std err	t	P>|t|	[0.025	0.975]
Intercept	64.0000	1.105	57.903	0.000	61.159	66.841
Temp_coded	2.1375	0.677	3.158	0.025	0.398	3.877
Layer_coded	-0.1738	0.677	-0.257	0.808		

-1.914	1.566				
Infill_coded		1.5163	0.677	2.240	0.075
-0.224	3.256				
I (Temp_coded ** 2)		-3.1938	0.996	-3.206	0.024
-5.755	-0.633				
I (Layer_coded ** 2)		3.4137	0.996	3.426	0.019
0.853	5.975				
I (Infill_coded ** 2)		1.6987	0.996	1.705	0.149
-0.862	4.260				
Temp_coded:Layer_coded		0.2350	0.957	0.246	0.816
-2.226	2.696				
Temp_coded:Infill_coded		0.3550	0.957	0.371	0.726
-2.106	2.816				
Layer_coded:Infill_coded		**0.6125**	**0.957**	**0.640**	**0.550**
-1.848	**3.073**				

Omnibus:	1.191	Durbin-Watson:	1.405
Prob(Omnibus):	0.551	Jarque-Bera (JB):	0.760
Skew:	0.000	Prob(JB):	0.684
Kurtosis:	**1.898**	**Cond. No.**	**4.24**

Notes:
[1] Standard Errors assume that the covariance matrix of the errors is correctly specified.

--- ANOVA Table (Type II Sum of Squares) ---

	sum_sq	df	F	PR(>F)
Temp_coded	36.551250	1.0	9.973015	0.025151
Layer_coded	0.241513	1.0	0.065897	0.807636
Infill_coded	18.392113	1.0	5.018291	0.075200
I (Temp_coded ** 2)	37.661683	1.0	10.275997	0.023845
I (Layer_coded ** 2)	43.029006	1.0	11.740472	0.018707
I(Infill_coded ** 2)	10.655083	1.0	2.907241	0.148902
Temp_coded:Layer_coded	0.220900	1.0	0.060273	0.815824
Temp_coded:Infill_coded	0.504100	1.0	0.137544	0.725929

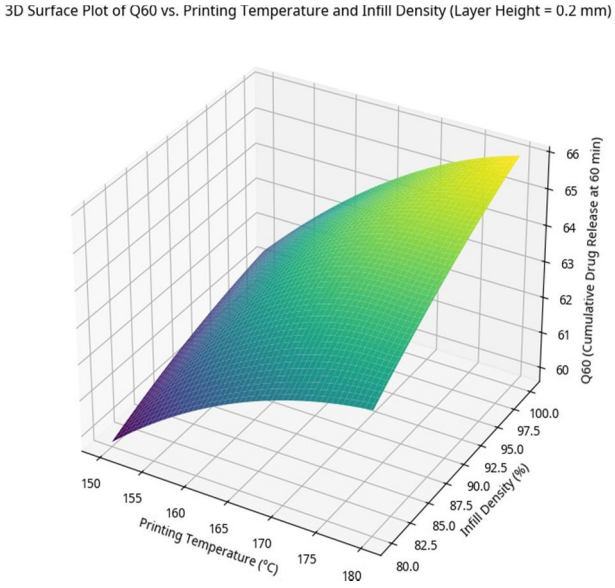
The statistical analysis reveals that the model is significant (F-statistic = 4.711, p-value= 0.0513), indicating that the selected factors have a collective impact on Q60. The R- squared value of 0.895 suggests that the model explains approximately 89.5% of the variability in Q60. Notably, Printing Temperature and the quadratic terms for Printing Temperature and Layer Height are statistically significant factors affecting Q60. Infill Density shows a marginal significance. The interactions between factors are not statistically significant.

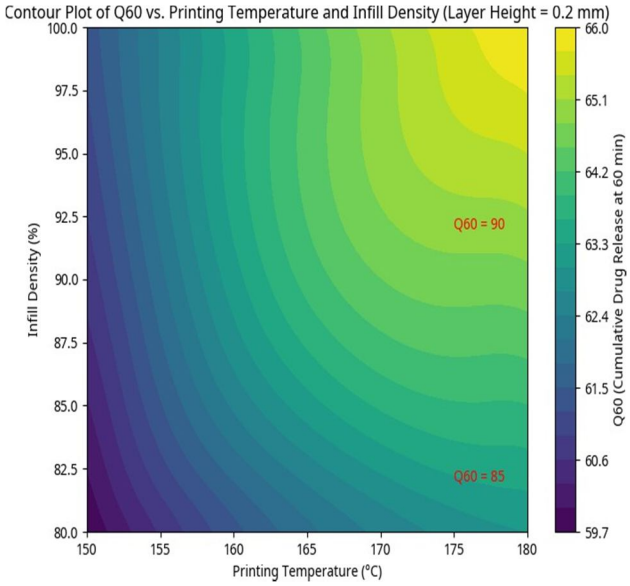
G. 3D Surface and Contour Plot

The 3D surface and contour plots illustrate the influence of printing temperature and infill density on Q60 (cumulative drug release at 60 minutes) at a fixed layer height of 0.2 mm.

The contour plot highlights the optimization space, focusing on the target Q60 range of 45–75%, which corresponds to the desired sustained-release profile.

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H. Optimized Formulation Parameters

Based on statistical modeling and ANOVA, the optimized formulation was identified to meet the target Q60 range (45–75%).

Key Findings from Statistical Analysis

Model Significance: The model was statistically significant ($F = 4.711$, $p = 0.0513$), indicating that the selected process parameters collectively influence Q60.

Coefficient of Determination: An R^2 value of 0.895 and an Adjusted R^2 of 0.705 confirm that the model explains a substantial portion of Q60 variability.

Significant Factors and Their Effects on Q60

Printing Temperature (Coded Coefficient: +2.1375): Significant ($p = 0.025$). A positive effect indicates that higher printing temperatures increase Q60.

Infill Density (Coded Coefficient: +1.5163): Marginally significant ($p = 0.075$). Higher infill density tends to increase Q60.

Quadratic Effect of Printing Temperature (Coefficient: -3.1938): Significant ($p = 0.024$). The negative effect suggests non-linearity, with Q60 plateauing or decreasing at higher temperatures.

Quadratic Effect of Layer Height (Coefficient: +3.4137): Significant ($p = 0.019$). The positive effect indicates a non-linear relationship, where both very low and very high layer heights deviate from the optimal range, while a mid-range height supports sustained release.

I. Optimized Parameters for Sustained Release (Q60: 45–75%)

To achieve the desired sustained-release range, the following considerations were made:

Printing Temperature: Lower temperatures (150–165 °C) help achieve Q60 values near the lower bound of the target range, while mid-range (~165 °C) balances release.

Infill Density: Moderate values (~85–90%) are optimal; higher infill tends to increase Q60 excessively.

Layer Height: A mid-range value (~0.2 mm) is optimal due to the quadratic effect, preventing over-release or under-release.

At the design center point (165 °C, 0.2 mm, 90% infill), the observed Q60 values were 63.5–64.5%, aligning precisely with the sustained-release target window.

Predicted Q60 at Center Point

Using the regression model, the predicted Q60 at the center point (Temp = 165 °C, Layer = 0.2 mm, Infill = 90%) is:

$Q\,60 = 64.0\%$

This predicted value falls well within the 45–75% sustained-release target, confirming the suitability of these optimized parameters.

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IV. CONCLUSION

This study successfully demonstrated the development of generic sustained-release 3D-printed Metformin HCl tablets using hot-melt extrusion and fused deposition modeling. Solid-state analysis confirmed the complete amorphization of Metformin within the polymer matrix, ensuring stability during processing. Dissolution studies revealed that all formulations achieved controlled release over 12 hours, with the Original Formulation showing the highest similarity (f_2 = 89.07) to the reference product *Glucophage XR*. Release kinetics were best explained by the Higuchi model, indicating diffusion-controlled drug release, with variations in erosion contribution depending on formulation design.

Overall, the results confirm that FDM 3D printing can be a reliable platform for producing robust sustained-release oral dosage forms, while formulation optimization via DoE enables precise (Yu et al., 2014) tailoring of drug release profiles.

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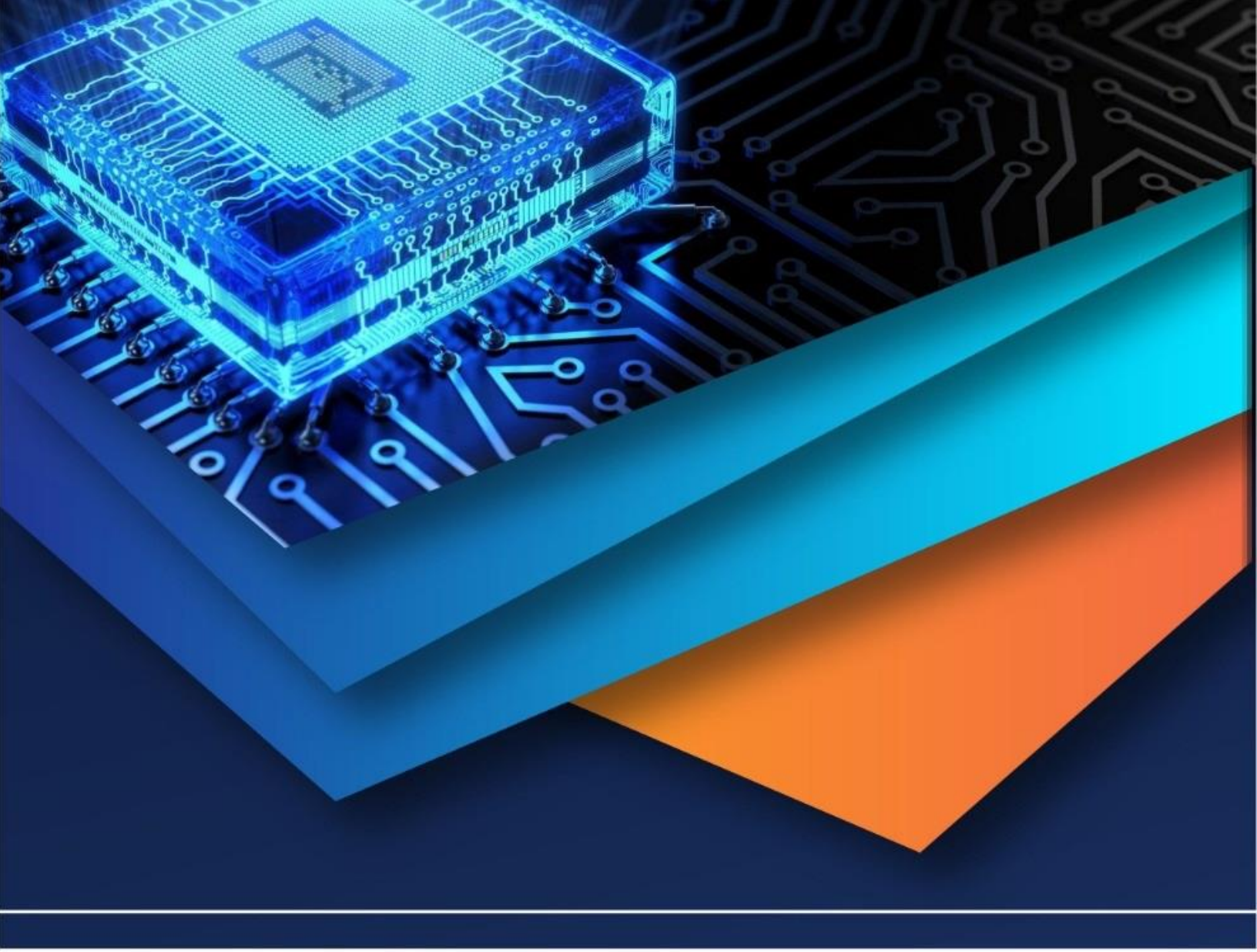
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