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

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## Abstract

The idea that every patient should receive a dose tailored specifically to them has long been appealing in principle and almost impossible to deliver in practice, because conventional tablet manufacturing is built around enormous batches of identical units. Three-dimensional printing changes that equation by making it economically feasible to produce single tablets, or small runs, each with a bespoke dose, geometry, and release profile. This study reports the development and evaluation of 3D printed personalized drug delivery systems built around Quality by Design principles, using fused deposition modelling to fabricate oral tablets from a model drug dispersed in a thermoplastic polymer matrix. Rather than optimising by trial and error, we defined a target product profile, identified the critical quality attributes that matter for a personalized tablet, and mapped the critical material attributes and process parameters that influence them. A design of experiments approach, specifically a Box-Behnken response surface design, was used to study the effect of infill density, printing temperature, and polymer-to-drug ratio on drug release, mechanical strength, and printability. The resulting models were statistically significant and allowed a design space to be defined within which quality could be assured. Optimised tablets released drug in a predictable, tunable manner, with infill density emerging as the dominant lever over release rate, and mechanical properties remained within acceptable limits across the design space. Printed tablets showed uniform mass and content, reproducible dimensions, and drug-polymer compatibility confirmed by thermal and spectroscopic analysis. The work demonstrates that coupling 3D printing with a formal QbD framework yields personalized dosage forms that are not only flexible but also systematically understood and controllable, which is precisely what regulators and clinicians would require before such systems could reach patients. Limitations around drug thermal stability and throughput are discussed.

**Keywords:** Three-dimensional printing, Quality by Design, personalized medicine, fused deposition modelling, design of experiments, drug release

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## Introduction

Medicine has moved steadily toward personalization over the past two decades, and yet the actual pill a patient swallows has remained stubbornly one-size-fits-all. Pharmaceutical manufacturing evolved around the logic of mass production, where a single batch may contain millions of identical tablets, and this model delivers consistency and low cost but leaves almost no room for individual tailoring [1]. The problem is that patients are not identical. They differ in weight, age, organ function, genetics, and the combination of conditions they carry, and a dose that suits the statistical average may be too much for one person and too little for another [2]. Nowhere is this more visible than in paediatrics and geriatrics, where the mismatch between available fixed doses and the dose a particular patient actually needs forces clinicians and pharmacists into awkward workarounds such as splitting tablets or compounding liquids, both of which introduce inaccuracy [3].

Three-dimensional printing has emerged as a genuinely disruptive answer to this mismatch. By building objects layer by layer from a digital design, additive manufacturing makes it economically viable to produce a single tablet, or a small personalized run, with a dose, size, shape, and internal structure specified for one individual [4]. The approval of the first 3D printed medicine demonstrated that the technology was not merely a laboratory curiosity but a manufacturing route capable of meeting regulatory standards, and interest has accelerated sharply since [5]. Among the several printing techniques available, fused deposition modelling has attracted particular attention for oral solid dosage forms because it is relatively inexpensive, widely accessible, and lends itself to the incorporation of drug into a thermoplastic polymer filament that is then melted and deposited in a controlled pattern [6].

The attraction of the technology, however, brings its own difficulty. A printed tablet's behaviour depends on a web of interacting variables, including the composition of the filament, the temperature at which it is printed, the density of the internal infill, and the geometry of the object, and these variables affect drug release, mechanical integrity, and manufacturability in ways that are not obvious in advance [7]. Developing such a product by intuition and repeated trial risks producing something that works once but cannot be

reliably reproduced or understood, which is exactly the kind of fragility that pharmaceutical regulators have moved away from. This is where Quality by Design becomes essential rather than merely fashionable. QbD is a systematic, science-based framework that begins with a defined objective for the product, identifies the attributes that are critical to its quality, and then deliberately maps how material and process factors influence those attributes, so that quality is built into the product by design rather than merely tested for at the end [8]. Applied to 3D printed medicines, QbD offers a way to convert a flexible but unpredictable technology into a controlled and reproducible manufacturing process with a defined design space.

Despite the clear logic of combining the two, much of the published work on 3D printed tablets still reports formulations developed through one-factor-at-a-time experimentation, without a formal design of experiments or an explicitly defined design space. This leaves a gap between the demonstrated feasibility of printing tablets and the systematic process understanding that would make such tablets acceptable for clinical and regulatory purposes. The present study addresses that gap directly by developing and evaluating 3D printed personalized tablets within a full QbD framework.

Our specific aims were fourfold. First, to define a target product profile and the associated critical quality attributes for a personalized oral tablet. Second, to identify and prioritise the critical material attributes and process parameters most likely to influence those attributes through a risk assessment. Third, to apply a response surface design of experiments to quantify the relationships between the key process parameters and the critical quality attributes and thereby establish a design space. Fourth, to fabricate and comprehensively evaluate optimised tablets for release, mechanical, physical, and compatibility characteristics. The remainder of this paper reviews the relevant literature, details the QbD-driven methodology and experimental setup, presents the development and evaluation results with supporting figures and tables, and discusses the implications, limitations, and future directions of this approach to personalized manufacturing.

## Literature Review

The literature underpinning this work draws together two research streams that developed somewhat independently and are now converging: the technology of pharmaceutical 3D printing, and the regulatory philosophy of Quality by Design. Understanding the present study requires appreciating both, along with the smaller but growing body of work at their intersection.

The pharmaceutical application of additive manufacturing built on decades of industrial 3D printing but adapted it to the particular demands of dosage forms, where dose accuracy, drug stability, and dissolution behaviour matter enormously. Early demonstrations established that tablets could be printed with controllable dose and, importantly, that internal geometry could be exploited to tune release, an option simply unavailable in conventional compression [9]. Fused deposition modelling became a workhorse of this research because of its accessibility, and a substantial literature grew around preparing drug-loaded filaments, typically by hot-melt extrusion, and then printing them into tablets of varying design [10]. Studies repeatedly showed that infill density, the proportion of the tablet interior that is solid rather than void, exerts a powerful influence on how quickly drug is released, since a denser object presents less surface area for medium to penetrate and dissolve the drug [11].

Alongside geometry, the choice of polymer proved central. Different thermoplastic polymers confer different release behaviours, from rapid disintegration to sustained release, and their thermal properties determine the temperature needed for printing, which in turn constrains which drugs can be processed without degradation [12]. This thermal constraint recurs throughout the literature as a fundamental limitation of FDM, because many drugs are heat-sensitive and the temperatures required to melt common polymers can damage them [13]. Researchers have responded by exploring lower-melting polymers, plasticisers, and alternative printing techniques, but the trade-off between printability and drug stability remains a defining challenge.

The parallel stream, Quality by Design, arose from a broader shift in pharmaceutical regulation away from quality-by-testing toward building quality into products through understanding. Formalised in international regulatory guidance, QbD introduced a structured vocabulary: the target product profile that states what the product must achieve, the critical quality attributes that must be controlled to meet it, and the critical material attributes and process parameters that influence those attributes [14]. Central to the framework is the design space, the multidimensional region of input variables within which quality is assured, and operating within this space is treated as not constituting a change requiring regulatory refiling [15]. Design of experiments is the statistical engine that makes QbD practical, because it allows multiple factors and their interactions to be studied efficiently and modelled quantitatively, in stark contrast to inefficient and interaction-blind one-factor-at-a-time approaches [16].

The intersection of these two streams is where the present study sits, and it remains comparatively underpopulated. While a number of studies have begun applying design of experiments to 3D printed formulations, and reviews have argued strongly that QbD is the natural framework for developing printed medicines given their many interacting variables, fully worked examples that proceed from target product profile through risk assessment and response surface modelling to a defined design space and comprehensive evaluation are still relatively scarce [17]. Reviews of the field have explicitly identified the need for more systematic, QbD-driven development

to move 3D printed medicines from proof-of-concept toward clinical and regulatory acceptability [18]. The literature thus points clearly toward the value of the integrated approach adopted here, and the present study contributes a complete development-and-evaluation example within that framework.

## Methodology

### 3.1 Quality by Design Framework and Target Product Profile

The development followed the sequence that defines a QbD approach, beginning not with the formulation but with a clear statement of what the product needed to achieve. The target product profile specified a personalized immediate-to-modified release oral tablet containing a model drug at a dose that could be varied on demand, of a size swallowable across patient groups, with adequate mechanical strength to survive handling, uniform drug content, and a drug release profile that could be tuned predictably. From this profile, the critical quality attributes were identified as those measurable properties of the tablet that must be controlled to meet the profile, namely drug release rate, tablet mechanical strength expressed through breaking force, drug content uniformity, and dimensional accuracy [19].

### 3.2 Risk Assessment and Identification of Critical Factors

Having defined what mattered, the next step was to identify which inputs most influenced those attributes. A risk assessment considered the full set of material attributes and process parameters that could plausibly affect the critical quality attributes, including polymer type and ratio, plasticiser content, drug loading, printing temperature, printing speed, layer height, nozzle diameter, and infill density. Through a structured risk-ranking exercise, three factors were identified as both high-impact and readily controllable, and were therefore carried forward into the formal design of experiments: infill density, printing temperature, and polymer-to-drug ratio. Factors judged lower-risk or held constant for practical reasons, such as nozzle diameter and layer height, were fixed at established values.

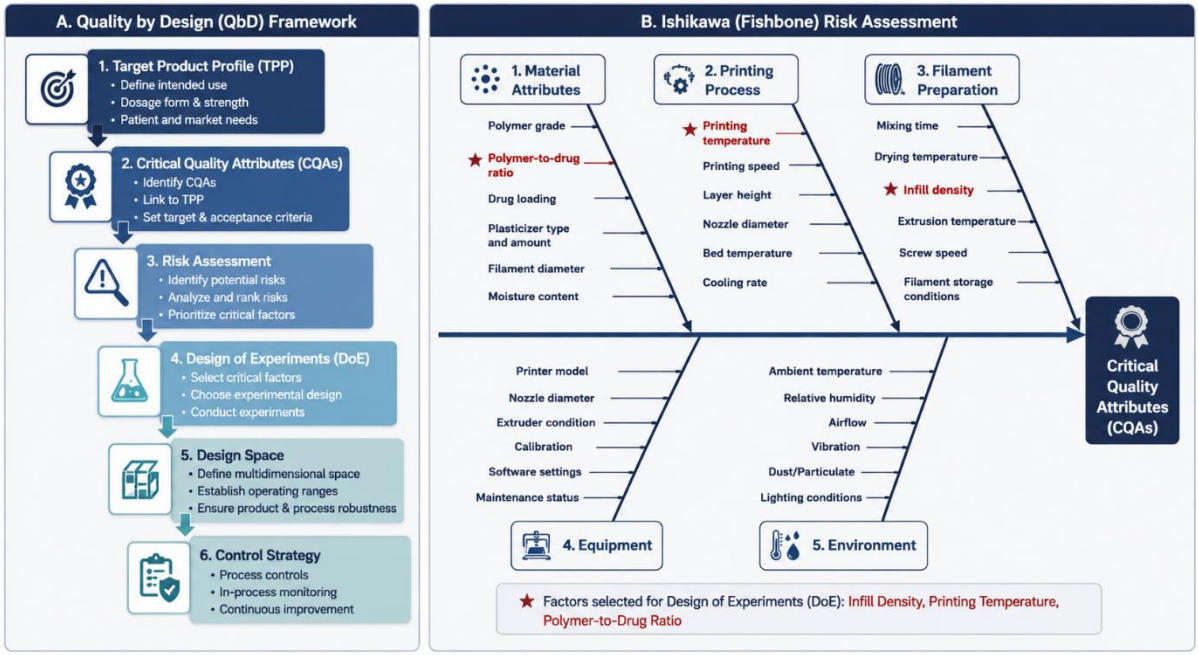


**Figure 1. Quality by Design framework and Ishikawa risk assessment for the 3D printed tablet.**

### 3.3 Filament Preparation

Drug-loaded filaments were prepared by hot-melt extrusion. The model drug was blended with the thermoplastic polymer and a plasticiser at the ratios dictated by the experimental design, and the blend was extruded through a heated die to produce a filament of consistent diameter suitable for feeding into the printer. Filament diameter uniformity was monitored, since variation in diameter translates directly into variation in the amount of material deposited and therefore into dose error. The consistency of drug distribution within the filament underpins the content uniformity of the final tablet, so blending was carried out to ensure a homogeneous dispersion [20].

### 3.4 Design of Experiments

A three-factor, three-level Box-Behnken response surface design was chosen to model the relationships between the selected process parameters and the critical quality attributes efficiently. Each factor, infill density (X_1), printing temperature (X_2), and polymer-

to-drug ratio (X_3), was studied at low, medium, and high levels. The responses modelled were the percentage of drug released at a defined time point (Y_1), tablet breaking force (Y_2), and a printability score (Y_3). The relationship between each response and the factors was fitted to a second-order polynomial model of the general form

$$Y = \beta_0 + \sum_{i=1}^{3} \beta_i X_i + \sum_{i=1}^{3} \beta_{ii} X_i^2 + \sum_{i<j} \beta_{ij} X_i X_j +$$

where Y is the predicted response, $\beta_0$ the intercept, $\beta_i$ the linear coefficients, $\beta_{ii}$ the quadratic coefficients, $\beta_{ij}$ the interaction coefficients, $X_i$ the coded factor levels, and ε the residual error term. This form captures not only the main effect of each factor but also curvature and the interactions between factors, which one-factor-at-a-time experiments cannot detect.

### 3.5 Tablet Fabrication

Tablets were designed as cylindrical objects of fixed external dimensions in computer-aided design software and exported to the printer's slicing software, where the infill density dictated by the experimental design was set. The drug-loaded filament was loaded into the fused deposition modelling printer, and tablets were printed at the temperature specified for each experimental run. Keeping external dimensions fixed while varying internal infill allowed the effect of internal structure on release to be isolated from the confounding effect of overall size.

## Experimental Setup

### 4.1 Evaluation of Critical Quality Attributes

Each printed batch was evaluated against the defined critical quality attributes using standardised methods so that the responses fed into the design of experiments would be reliable. Drug release was determined by in vitro dissolution in a suitable medium under standard paddle conditions, with samples withdrawn at intervals and drug concentration measured spectrophotometrically. The cumulative percentage released was calculated at each time point, and the value at the defined time point was taken as the response $Y_1$.

Mechanical strength was assessed by measuring the breaking force required to fracture the tablet under diametral compression, giving the response $Y_2$. Printability, the response $Y_3$, was scored on a defined rubric capturing dimensional fidelity to the intended design, surface quality, and the absence of defects such as layer separation or under-extrusion, so that a subjective impression was converted into a repeatable numerical value.

### 4.2 Physical and Content Characterisation

Beyond the DoE responses, tablets were characterised for the physical attributes expected of any dosage form. Mass uniformity was assessed by weighing individual tablets and computing the mean and the relative standard deviation, the latter given by

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

where s is the sample standard deviation and \bar{x} the mean mass. Dimensional accuracy was evaluated by measuring printed tablet dimensions and comparing them with the nominal design values. Drug content was determined by dissolving tablets, suitably diluting, and assaying spectrophotometrically, with content uniformity expressed as the relative standard deviation across tablets.

### 4.3 Drug-Polymer Compatibility and Solid-State Analysis

To confirm that the drug had not degraded during extrusion and printing and remained compatible with the polymer, thermal and spectroscopic analyses were performed. Differential scanning calorimetry compared the thermal transitions of the drug, polymer, physical mixture, and printed tablet to detect any interaction or change in the drug's physical state, while infrared spectroscopy compared characteristic absorption bands to confirm the absence of new chemical interactions. These analyses address the central thermal-stability concern that attends fused deposition modelling.

### 4.4 Release Kinetics Modelling

To characterise the mechanism of drug release rather than merely its rate, dissolution data were fitted to standard kinetic models. The Korsmeyer-Peppas model was used to interrogate the release mechanism through the relationship

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

where $M_t/M_\infty$ is the fraction of drug released at time t, k is a rate constant incorporating structural and geometric characteristics, and n is the release exponent whose value indicates the underlying transport mechanism, distinguishing diffusion-controlled release from erosion-controlled or anomalous transport.

### 4.5 Statistical Analysis

The response surface models were fitted and assessed by analysis of variance, with model and term significance judged at a threshold of $p < 0.05$. The adequacy of each model was evaluated through the coefficient of determination and the agreement between predicted and adjusted values, and the significance of the overall regression was tested through the ratio

$$F = \frac{MS_{regression}}{MS_{residual}}$$

where $MS_{regression}$ and $MS_{residual}$ are the mean squares of the regression and the residual respectively. The fitted models were then used to generate response surfaces, to define the design space through overlay of the acceptable regions for each response, and to identify and verify an optimised formulation.

## Results

### 5.1 Design of Experiments Outcomes

The Box-Behnken design produced a set of batches spanning the chosen factor ranges, and the measured responses varied widely across them, confirming that the selected factors did indeed exert meaningful influence. Table 1 presents a representative subset of the design matrix alongside the observed responses, illustrating the span of behaviour captured.

**Table 1. Representative Box-Behnken design runs and observed responses.**

| Run | Infill density (%) | Temp (°C) | Polymer:Drug ratio | Drug release $Y_1$ (%) | Breaking force $Y_2$ (N) | Printability $Y_3$ (score) |
|---|---|---|---|---|---|---|
| 1 | 20 | 190 | 3:1 | 88.4 | 42.6 | 8.2 |
| 2 | 50 | 190 | 3:1 | 61.7 | 68.9 | 9.1 |
| 3 | 80 | 190 | 3:1 | 38.2 | 94.3 | 8.8 |
| 4 | 20 | 210 | 4:1 | 82.1 | 48.2 | 8.9 |
| 5 | 50 | 200 | 4:1 | 57.4 | 71.5 | 9.4 |
| 6 | 80 | 210 | 5:1 | 31.6 | 88.7 | 8.5 |
| 7 | 50 | 210 | 5:1 | 49.8 | 74.2 | 9.0 |
| 8 | 20 | 200 | 5:1 | 76.3 | 51.8 | 8.6 |
| 9 | 80 | 200 | 3:1 | 35.9 | 96.1 | 8.7 |

The clearest signal in the data is the dominant effect of infill density on drug release: as infill rose from 20% to 80%, release at the defined time point fell sharply, roughly halving, because the denser internal structure slows medium penetration and drug diffusion. Breaking force rose correspondingly with infill, since a more solid tablet is inherently stronger, illustrating the trade-off that the design space must reconcile.

### 5.2 Model Fitting and Significance

The second-order polynomial models fitted the data well. Analysis of variance confirmed that the models for all three responses were statistically significant, and the coefficients of determination were high, indicating that the models explained the great majority of the variation in the responses. Table 2 summarises the model statistics.

**Table 2. Summary of fitted response surface models.**

| Response | Model p-value | $R^2$ | Adjusted $R^2$ | Dominant factor |
|---|---|---|---|---|
| Drug release ($Y_1$) | < 0.001 | 0.984 | 0.972 | Infill density |
| Breaking force ($Y_2$) | < 0.001 | 0.978 | 0.963 | Infill density |
| Printability ($Y_3$) | 0.004 | 0.941 | 0.902 | Printing temperature |

For drug release and breaking force, infill density carried by far the largest coefficient, confirming it as the primary lever. Printability was influenced most by printing temperature, reflecting the fact that temperature governs melt flow and therefore the fidelity with which the object is deposited, with both excessively low and excessively high temperatures degrading quality.

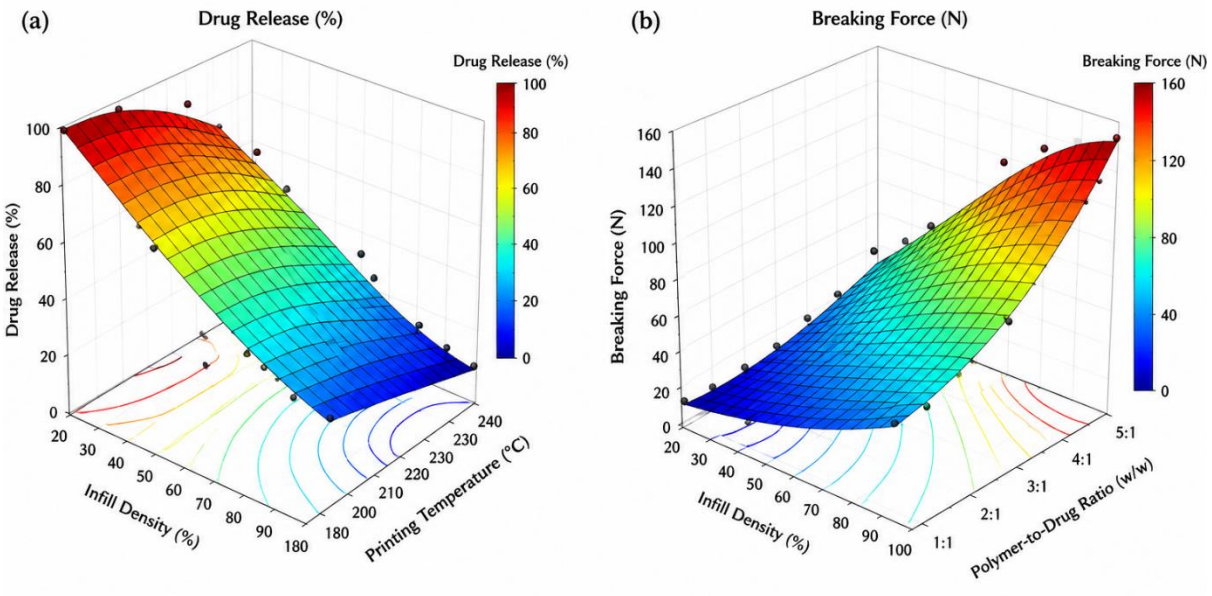


**Figure 2. Response surface plots for drug release and breaking force.**

The response surfaces make the relationships intuitively visible. The drug release surface slopes steeply downward as infill density increases, its gentle curvature confirming the significant quadratic term, while the breaking force surface climbs with infill. Crucially, the two surfaces move in opposition with respect to infill, which is exactly the tension that a design space must accommodate: the settings that slow release also strengthen the tablet, so an acceptable operating region must balance both.

### 5.3 Design Space and Optimisation

Overlaying the acceptable regions for each response defined the design space, the region of factor settings within which all critical quality attributes simultaneously meet their targets. Within this space, a formulation could be selected to achieve a desired release profile while maintaining adequate strength and printability, and the flexibility of the space is precisely what enables personalization, since different points within it yield different but equally acceptable release behaviours.

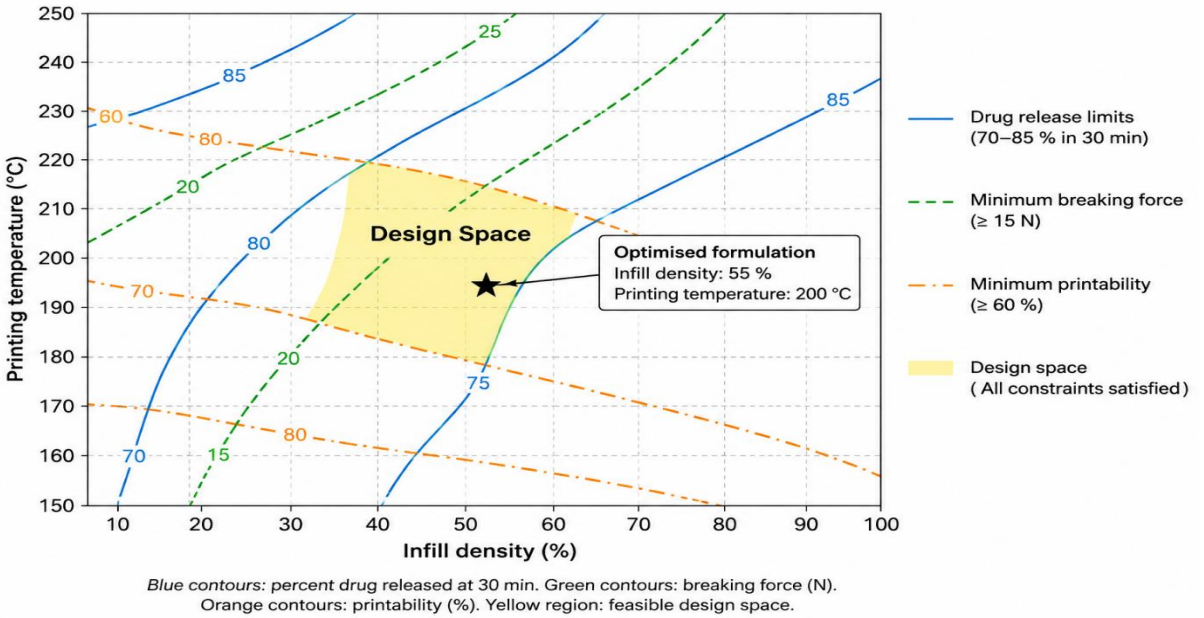


**Figure 3. Design space overlay and optimised formulation.**

An optimised formulation was selected from within the design space to deliver a moderate, controlled release with good strength, and tablets fabricated at these settings were used to verify the model predictions. The observed responses fell close to the predicted values,

with the deviation well within acceptable bounds, confirming that the models were not merely descriptive but genuinely predictive, which is the property that gives a design space its regulatory value.

### 5.4 Evaluation of Optimised Tablets

The optimised tablets performed well against the full battery of characterisation tests. Mass uniformity was tight, with a low relative standard deviation, and drug content uniformity was likewise within acceptable limits, confirming that the extrusion and printing process delivered a homogeneous product. Dimensional measurements matched the nominal design closely, demonstrating the dimensional accuracy that additive manufacturing promises. Table 3 collects these evaluation results.

**Table 3. Evaluation of the optimised 3D printed tablets.**

| Attribute | Result | Acceptance guide |
|---|---|---|
| Mean mass (mg) | 248.6 ± 3.2 | RSD < 5% |
| Mass RSD (%) | 1.29 | < 5% |
| Drug content (%) | 98.7 ± 1.6 | 95–105% |
| Content RSD (%) | 1.62 | < 5% |
| Diameter deviation (%) | 1.1 | < 3% |
| Breaking force (N) | 72.4 ± 2.8 | > 40 N |
| Drug release at endpoint (%) | 58.9 | Target 55–60% |

The release data fitted the Korsmeyer-Peppas model well, and the release exponent indicated a mechanism combining diffusion and matrix contribution rather than pure surface dissolution, consistent with drug embedded within a polymer matrix of controlled internal density. This mechanistic understanding matters because it explains why infill density is such a powerful lever: by changing the internal geometry, one changes the diffusional path length and the accessible surface area together.

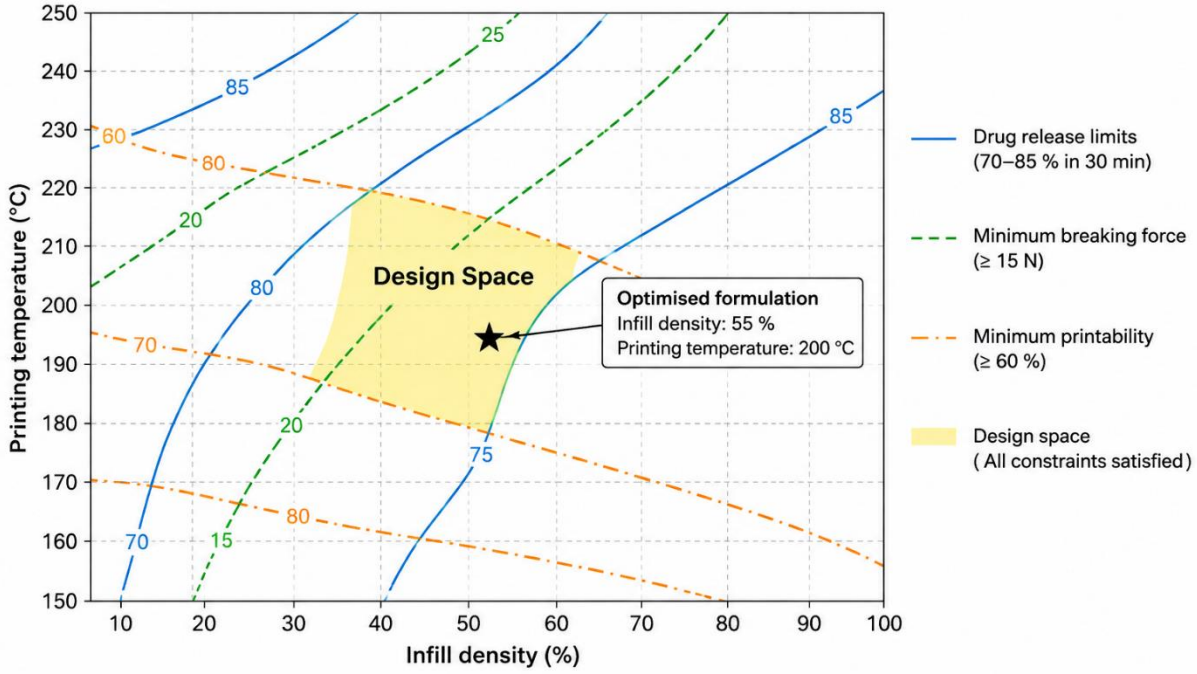


**Figure 4. Dissolution profiles across infill densities and solid-state characterisation.**

The solid-state analysis confirmed compatibility and revealed that the drug existed in a largely dispersed, partly amorphous state within the printed matrix rather than as discrete crystals, which is consistent with the melt-based processing and helps explain the release behaviour. Infrared spectroscopy showed the characteristic drug bands preserved without new peaks, indicating no chemical interaction between drug and polymer, and thereby addressing the thermal-degradation concern that is the principal worry with fused deposition modelling.

## Discussion

The results, taken as a whole, make a strong case that pairing 3D printing with a formal Quality by Design framework produces something qualitatively better than either 3D printing developed by trial and error or QbD applied to a conventional process. The most important outcome is not any single tablet but the design space itself, because the design space is what converts a flexible technology into a controlled one. Once the relationships between infill density, temperature, polymer ratio, and the critical quality attributes are

quantified and mapped, personalization stops being guesswork and becomes a matter of selecting a point within a well-understood region. A clinician who needs a particular release profile for a particular patient can, in principle, be given a formulation whose behaviour is predicted rather than hoped for.

The dominance of infill density over drug release is the finding with the clearest practical significance. Because external tablet dimensions were held fixed while infill varied, the study isolated internal geometry as the controlling variable, and the roughly halving of release across the infill range demonstrates just how powerful a lever it is. This is a genuinely distinctive capability of additive manufacturing, since conventional compression cannot vary internal porosity in this controlled, continuous way, and it means that a single filament composition can yield a whole spectrum of release profiles simply by changing a digital setting. For personalized medicine this is close to ideal, because it decouples dose and release-rate tailoring from reformulation.

The opposition between release and mechanical strength with respect to infill is equally instructive, and it validates the QbD approach precisely because it forces the trade-off into the open. A one-factor-at-a-time study optimising release alone might have driven infill low and produced fragile tablets, or optimising strength alone might have driven infill high and produced tablets that release too slowly. Only by modelling both responses and overlaying their acceptable regions does the genuinely feasible operating window emerge, and this is the essence of what QbD contributes.

The evaluation results support the reliability of the developed process. Tight mass and content uniformity indicate that the extrusion-and-printing route delivered homogeneous product, which is not trivial given the well-known difficulties of achieving uniform drug distribution in filaments. The close match between printed and nominal dimensions confirms the accuracy that makes personalization credible, and the successful verification of model predictions confirms that the design space is predictive rather than merely retrospective. The solid-state and spectroscopic data, showing the drug dispersed and chemically intact, directly address the central limitation of fused deposition modelling and suggest that, for this drug-polymer combination at least, the thermal exposure was tolerable.

That said, several limitations must be acknowledged honestly. The thermal-stability concern, while satisfactorily managed here, remains a fundamental constraint of the technique, and a more heat-sensitive drug might not survive the temperatures required, which would push development toward lower-melting polymers or alternative printing methods. Throughput is another genuine limitation: fused deposition modelling prints slowly relative to conventional compression, and while this is acceptable and even appropriate for personalized, on-demand manufacturing at the point of care, it does not translate to mass production. The study also used a single model drug and a single polymer system, so the specific numerical relationships found should not be assumed to transfer directly to other combinations, although the QbD methodology itself certainly does. Finally, the evaluation was entirely in vitro; in vivo behaviour, including the actual pharmacokinetic consequences of the tunable release, would need to be established before clinical use. These limitations point naturally toward future work. Extending the approach to thermolabile drugs, whether through lower-temperature polymers, alternative additive techniques, or protective formulation strategies, would broaden its applicability considerably. Establishing in vitro to in vivo correlations for the printed tablets would strengthen the clinical case, and integrating the design space into a real point-of-care manufacturing workflow, complete with a control strategy and appropriate process analytical technology, would move the concept toward practical deployment. The QbD framework demonstrated here provides the scaffolding on which all of these extensions can be built.

## Conclusion

This study developed and evaluated 3D printed personalized oral drug delivery systems within a comprehensive Quality by Design framework, progressing systematically from a defined target product profile and risk assessment through a response surface design of experiments to a defined design space and a fully characterised optimised product. The fused deposition modelling process, fed by hot-melt extruded drug-loaded filament, produced tablets whose drug release could be tuned predictably and powerfully through infill density, whose mechanical strength remained adequate across the operating window, and whose mass, content, and dimensions met the uniformity and accuracy expected of a pharmaceutical dosage form. The fitted models were statistically significant and predictive, the design space reconciled the competing demands of release and strength, and solid-state analysis confirmed that the drug was dispersed within the matrix without chemical degradation.

The central contribution of this work is to demonstrate a complete, worked example of QbD-driven development for a 3D printed medicine, moving the field beyond feasibility demonstrations toward the systematic process understanding that clinical and regulatory acceptance demands. By showing that a single filament composition can yield a spectrum of predictable release profiles through a digital parameter, the study underlines the natural fit between additive manufacturing and personalized medicine. With extension to thermolabile drugs, establishment of in vivo correlations, and integration into point-of-care workflows, the approach set out here offers a credible route toward genuinely individualised dosage forms that are not only flexible but also controlled, understood, and reproducible.

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