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Evaluation of 3D Printed Personalized Drug Delivery Systems Using Quality by Design Principles

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ABSTRACT

Once a 3D printed personalized dosage form has been developed, the harder and arguably more consequential question becomes whether it can be trusted, and answering that requires an evaluation framework rigorous enough to satisfy both clinicians and regulators. This study focuses squarely on the evaluation of 3D printed personalized oral drug delivery systems produced by fused deposition modelling, applying Quality by Design principles not to invent a formulation but to structure a systematic, risk-based assessment of quality. Beginning from a defined target product profile, the critical quality attributes of a personalized tablet were established, and a comprehensive evaluation was designed to test each attribute against acceptance criteria, with the influence of key variables interpreted through a design-of-experiments lens. Printed tablets across a range of infill densities and geometries were evaluated for dimensional accuracy, mass and content uniformity, mechanical strength, disintegration and dissolution behaviour, release kinetics and mechanism, drug-polymer compatibility, and physical stability under accelerated conditions. Dimensional fidelity was high and mass and content uniformity fell within acceptable limits, confirming reproducible manufacture. Drug release was strongly and predictably governed by infill density, and kinetic modelling indicated a diffusion-and-matrix mechanism consistent with the internal structure. Thermal and spectroscopic analyses confirmed that the drug remained chemically intact and dispersed within the polymer, addressing the principal thermal-stability concern of the technique, and accelerated stability testing showed the tablets retained their critical attributes over the study period. Framing the evaluation within QbD allowed the results to be interpreted not as isolated pass-or-fail tests but as evidence about a controllable design space. The study demonstrates that a QbD-structured evaluation provides the depth of quality assurance that personalized 3D printed medicines will require before clinical adoption, and highlights dissolution behaviour and stability as the attributes most deserving of ongoing control.

KEYWORDS: Three-dimensional printing, evaluation, Quality by Design, personalized medicine, dissolution, stability

INTRODUCTION

The promise of 3D printed personalized medicines is by now widely appreciated: the ability to fabricate a dosage form with a dose, size, shape, and release profile tailored to an individual patient addresses a genuine and long-standing gap in a pharmaceutical system built around mass-produced, fixed-dose units [1]. As the technology has matured from proof-of-concept toward the threshold of clinical use, however, the centre of gravity of the challenge has shifted. The question is no longer only whether such tablets can be printed, which has been amply demonstrated, but whether the printed product can be shown to meet the standards of quality, safety, and reliability that any medicine must satisfy before it reaches a patient [2]. Evaluation, in other words, has become as important as fabrication.

This shift matters because personalized manufacturing inverts one of the assumptions on which conventional pharmaceutical quality control rests. Traditional quality assurance relies heavily on the statistical logic of large batches, where a sample can be taken to represent millions of identical units, but a personalized 3D printed

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product may be a batch of one, or a small run of individually specified tablets, for which that sampling logic does not straightforwardly apply [3]. This raises a real and practical difficulty: how does one assure the quality of a product that is, by design, different for every patient? The answer cannot be to test every attribute of every tablet destructively, so it must instead rest on demonstrating that the manufacturing process is understood and controlled well enough that quality can be relied upon, and on evaluating the product against critical attributes in a way that reflects that understanding [4].

Quality by Design provides exactly the philosophy needed for this. Rather than treating quality as something confirmed by end-product testing alone, QbD builds quality on process understanding, defining the critical quality attributes that must be controlled and relating them to the variables that influence them [5]. When applied to evaluation specifically, as this study does, QbD reframes the exercise: individual tests are no longer isolated hurdles but coordinated evidence about whether the product sits reliably within an understood and acceptable region of behaviour. This is a more powerful and more appropriate stance for personalized products than a conventional checklist of release specifications, because it accommodates variation by design while still assuring quality.

The particular technology examined here, fused deposition modelling, is the most accessible and widely studied route to printed oral tablets, but it carries characteristic features that make thorough evaluation essential [6]. Its reliance on melting a drug-loaded filament raises persistent concerns about thermal degradation of the drug, its layer-by-layer construction can introduce dimensional and structural variability, and its exploitation of internal infill to control release means that release behaviour is intimately tied to printing parameters in ways that must be verified rather than assumed [7]. Each of these features corresponds to a critical quality attribute that a rigorous evaluation must probe.

Despite the clear importance of evaluation, much of the literature has concentrated on demonstrating novel printing capabilities, with comparatively less emphasis on comprehensive, QbD-structured evaluation of the resulting products against the full range of critical quality attributes, including the stability behaviour that determines shelf life. This leaves a gap between showing that a personalized tablet can be made and showing that it can be trusted over its intended use. The present study addresses that gap by conducting a systematic, QbD-framed evaluation of 3D printed personalized tablets.

The specific aims were threefold. First, to define, within a QbD framework, the critical quality attributes that a comprehensive evaluation of a personalized 3D printed tablet must address. Second, to evaluate printed tablets across a range of infill densities and geometries against those attributes, including dimensional accuracy, uniformity, mechanical strength, disintegration and dissolution, release kinetics, and drug-polymer compatibility. Third, to assess the physical stability of the tablets under accelerated conditions and to interpret the whole body of evaluation evidence in terms of the controllability of the product. The remainder of the paper reviews the relevant literature on evaluation of printed medicines, details the QbD-structured evaluation methodology and experimental setup, presents the evaluation results with supporting figures and tables, and discusses their implications for the quality assurance of personalized 3D printed medicines.

LITERATURE REVIEW

The literature relevant to evaluating 3D printed medicines spans the methods used to characterise dosage forms, the particular quality challenges introduced by additive manufacturing, and the QbD philosophy that increasingly frames how such evaluation should be conducted and interpreted. Together these define the context for a study focused specifically on evaluation.

Characterisation of oral solid dosage forms rests on a well-established repertoire of tests, and the pharmaceutical literature has long treated attributes such as uniformity of mass and content, mechanical strength, disintegration, and dissolution as the core measures of quality [8]. Dissolution testing in particular has a central place, because the rate and extent of drug release govern how the drug becomes available for absorption, and standardised dissolution methods provide the primary in vitro window onto in vivo behaviour [9]. For controlled-release

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products especially, characterising not just the rate of release but its underlying mechanism through kinetic modelling has become standard practice, allowing researchers to distinguish diffusion-controlled from erosion-controlled release and to understand why a given formulation behaves as it does [10].

When these established methods are applied to 3D printed tablets, characteristic new considerations arise. A recurring theme in the literature is that internal geometry, and infill density in particular, exerts a dominant influence on drug release from printed tablets, so that the same filament can yield very different release profiles depending on how densely the interior is filled [11]. This makes dissolution evaluation across a range of infill settings especially informative, since it maps the release behaviour that personalization exploits. Studies have also drawn attention to the dimensional fidelity of printed tablets, noting that the accuracy with which a printer reproduces the intended design is itself a quality attribute, because deviations translate into dose and behaviour errors [12].

The thermal dimension of fused deposition modelling has generated its own substantial evaluation literature. Because the technique melts a drug-loaded filament, the potential for thermal degradation of the drug is a persistent concern, and solid-state characterisation through thermal analysis and spectroscopy has become a standard part of evaluating printed tablets, used to confirm both that the drug remains chemically intact and to determine whether it exists in crystalline or amorphous form within the matrix [13]. The physical state of the drug matters because it influences both dissolution and stability, and printed tablets frequently show partial or complete conversion of the drug to an amorphous dispersion during melt processing [14].

Stability evaluation, while fundamental to any medicine, has received comparatively less attention in the printed-medicines literature than fabrication and immediate characterisation, yet it is critical because amorphous dispersions and printed structures may change over time [15]. The QbD philosophy that increasingly frames pharmaceutical development provides the organising logic for pulling all of these evaluation threads together, treating the various tests as coordinated evidence about the control of critical quality attributes rather than as isolated checks, and reviews of the field have argued that this systematic, risk-based approach is exactly what is needed to bring 3D printed medicines to clinical and regulatory acceptance [16]. The present study responds to that argument by structuring a comprehensive evaluation, including stability, within an explicit QbD frame.

METHODOLOGY

3.1 Quality by Design Framework for Evaluation

The evaluation was structured according to Quality by Design logic, meaning it began not with a list of tests but with a definition of what quality meant for the product. A target product profile for a personalized oral tablet specified the essential requirements: accurate and variable dose, swallowable dimensions, adequate mechanical strength, uniform drug content, tunable and reproducible release, chemical integrity of the drug, and stability over the intended period of use. From this profile, the critical quality attributes to be evaluated were derived as dimensional accuracy, mass and content uniformity, mechanical strength, disintegration and dissolution behaviour, release mechanism, drug-polymer compatibility and solid state, and physical stability [17].

3.2 Test Samples

The tablets subjected to evaluation were oral cylindrical tablets fabricated by fused deposition modelling from a drug-loaded thermoplastic filament, printed across a deliberately chosen range of infill densities and, for a subset, differing external geometries, so that the evaluation would capture the span of behaviour that personalization produces rather than a single design point. Holding external dimensions constant while varying infill for the primary series allowed the influence of internal structure on the evaluated attributes to be assessed cleanly.

3.3 Risk-Based Prioritisation of Attributes

Consistent with the QbD framework, a risk assessment was used to prioritise the critical quality attributes according to their likely impact on safety and efficacy and their sensitivity to manufacturing variation. Dissolution behaviour, being both directly linked to therapeutic effect and highly sensitive to printing

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parameters, was prioritised as the attribute demanding the most thorough evaluation, followed by content uniformity, drug integrity, and stability. This prioritisation shaped the depth of testing applied to each attribute [18].

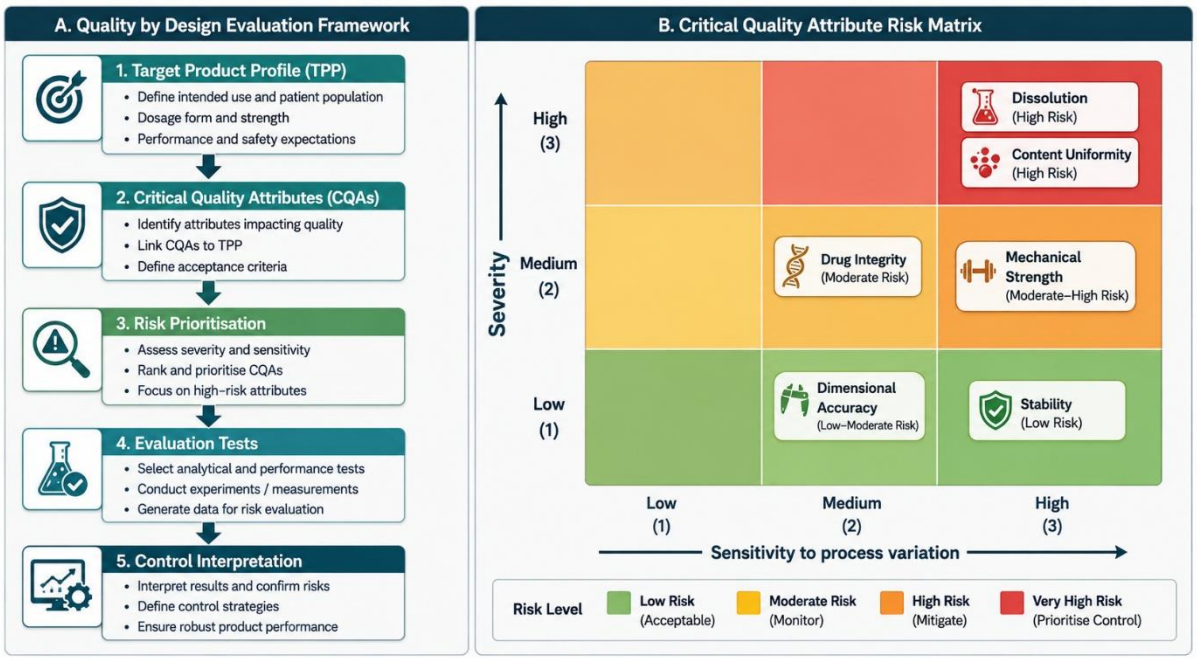

Figure 1. Quality by Design evaluation framework and critical quality attribute risk matrix.

3.4 Interpretive Design-of-Experiments Lens

While this study centred on evaluation rather than formulation development, the influence of the primary process variable, infill density, on the evaluated responses was interpreted through a design-of-experiments perspective, relating the measured attributes to the input setting quantitatively. The dependence of a response Y on infill density X across the tested range was described by a fitted polynomial of the form

$$Y = \beta_0 + \beta_1 X + \beta_2 X^2 +$$

where β_0, β_1 and β_2 are the fitted coefficients capturing the linear and curvature effects and ε is the residual error. This allowed the evaluation results to be read as a controllable relationship rather than a set of disconnected observations.

EXPERIMENTAL SETUP

4.1 Dimensional and Physical Evaluation

Dimensional accuracy was evaluated by measuring the printed tablets and comparing the measured dimensions with the nominal values from the digital design, with the deviation expressed as a percentage. Mass uniformity was assessed by weighing individual tablets and computing the mean and relative standard deviation, where

$$RSD\ (\%) = \frac{s}{\bar{x}} \times 100$$

with s the standard deviation and \bar{x} the mean mass. These measures together established whether the printing process delivered reproducible physical units, which is the foundation on which all other quality claims rest.

4.2 Content Uniformity

Drug content was determined by dissolving individual tablets, diluting appropriately, and assaying the drug spectrophotometrically against a calibration curve, with content uniformity expressed as the mean percentage of the label claim and its relative standard deviation across tablets. Content uniformity is especially critical for a personalized product, since a printed tablet's dose accuracy depends on the homogeneity of the drug within the filament and the consistency of material deposition [19].

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4.3 Mechanical Strength and Disintegration

Mechanical strength was evaluated by measuring the breaking force required to fracture the tablet under diametral compression, ensuring the tablets could withstand handling. Disintegration behaviour was assessed under standard conditions to determine how the tablets broke down, which for the internal-infill designs studied is closely tied to how readily dissolution medium penetrates the structure.

4.4 Dissolution and Release Kinetics

Given its priority, dissolution received the most thorough evaluation. In vitro dissolution was conducted under standard paddle conditions in a suitable medium, with samples withdrawn at defined intervals and drug concentration determined spectrophotometrically to construct cumulative release profiles for tablets of differing infill density. To characterise the release mechanism, the profiles were fitted to the Korsmeyer-Peppas model,

$$\frac{M_t}{M_\infty} = k, t^{,n}$$

where M_t/M_∞ is the fraction released at time t, k is the kinetic constant, and n is the release exponent whose value classifies the transport mechanism. The similarity between dissolution profiles obtained under different conditions was compared quantitatively using the similarity factor,

$$f_2 = 50 \cdot \log\left\{\left[1 + \frac{1}{N}\sum_{t=1}^{N}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

where N is the number of time points and R_t and T_t are the percentages released from the reference and test profiles at time t, with values above the accepted threshold indicating equivalent profiles [20].

4.5 Drug-Polymer Compatibility and Solid-State Analysis

To confirm chemical integrity and determine the physical state of the drug, differential scanning calorimetry compared the thermal transitions of the drug, polymer, physical mixture, and printed tablet, and infrared spectroscopy compared characteristic absorption bands to detect any chemical interaction. These analyses directly probe the thermal-degradation risk inherent to fused deposition modelling.

4.6 Accelerated Stability Study

Physical stability was evaluated by storing printed tablets under accelerated conditions of elevated temperature and humidity for a defined period, with samples withdrawn at intervals and re-evaluated for the key critical quality attributes, principally drug content, dissolution behaviour, mechanical strength, and dimensional integrity. This addressed whether the printed structure and any amorphous drug dispersion remained stable over time, which determines shelf life.

4.7 Statistical Analysis

Evaluation data were expressed as mean ± standard deviation, and comparisons between groups, such as between infill densities or between stability time points, were made by analysis of variance with an appropriate post-hoc test at a significance threshold of $p < 0.05$. Fitted relationships between infill density and the evaluated responses were assessed through their coefficients of determination, and dissolution profile comparisons relied on the similarity factor described above.

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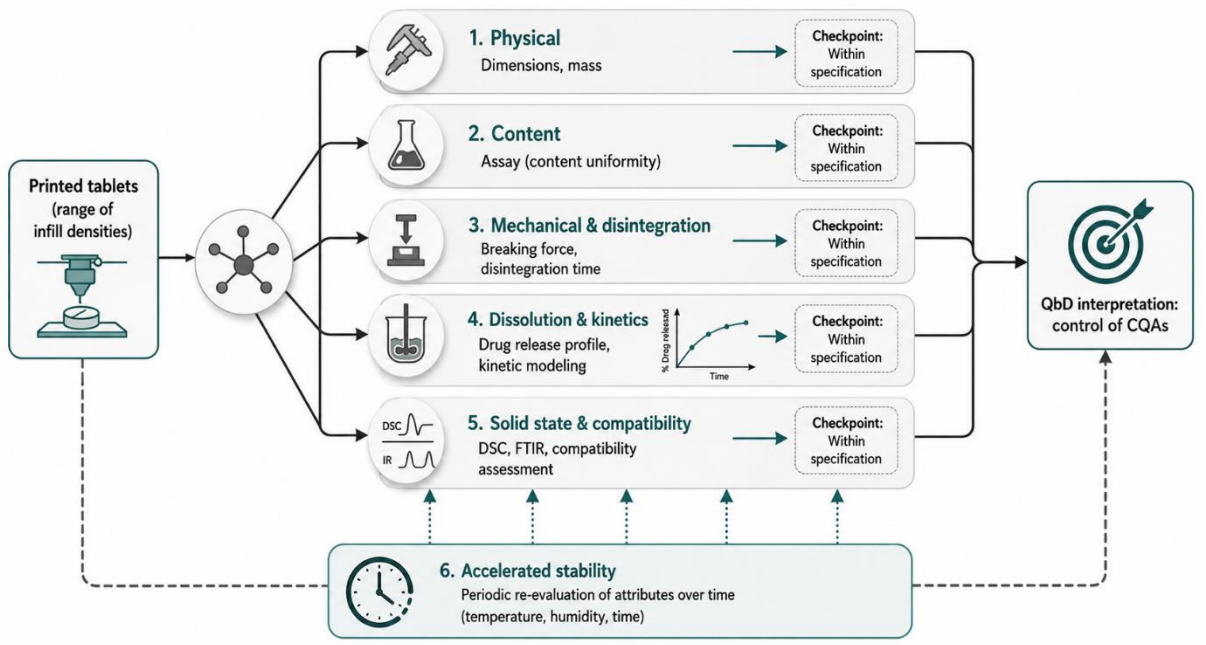

Figure 2. Comprehensive evaluation workflow across critical quality attributes.

RESULTS

5.1 Dimensional and Physical Evaluation

The printed tablets reproduced their intended designs closely, and the physical evaluation confirmed a reproducible manufacturing process. Dimensional deviations from the nominal design were small across the tablets, and mass uniformity was tight, with a low relative standard deviation, indicating consistent material deposition. Table 1 summarises the physical and content evaluation across a representative set of infill densities.

Table 1. Physical and content evaluation of printed tablets by infill density (mean ± SD).

Infill density (%)	Mean mass (mg)	Mass RSD (%)	Diameter deviation (%)	Drug content (%)	Content RSD (%)
20	168.4 ± 2.6	1.54	1.3	98.9 ± 1.7	1.72
40	204.7 ± 2.9	1.42	1.1	99.2 ± 1.5	1.51
60	241.3 ± 3.1	1.28	1.0	98.6 ± 1.8	1.83
80	278.6 ± 3.4	1.22	0.9	99.4 ± 1.4	1.41

Mass rose systematically with infill density, exactly as expected since a denser interior contains more material, while the relative standard deviation remained low throughout, confirming that deposition was consistent at every infill setting. Content uniformity was well within acceptable limits across the range, indicating that the drug was homogeneously distributed in the filament and that dose accuracy did not degrade as infill changed. Dimensional deviations were small and, if anything, tightened slightly at higher infill, consistent with a more solidly supported structure printing more faithfully.

5.2 Mechanical Strength and Disintegration

Mechanical evaluation showed that all tablets possessed adequate strength to survive handling, and that strength increased with infill density, reflecting the greater solid content of denser tablets. Disintegration behaviour varied in the opposite direction, with lower-infill tablets breaking down more readily because dissolution medium could penetrate their more open internal structure, foreshadowing the dissolution results.

5.3 Dissolution and Release Kinetics

Dissolution, the priority attribute, produced the most informative results. Release was strongly and systematically governed by infill density, with lower-infill tablets releasing drug rapidly and higher-infill tablets releasing it slowly and over a more extended period. Table 2 presents the release at a defined endpoint and the fitted kinetic parameters across infill densities.

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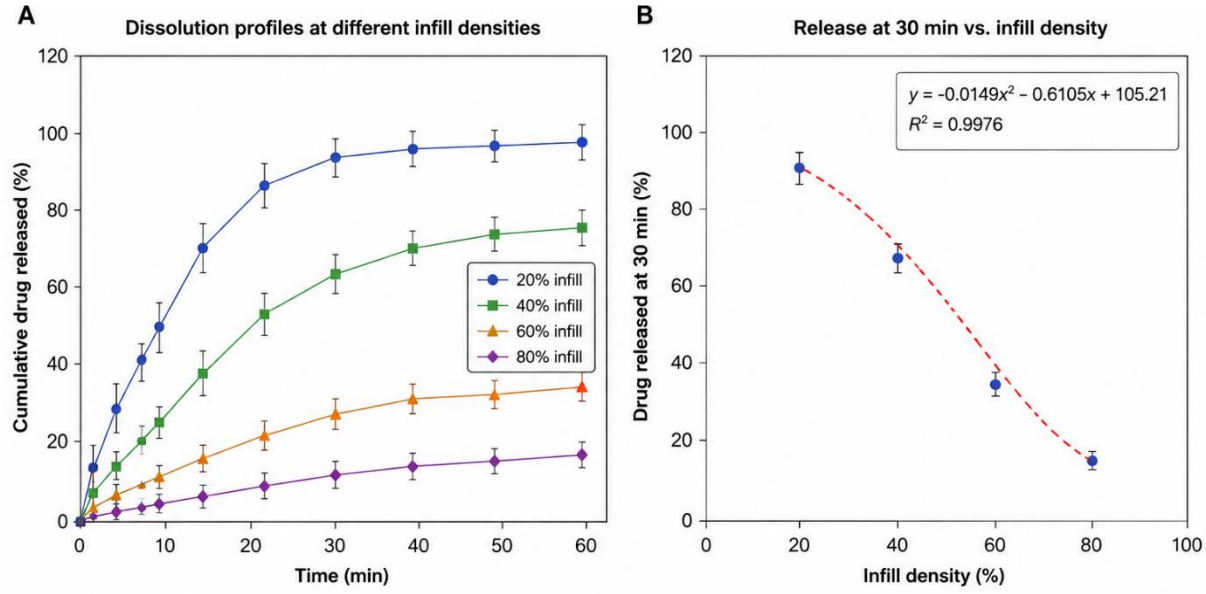
Table 2. Dissolution and release kinetics by infill density.

Infill density (%)	Release at endpoint (%)	Korsmeyer-Peppas n	Best-fit mechanism
20	91.6	0.48	Diffusion-dominated
40	74.2	0.53	Anomalous (diffusion + matrix)
60	58.7	0.57	Anomalous transport
80	41.3	0.61	Anomalous, matrix-influenced

The relationship between infill density and release was strong and well described by the fitted polynomial, with a high coefficient of determination, confirming that release could be treated as a controllable function of a single printing parameter. The Korsmeyer-Peppas exponent shifted gradually as infill increased, indicating a transition from more purely diffusion-driven release in open, low-infill structures toward increasingly matrix-influenced, anomalous transport in denser structures, which makes physical sense because a denser matrix lengthens the diffusional path and increases the contribution of the polymer network to controlling release.



(**A**) Dissolution profiles of 3D-printed tablets with different infill densities (20%, 40%, 60% and 80%) at 200 °C. Values are mean ± SD (n = 3). (**B**) Relationship between cumulative drug released at 30 min and infill density. Data points represent mean ± SD (n = 3) with quadratic regression fit (red dashed line).

Figure 3. Dissolution profiles and the infill-release relationship.

Profile comparison using the similarity factor confirmed that tablets printed at nominally identical settings produced equivalent dissolution profiles, with similarity factors comfortably above the accepted threshold, demonstrating reproducibility of release, while profiles at different infill densities were correctly distinguished as non-equivalent. This reproducibility is essential for a personalized product, because it means that specifying an infill density reliably specifies a release profile.

5.4 Drug-Polymer Compatibility and Solid State

The solid-state evaluation confirmed that the drug survived processing chemically intact and was dispersed within the polymer matrix. Thermal analysis showed the drug's characteristic melting endotherm substantially diminished in the printed tablet relative to the pure drug, indicating that much of the drug existed in a dispersed, partly amorphous state rather than as discrete crystals, consistent with melt-based processing. Infrared spectroscopy showed the characteristic drug absorption bands preserved without the appearance of new peaks, confirming the absence of chemical interaction between drug and polymer and thereby addressing the central thermal-degradation concern of fused deposition modelling.

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5.5 Accelerated Stability

The accelerated stability study showed that the tablets retained their critical quality attributes over the study period, which is a reassuring result given the known tendency of amorphous dispersions to change over time. Table 3 presents the key attributes at the start and end of the accelerated study.

Table 3. Critical quality attributes before and after accelerated stability storage (mean ± SD).

Attribute	Initial	After storage	Change
Drug content (%)	99.1 ± 1.5	97.8 ± 1.7	−1.3%
Release at endpoint (%)	58.7	56.9	−1.8%
Breaking force (N)	68.4 ± 2.7	70.1 ± 3.0	+1.7 N
Diameter deviation (%)	1.0	1.2	+0.2%

Drug content declined only marginally over the accelerated period, remaining within acceptable limits, and dissolution behaviour was essentially preserved, with the endpoint release changing only slightly and the profiles remaining similar by the similarity factor. Mechanical strength was maintained, showing a small increase that likely reflects minor relaxation or annealing of the printed structure under warm storage rather than any degradation, and dimensional integrity was retained. Taken together, these results indicate that the printed tablets were physically and chemically stable over the accelerated study.

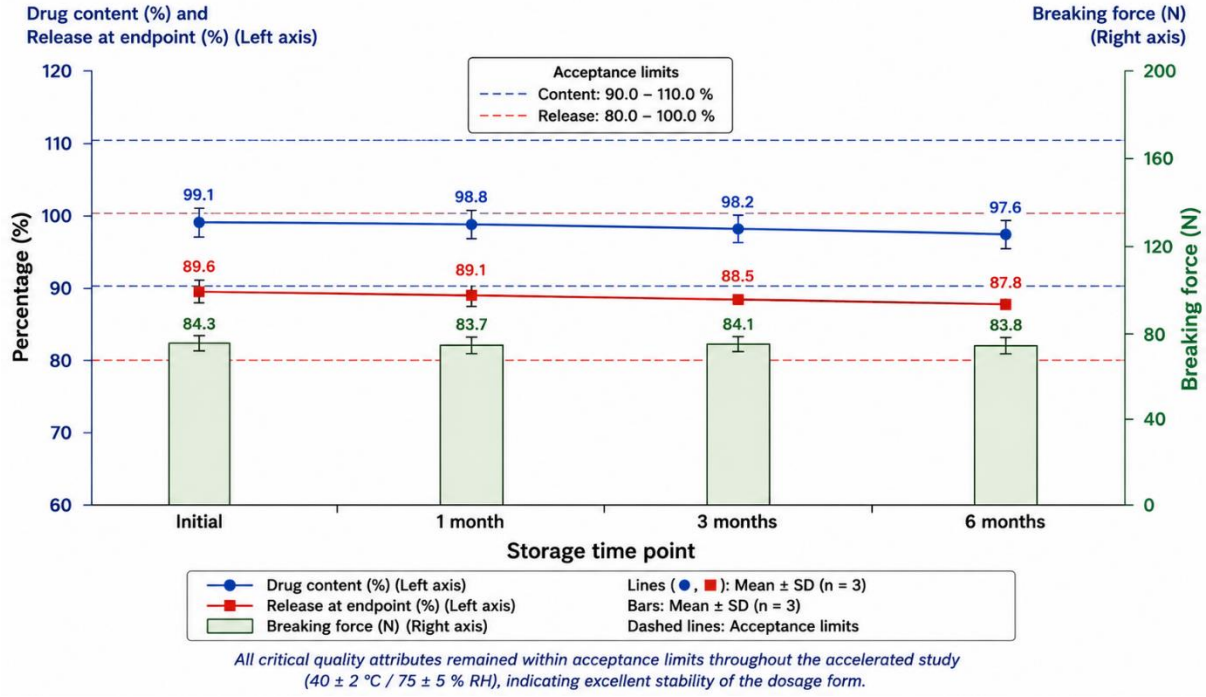

Figure 4. Stability of critical quality attributes over the accelerated study.

DISCUSSION

The body of evaluation evidence assembled here supports a clear overall conclusion: 3D printed personalized tablets produced by fused deposition modelling can meet the critical quality attributes expected of an oral dosage form, and, just as importantly, framing the evaluation within Quality by Design turns a collection of individual tests into coherent evidence about a controllable product. This framing is the study's central contribution to how such products should be assessed. A conventional evaluation might report that tablets passed uniformity, dissolution, and stability tests; the QbD-structured evaluation instead shows that the product sits reliably within an understood region of behaviour whose principal lever, infill density, has a quantified and predictable effect. That is a stronger and more appropriate basis for trusting a personalized product than a checklist of passes.

The dissolution results deserve emphasis because dissolution was prioritised in the risk assessment and because it carries the most direct link to therapeutic effect. The strong, well-fitted dependence of release on infill density

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confirms that release behaviour is not an uncontrolled property of the printed tablet but a designed and reproducible one, and the shift in release mechanism from diffusion-dominated toward matrix-influenced transport as infill increases gives a mechanistic explanation for why that control works. The demonstration, through the similarity factor, that nominally identical settings yield equivalent profiles is quietly one of the most important findings, because reproducibility of release is precisely what allows a specified infill to be trusted to deliver a specified profile, which is the foundation of the whole personalization proposition.

The physical and content evaluation reinforces this picture of a controlled process. Tight mass and content uniformity across every infill density show that dose accuracy is preserved as the release-controlling parameter is varied, which is not something that could be taken for granted, and the close dimensional fidelity confirms that the digital design translates faithfully into the physical object. These results address, in evaluation terms, the concerns about variability that attend layer-by-layer construction.

The solid-state and compatibility evaluation confronts the defining limitation of fused deposition modelling directly and, for this drug-polymer system, resolves it reassuringly. The preservation of the drug's characteristic spectroscopic bands without new peaks indicates that the thermal exposure of printing did not chemically degrade the drug, and the diminished melting endotherm shows the drug dispersed within the matrix, which both explains the release behaviour and connects to the stability question. The accelerated stability results then close an important gap that the printed-medicines literature has often left open, showing that the tablets, including any amorphous drug dispersion, retained their critical attributes over the accelerated period. Because amorphous forms can recrystallise and printed structures can relax over time, this stability evidence is essential to any claim that such tablets could be stored and used rather than merely printed and immediately consumed.

Several limitations should nonetheless be stated plainly. The evaluation, thorough as it is, remains entirely in vitro, and while dissolution and its reproducibility provide a strong in vitro window onto expected behaviour, actual in vivo pharmacokinetics would need to be established, ideally supported by an in vitro to in vivo correlation, before clinical claims could be made. The stability study was accelerated rather than long-term, so while it is a good early indicator, real-time stability over the intended shelf life would be required for a marketable product. The evaluation also examined a single drug-polymer system, so the specific numerical findings, particularly the exact infill-release relationship and the stability behaviour, should not be assumed to transfer to other combinations, even though the QbD-structured evaluation methodology certainly does. Finally, the challenge of quality-assuring batches of one remains only partly addressed: this study assures quality by demonstrating process understanding and control, which is the right strategy, but implementing that strategy at the point of care would require appropriate in-line monitoring and process analytical technology that lie beyond the present scope.

These limitations map directly onto worthwhile future work. Establishing in vivo behaviour and in vitro to in vivo correlations would strengthen the clinical case considerably, and extending stability evaluation to real-time conditions would support shelf-life claims. Applying the same QbD-structured evaluation to a range of drug-polymer systems would test the generality of the approach, and developing non-destructive, in-line evaluation methods suited to personalized, small-batch manufacturing would help solve the batch-of-one quality assurance problem in practice. The evaluation framework demonstrated here provides a solid basis for all of these developments.

CONCLUSION

This study conducted a comprehensive, Quality by Design-structured evaluation of 3D printed personalized oral drug delivery systems produced by fused deposition modelling, assessing them against a full set of critical quality attributes derived from a defined target product profile. The printed tablets reproduced their intended designs with high dimensional fidelity, maintained tight mass and content uniformity across a wide range of infill densities, and possessed adequate mechanical strength. Dissolution, prioritised as the most critical attribute, was strongly and predictably governed by infill density, with reproducible profiles at identical settings and a mechanistically sensible shift in release behaviour as internal density increased. Solid-state and

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spectroscopic analysis confirmed that the drug remained chemically intact and dispersed within the polymer matrix, addressing the principal thermal-stability concern of the technique, and accelerated stability testing showed that the tablets retained their critical quality attributes over the study period.

The central contribution of this work is to show that framing the evaluation within Quality by Design transforms it from a set of isolated pass-or-fail tests into coordinated evidence about a controllable, well-understood product, which is exactly the depth of quality assurance that personalized 3D printed medicines will require before clinical adoption. By identifying dissolution behaviour and stability as the attributes most deserving of ongoing control, and by demonstrating that release can be reliably specified through a single printing parameter, the study offers a practical blueprint for how such products should be evaluated. With the addition of in vivo correlation, real-time stability data, evaluation across diverse drug-polymer systems, and in-line monitoring suited to small-batch manufacture, the QbD-structured evaluation approach set out here provides a credible foundation for bringing personalized 3D printed medicines safely and reliably to patients.

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