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REVIEW ARTICLE

Changing the dose without changing the release: design strategies, evidence and validation for strength families of 3D printed oral medicines

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ABSTRACT

Three-dimensional (3D) printing lets a pharmacist or manufacturer set the strength of an oral medicine digitally, but the decision that changes the dose can also change how fast the drug is released. Larger tablets hydrate and erode more slowly, lower infill admits fluid faster, and higher drug loading alters the polymer network. A correct dose therefore says little about whether the release profile has been kept. This critical narrative review asks which design strategies allow the dose to change while the fractional release profile is preserved, and what evidence such a claim requires. The primary studies identified support three approaches: shaping the geometry to hold the surface-area-to-volume ratio, changing the number of identical units, and allocating drug within a fixed architecture, either by varying the drug concentration or by spatial allocation of drug and placebo regions. Each works within a stated formulation and dose range. Reported limits include the lowest strengths (where analytical sensitivity, mechanical weakness and variability converge), changes in drug concentration, and structures that look equivalent in the design file but differ in pore access. Many studies compare release qualitatively or at a single time point, and few report formal similarity statistics, so dose flexibility is better established than release preservation. We propose a strength-family framework that links the clinical use case, dose accuracy, measured structure, discriminatory dissolution, stress testing and clinical bridging, and we set it against current European and UK regulatory texts. Future studies should report absolute and fractional release, state analytical sensitivity at the lowest dose, and test designs against realistic material and process variation.

Keywords: pharmaceutical 3D printing; personalised medicine; dose titration; drug release; minitablets; dissolution similarity; strength family

HIGHLIGHTS

- • Dose flexibility is better established than preservation of fractional drug release.
- • Hollow geometries can raise dose with similar dissolution in specific formulations.
- • Identical minitablets can preserve profiles when the units release independently.
- • The lowest strengths and changes in drug loading define important design limits.
- • Strength families need discriminatory dissolution, structural checks and bridging.

1. INTRODUCTION

Commercial oral medicines come in a small set of fixed strengths. Patients who need something in between, such as children, older adults, and people being titrated onto a drug with a narrow dose window, are usually given a split tablet or a compounded preparation. Splitting is imprecise. In a hospital pharmacy comparison, quartered 25 mg metoprolol tablets had mean drug contents of 64% and 90% of the intended 6.25 mg for two commercial products, with individual units ranging from 24.9% to 142.8% across the two products [1]. Split commercial caffeine tablets in another study fell 21% to 29% below the target dose [2].

Three-dimensional (3D) printing offers a different route, because the amount of drug-containing material deposited can be set in the

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digital design. The difficulty is that dose and release are not independent. They are determined by the same formulation and the same structure. A larger tablet takes longer to hydrate and has a longer diffusion path, whereas reduced infill lets fluid reach the interior sooner. A printed tablet can therefore contain exactly the prescribed amount of drug and still release it on the wrong time course. Early work on tablet geometry showed this clearly [3], and later studies set out to design deliberately for similar fractional release across doses [4, 5].

The clinical aim also needs to be stated before a design is chosen. During titration, an unchanged percentage-release profile is usually wanted, so that each increase in dose delivers proportionally more drug at every time point. In other cases the prescriber needs a different release profile along with a different strength. Printing does not settle which of these applies. The product requirement has to come first, and the printing method should be selected to meet it.

Recent reviews have covered quality by design and process analytical technology for on-demand printing [6]. The present review is narrower. It asks which strategies change the oral dose while preserving a predefined fractional release profile, and what a study has to show before that can be claimed. We distinguish dose accuracy, dissolution similarity and systemic exposure, appraise what the primary experiments establish, correct several common over-readings of the literature, and propose a validation framework for a family of strengths. We then relate that framework to current European and UK regulatory documents.

The review is narrative. Europe PMC, PubMed, publisher platforms (ScienceDirect, MDPI and Wiley Online Library) and regulatory websites were searched up to 10 November 2026, with no lower date limit (the earliest primary study retained was published in 2015 [3]) for work on pharmaceutical 3D printing, dose titration, dose-independent release, geometric scaling, surface area to volume ratio, minitablets, dissolution prediction and additional strengths. The principal search strings combined '3D print*' or 'additive manufactur*' with 'dose titration', 'dose-independent release', 'geometr* scaling', 'surface area to volume', 'minitablet*', 'dissolution similarity' or 'f_2', and with 'additional strength*' or 'biowaiver', and were adapted to each platform. Primary studies that compared more than one dose, geometry, composition or process condition were prioritised, and mechanistic, analytical and clinical studies were added where they bore on how release preservation should be interpreted. Studies were retained when they described an oral dosage form made by additive manufacturing and reported release or dissolution data for more than one strength, geometry, composition or process condition, or when they supplied the mechanistic, analytical, regulatory or clinical information needed to interpret such data. Studies of non-oral products, of vat photopolymerisation or inkjet printing, and of a single design without a dose-related comparison were excluded. Company and press-release information was used only to document marketed-product and development milestones and is identified as such in the text and tables. The scope is oral products made by extrusion and powder-bed methods. Preserved release is taken to mean comparable fractional release over the intended period, not identical milligrams released per hour. Phrases such as “changing the dose without changing the release” and “dose-independent release” are therefore used here, and in some cited titles, only to mean similar fractional dissolution profiles across strengths within the studied design range and under stated test conditions, and not absolute mechanistic independence of release from dose.

2. WHAT HAS TO BE PRESERVED

2.1 Dose accuracy and release preservation

Dose accuracy is agreement between measured drug content and the prescribed amount. Release preservation is agreement between time-dependent release profiles after the strength has changed. The two fail independently. A unit can have the correct mass and the wrong drug concentration, or the correct content and a different pore network. Two units can release the same percentage at every sampling time and both contain less drug than intended. **Table 1** lists the outcomes that studies tend to run together.

Table 1. Outcomes that should be distinguished when evaluating personalised strengths.

Outcome	Relevant comparison	What the finding does not establish
Dose accuracy	Measured drug content against the prescribed dose	Content uniformity across other units or batches
Uniformity of dosage units	Distribution of individual drug contents	Preservation of release behaviour
Fractional release similarity	Percentage released over time across strengths	Identical absolute release rates, or human bioequivalence
Absolute release	Milligrams released over time	Comparable fractional release when strengths differ
Systemic exposure	Pharmacokinetic measures under a defined study design	Transferability to every strength or patient group

For a dose D, the released fraction at time t is $F(t) = M(t)/D$, where $M(t)$ is the cumulative mass released. If two strengths share the same $F(t)$, the larger one releases more milligrams at any corresponding time. That is compatible with release preservation. It differs from keeping the absolute release rate constant as the dose rises. Authors should report both percentage and mass release, and decide which comparison they intend before choosing a similarity method.

2.2 Geometry and the dose equation

For a homogeneous formulation, the dose follows from a simple material balance:

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$$D = x \times \rho_s \times \varphi \times V_g$$

Here x is the mass fraction of active pharmaceutical ingredient (API) in the solid, ρ_s is the solid density, φ is the solid volume fraction of the printed object, and V_g is its envelope volume, including any designed voids. The relation assumes uniform composition and a well-defined material state. Residual solvent or drug redistribution would call for a fuller mass balance. It also shows the routes to a different dose: change x, change φ, or change V_g.

When a tablet is enlarged proportionally by a linear factor λ, the envelope volume rises by λ^3 and the external area by λ^2. At unchanged composition and relative density, an 8-fold dose requires doubling every dimension, and the external surface-area-to-volume ratio (SA/V) falls by half **(Figure 1 and Figure 2A)**. This explains why resizing alone can alter release even when the formulation is untouched. It does not predict a fixed 2-fold change in release time, because the effective wetted area and the transport mechanism may change as well.

A simple surface-flux description sharpens the point. If $dM/dt = J(t) \times A_{eff}(t)$, the fractional release rate is $dF/dt = J(t) \times A_{eff}(t)/D$. The effective wetted area A_{eff} can differ greatly from the external area in the design file. It can grow as fluid enters connected pores, shrink if pores collapse, and change as the matrix swells or erodes. Windolf and colleagues derived empirical relations between SA/V and release for printed tablets [7], but the fitted parameters belong to the formulations and test conditions they studied.

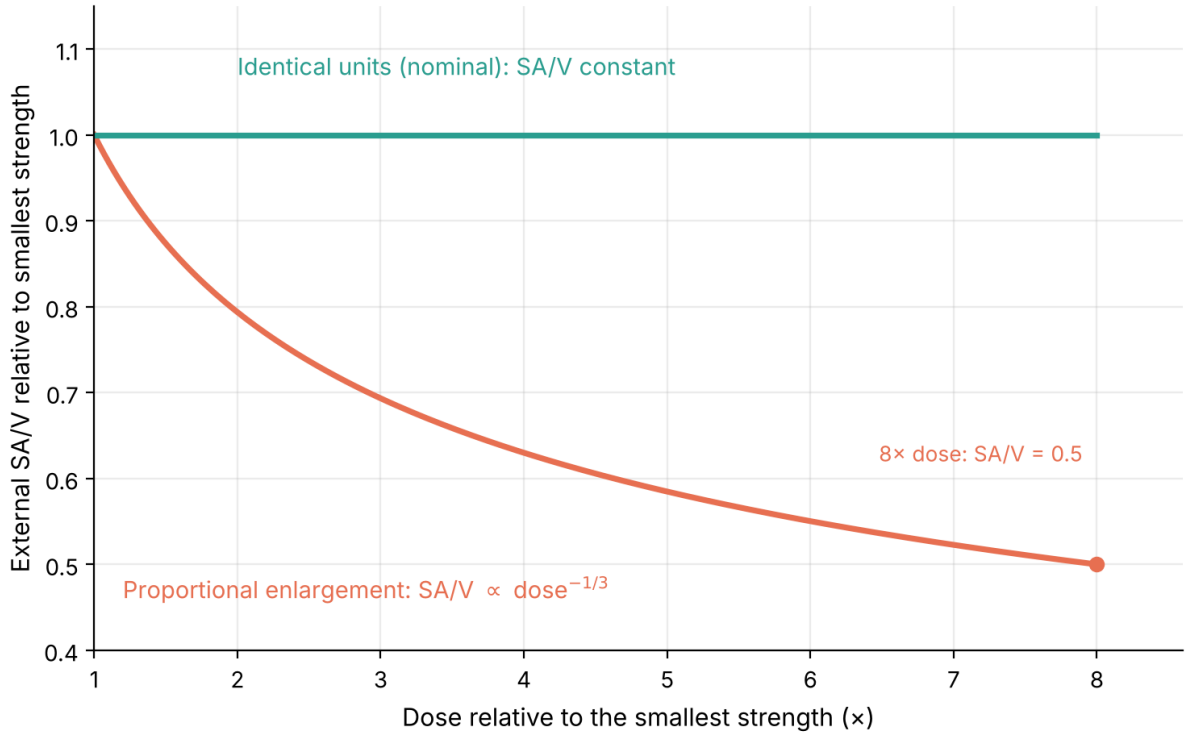


Figure 1. External SA/V relative to the smallest strength under proportional enlargement and under repetition of identical units. The curves are idealised: composition and relative density are held constant, and the units are assumed to wet independently.

2.3 The mechanism decides which descriptor matters

External area dominates in an initially dense, eroding matrix. In a swelling system, diffusion length and gel properties may matter more. In a porous tablet, how well the pores connect to the interior can outweigh nominal porosity, and in a rapidly disintegrating unit the particle population produced by disintegration becomes the release structure. The most direct illustration comes from Arburg Plastic Freeforming (APF) of paracetamol at 28.6% w/w in two polymers [8]. In Eudragit E PO tablets whose dimensions were scaled to hold the dose constant, release did not change significantly across 30% to 70% infill, but at 90% infill the geometry did matter: mean dissolution time was 9.3 min for constant-diameter tablets and 24.1 min for constant-height tablets. In Soluplus, a swelling matrix, the level of porosity governed release, and neither pore pattern nor SA/V explained the differences. No similarity factors were reported.

The lesson is that SA/V is a candidate design rule, and it needs evidence that the same release mechanism operates across every proposed strength. The descriptor used in development should describe the wetted, evolving dosage form and not only the dry object in the CAD file.

3. PRINTING PLATFORMS AND HOW EACH ONE SETS THE DOSE

Platforms differ in what the designer can vary and in what can go wrong when the dose changes (**Table 2**). Most of the dose-release evidence reviewed here comes from filament-based fused deposition modelling (FDM). Semi-solid extrusion (SSE) has been used widely in hospital and point-of-care studies [1, 9, 10], partly because it avoids heating the drug.

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Table 2. Platforms represented in the dose and release literature and their main dose-related risks.

Platform	How dose is set	Studies discussed	Main risk to release preservation
FDM from hot-melt extruded filament	Tablet size, infill, drug loading, unit count	[2, 4, 5, 11]	Filament diameter and thermal history; drug-polymer state changes with loading
Arburg Plastic Freeforming	Scaling at constant dose, infill level	[8]	Release depends on polymer swelling behaviour and critical infill
Semi-solid extrusion	Deposited volume or layer number of a single ink	[1, 9, 10]	Post-printing drying changes dimensions, pores and release
Selective laser sintering (SLS)	Tablet size within a powder bed	[12, 13]	Porosity and mechanical weakness at low mass
Binder jetting (powder bed)	Printed layers and binder droplets	[14] (manufacturer press release)	Not examined in the dose-release studies reviewed here

4. STRATEGIES FOR PRESERVING RELEASE ACROSS STRENGTHS

The approaches below are classified as follows **(Figure 2 and Table 3)**. Proportional enlargement (Section 2.2) is the reference case against which the strategies are judged. Three principal strategies are discussed: (1) shaping the geometry to hold the SA/V relationship (Section 4.1); (2) changing the number of identical units (Section 4.2); and (3) allocating drug within a fixed architecture (Sections 4.3 and 4.4). Strategy 3 has two variants, varying the drug concentration (3a) and spatial allocation or reservoir designs (3b). Both keep the external envelope fixed and change the dose through the drug placed in it, so they are treated as one strategy with different risks. Rapidly releasing products (Section 4.5) are a special case in which release is less sensitive to the strategy chosen, and not a separate strategy.

4.1 Holding the surface-area-to-volume relationship (Strategy 1)

Instead of enlarging every dimension, the geometry can be modified so that volume rises while a relevant area-to-volume relationship stays similar **(Figure 2B)**. Hollow structures are one way to do this. Wall thickness, openings and overall dimensions can be chosen to vary the drug-containing volume without the large drop in specific external area that proportional enlargement causes.

Windolf and colleagues applied a hollow-cylinder model to pramipexole, levodopa and praziquantel in polyvinyl alcohol (PVA) and in an ethylene-vinyl acetate (EVA)/PVP-VA matrix [4]. Dose varied up to 8-fold for the PVA formulations and 5.5-fold for the EVA formulation, with similarity factors above 50 and a dose step of about 0.13 mg per printed layer. This is direct evidence that purposeful geometry can support a useful dose range in specific material systems. It does not establish a universal architecture or proportional exposure in patients. Buyukgoz and colleagues, working with griseofulvin in hydroxypropyl cellulose across five tablet designs, also found SA/V to be the dominant factor in release and concluded that changing tablet size alone is unlikely to deliver the required profile [5].

Implementation depends on controlling the dimensions that govern release. A small error is a large fraction of a thin wall or narrow channel, and channels have been used on purpose to speed release from printed tablets [15]. Development should compare measured dimensions and accessible structure with the nominal design, especially near the smallest strength.

4.2 Changing the number of identical units (Strategy 2)

A second option fixes the unit and changes its count **(Figure 2C)**. For n identical units with dose d, area a and volume v, the total dose is nd and the nominal area-to-volume ratio is $na/nv = a/v$. If the units wet and release independently, the combined fractional profile should stay close to that of one unit.

Buyukgoz and colleagues made griseofulvin minitablets from a 1% w/w filament and obtained doses from 0.19 mg (1 unit) to 3.91 mg (20 units) with a linear dose-count relationship [11]. Composite groups of 5 to 20 units gave similar profiles by a bootstrap f_2 test. A single 1% unit, carrying roughly 190 µg, behaved slightly differently and had large variability, which the authors attributed to its very low drug amount. Single units at 10% and 20% loading resembled each other but not the 1% unit, and halved and quartered tablets differed significantly from one another. The study therefore supports unit-count scaling for groups of low-loading units, and it also shows where the approach stops working: at the analytical floor (where failure of the concept cannot be separated from limited analytical sensitivity), and across a wide range of drug concentration.

The approach shifts risk to dispensing. More units mean more chances for counting, transfer and administration errors. A programme should set a practical upper unit count and check whether units aggregate, float, stick to a dosing vessel or are given with food. Acceptability and swallowability of multiple minitablets in children and older adults also need to be established for each product. None of this follows from the geometric argument.

4.3 Varying concentration within a fixed architecture (Strategy 3a)

Changing x while keeping the dimensions fixed varies dose without changing the external geometry on purpose. The drug, however, is also part of the material. A different loading can change melt viscosity, solid-state form, wetting and the fraction of continuous polymer, so fixed dimensions do not guarantee fixed fractional release. In the griseofulvin and hydroxypropyl cellulose work, filaments covered 0% to 30% drug, and duo-tablets with internal

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placebo regions showed lag times that grew with the thickness of the placebo shell [5]. Evidence at an intermediate concentration cannot safely be extended to a loading at which the polymer network becomes discontinuous or crystalline drug becomes a connected phase.

Using several feedstocks can reduce the number of units a patient takes, but it adds material-management and selection risks. Each feedstock needs a defined composition and storage specification, and the product family should state which concentration and geometry combinations are allowed, so that arbitrary combinations cannot be chosen at the point of dispensing.

4.4 Spatial allocation and reservoir designs (Strategy 3b)

Printed placebo regions, drug compartments and outer barriers can set the drug amount separately from the release-controlling features **(Figure 2D)**. The separation is useful, but a drug region introduces lag time or changes the path between drug and medium, so a larger placebo region cannot be treated as a purely volumetric change. Printed coating shells around immediate-release tablets showed that both the shell formulation and the gap between core and shell influence release [16], and core-shell printlets have produced tunable zero-order profiles [17]. These studies show architectural control of release. They do not show that a fractional profile is preserved across doses. In a design with a roughly constant absolute rate, a larger load prolongs delivery, which may or may not suit the clinical aim.

4.5 Rapidly releasing products (special case)

When every strength disintegrates and dissolves quickly, modest geometric differences should matter little. Two studies are often cited in this context, and neither supports as much as it is credited with.

Krueger and colleagues printed caffeine tablets of 25, 50 and 100 mg by FDM, changing tablet size at a fixed 50% grid infill [2]. Assayed content was within about 1% to 4% of target. In 0.1 M HCl (n = 3), roughly 70% of the drug was released between 50 and 60 min and release was essentially complete by 90 min. That profile is slower than usual immediate-release expectations, and the authors fitted release models instead of calculating similarity factors between strengths. Zheng and colleagues printed prednisone tablets of 5 to 25 mg by selective laser sintering, changing only the diameter at a fixed 3.6 mm height with a 5% w/w feedstock [12]. Contents averaged 97.8% of design, disintegration took 33 to 71 s, and release was complete within 25 min, with profiles compared qualitatively to commercial tablets. The 5 mg tablets, however, had a breaking force below 10 N.

Both studies support dose flexibility. Neither calculated a similarity factor between strengths, and the caffeine tablets cannot be described as rapidly releasing. In conventional regulatory practice, profile comparison is not required when two products dissolve very rapidly, which is typically taken as 85% or more within 15 min, so f_2 would not be the appropriate tool for the prednisone data in any case. The prednisone result is also a reminder that the lowest strength is where mechanical and analytical limits first appear. **Table 3** compares the strategies discussed in this section (the special case of rapidly releasing products is not listed separately), with the conditions under which each has been shown to work.

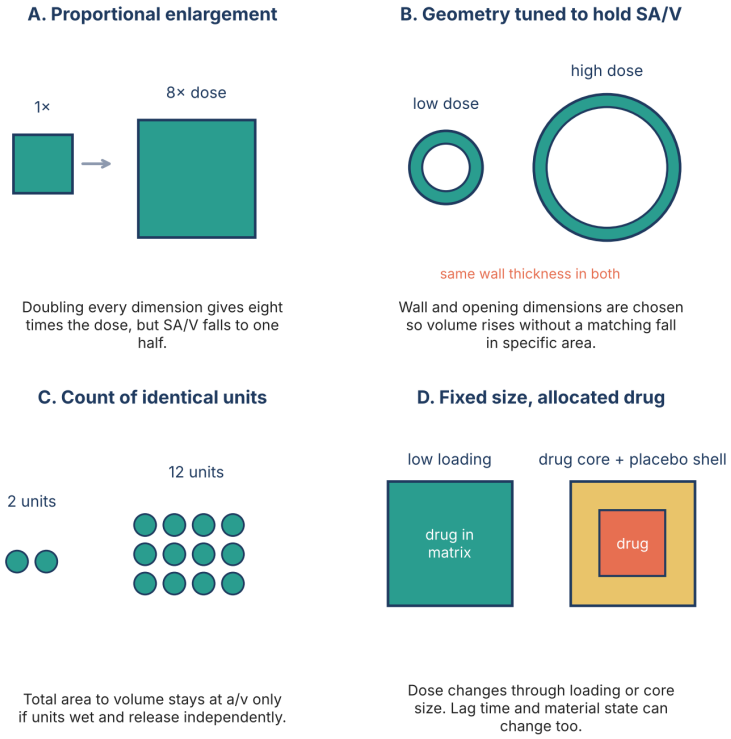


Figure 2. Four ways of changing dose, and what each one asks of the release mechanism. (A) Reference case: proportional enlargement lowers SA/V. (B) Strategy 1: hollow geometry can hold SA/V. (C) Strategy 2: a count of identical units keeps the nominal total area-to-volume ratio. (D) Strategy 3: loading (3a) or core size (3b) changes dose in a fixed envelope.

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Table 3. Comparison of dose-adjustment strategies: principle, evidence, advantages and limitations. Strategy 3 (fixed architecture) has two variants, 3a and 3b.

Strategy	Principle	Evidence reviewed	Advantages	Limitations and conditions
Reference case: proportional enlargement	All dimensions scaled; SA/V falls as dose rises	[2, 3, 8, 12]	One formulation and one design rule; simple to implement	Release changes unless the mechanism is insensitive to size (Eudragit up to 70% infill); lowest strength can be mechanically weak
Strategy 1: geometry tuned to hold SA/V	Wall, opening and overall dimensions chosen for constant specific area	[4, 5]	8-fold (PVA) and 5.5-fold (EVA) dose range with f_2 above 50; fine dose steps of about 0.13 mg per layer	Formulation-specific; thin walls and channels are sensitive to dimensional error [15]
Strategy 2: number of identical units	Total a/v equals unit a/v if units release independently	[11]	Linear dose from 0.19 to 3.91 mg; groups of 5 to 20 units similar	Single low-dose unit variable; dispensing burden and acceptability to be shown
Strategy 3a: drug concentration in a fixed architecture	Loading x varied at constant dimensions	[5, 11]	External geometry unchanged; a single 20% unit delivered 3.76 mg, so fewer units are needed	Loading changes material behaviour; 10% and 20% units differed from 1%
Strategy 3b: spatial allocation in a fixed architecture	Drug cores, placebo regions and barriers separate dose from release control	[5, 16, 17]	Tunable lag and zero-order release	Lag grows with shell thickness; fractional preservation across doses not shown

5. WHAT THE PRIMARY EVIDENCE ESTABLISHES

Evidence for release preservation: Direct, a prespecified profile-similarity assessment between strengths (f_2 or bootstrap f_2);

Supportive/partial, dose accuracy with a qualitative, mean-dissolution-time, model-fitting or single-endpoint release comparison; Not demonstrated, no release comparison between strengths. The classification is the authors' reading of what each report presents. HPC, hydroxypropyl cellulose; PVA, polyvinyl alcohol; EVA/PVP-VA, ethylene-vinyl acetate/vinylpyrrolidone-vinyl acetate.

First, dose flexibility has a wider evidence base than release preservation. Dose-mass linearity, content uniformity and an acceptable dissolution endpoint are useful, but they answer a different question from whether the fractional profile is retained. Of the studies in **Table 4**, formal similarity statistics were reported by Windolf and colleagues [4] and by Buyukgoz and colleagues [11]. The caffeine, Arburg and prednisone studies compared profiles, mean dissolution time or fitted models [2, 8, 12]. On the classification in **Table 4**, two of the eight entries give direct evidence of release preservation, four give supportive or partial evidence, and two do not address it, so the central conclusion is visible at a glance: dose flexibility is more strongly established than preservation of release.

Second, the extremes are the informative cases. The lowest strength carried the weak tablets in the prednisone study and the variable profile in the minitablet study, and the highest infill carried the geometry effect in Eudragit. Reports should present these as boundaries of the design and not as exceptions to a trend. The lowest strength is the most consistent of these boundaries, and it is discussed further in Section 11. Third, replicate numbers are small by regulatory standards. Dissolution was run in triplicate in the caffeine study, whereas current guidance for additional strengths asks for at least 12 units per strength, as discussed in Section 6.4. Conclusions in the literature are mostly drawn from a single drug-polymer pair, and extrapolation to other systems needs its own evidence. **Table 4** sets out the central studies with the quantities that bear on release preservation. Three observations follow from it. **Table 4** also states the source type of each study and classifies the strength of its evidence for release preservation as direct, supportive or partial, or not demonstrated.

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Table 4. Primary studies relevant to dose and release control, with the reported comparison and its boundary. Source type (in italics) and strength of evidence for release preservation are indicated.

Study	Platform and material	How dose was varied	Release comparison reported	Evidence for release preservation	Boundary of interpretation
Windolf 2022 [4] *Primary experimental study*	FDM; pramipexole, levodopa, praziquantel in PVA and EVA/PVP-VA	Hollow-cylinder geometry; 8-fold (PVA), 5.5-fold (EVA)	f_2 above 50	Direct	Formulation-specific, in vitro only
Buyukgoz 2020 [5] *Primary experimental study*	FDM; griseofulvin in HPC, 0% to 30% drug	Five designs, including drug loading and placebo shells	Release profiles by design	Supportive/partial	SA/V dominant; shell thickness adds lag
Buyukgoz 2022 [11] *Primary experimental study*	FDM minitablets; griseofulvin 1% to 20%	1 to 20 identical units; 0.19 to 3.91 mg	Bootstrap f_2; 5 to 20 units similar	Direct (groups of 5 to 20 units only)	Single 1% unit differed; loadings not interchangeable
McDonagh 2022 [8] *Primary experimental study*	APF; paracetamol in Eudragit E PO and Soluplus	Scaling at constant dose; 30% to 90% infill	Profiles and mean dissolution time; no f_2	Supportive/partial	Eudragit: geometry mattered at 90% infill. Soluplus: porosity governed
Krueger 2023 [2] *Primary experimental study*	FDM; caffeine	25, 50, 100 mg by tablet size at 50% infill	Model fitting; no f_2; n = 3	Supportive/partial	About 70% release at 50 to 60 min
Zheng 2025 [12] *Primary experimental study*	SLS; prednisone 5% w/w	5 to 25 mg by diameter at 3.6 mm height	Qualitative comparison; no f_2	Supportive/partial	5 mg tablets: breaking force below 10 N
Larsen 2026 [1] *Hospital pharmacy study*	SSE; metoprolol	6.25 and 12.5 mg	Dose accuracy only	Not demonstrated	One batch per condition; industry-funded
Jørgensen 2025, 2026 [18, 19] *Primary experimental study*	Extended-release printlets; Raman and NIR	Not a dose-scaling design	Content prediction; dissolution prediction	Not demonstrated	Prediction limited to the studied formulation and design domain

6. A VALIDATION FRAMEWORK FOR A FAMILY OF STRENGTHS

The following framework applies established pharmaceutical development logic to a specific problem. It is intended as a development proposal and not as a regulatory checklist. **Figure 3** gives the sequence.

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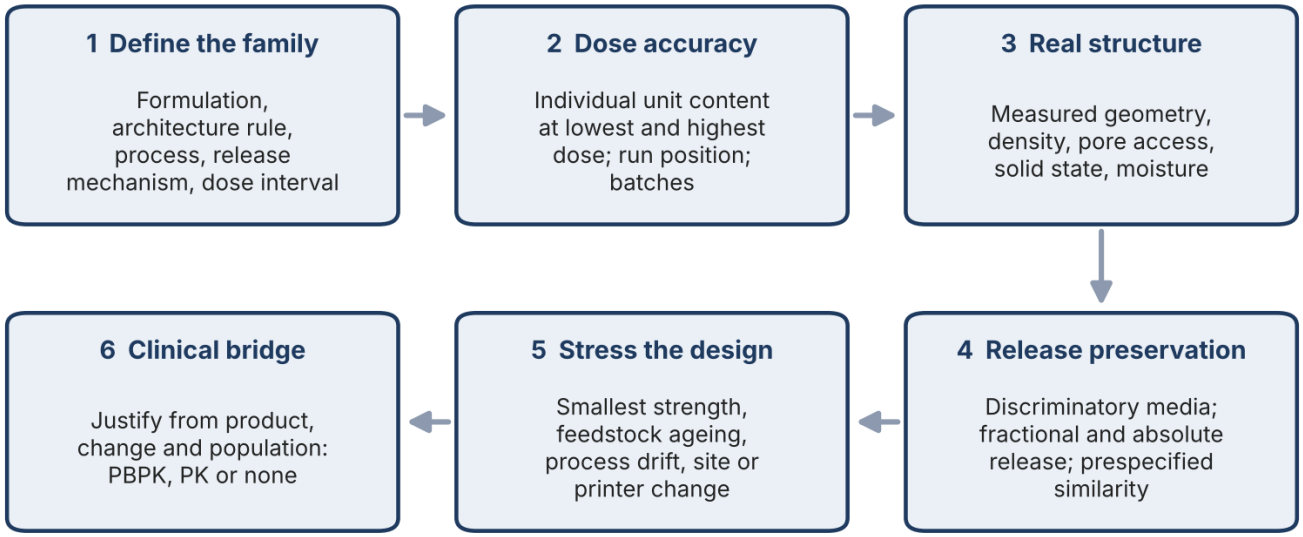


Figure 3. Proposed sequence for validating a family of printed strengths.

6.1 Define the family before choosing strengths

A family of strengths can be defined by its formulation, architectural rule, manufacturing process, intended release mechanism and permitted dose interval. This makes clear which attributes stay fixed and which change by design. A constant composition with a controlled geometry range is a different family from one built from several concentrations or from different unit counts.

The plan should name a reference strength and justify the most challenging additional strengths. Endpoints deserve attention, but an intermediate strength is also needed when there is a structural transition, a change in unit count or a different toolpath regime. Testing only the extremes does not suffice when the relation between design and performance is discontinuous.

6.2 Establish dose accuracy independently

The dose-volume relation should rest on measured drug content across the family. Verification should cover individual units, relevant batches, and the start, middle and end of a print run where segregation or equipment drift is possible. A balance detects mass errors but cannot detect a change in API concentration.

The hospital metoprolol study illustrates what printing can add [1]. Printed 6.25 mg and 12.5 mg doses gave mean contents of 98.0% to 103.4% of target, with acceptance values of 14 or below against a limit of 15. Split commercial tablets, in the same study, had mean contents of 64% to 90% of target and a much wider spread. Two cautions apply. Each printed condition was a single batch, so the statistics are largely descriptive, and several authors are employees of the company that makes the printing system, which also funded the study. The study also says nothing about release, which would still have to be established for the low-dose formulation. **Table 5** sets the printed approaches against tablet splitting, using the dose-accuracy figures reported in the studies reviewed.

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Table 5. Dose accuracy and release evidence for conventional and printed approaches to non-standard strengths.

Approach	Dose accuracy reported	Release evidence	Practical considerations
Splitting commercial tablets	Quartered 25 mg metoprolol tablets: mean 64% to 90% of 6.25 mg, individual units 24.9% to 142.8% [1]; split caffeine tablets 21% to 29% below target [2]	Halved and quartered printed tablets gave profiles that differed from one another [11]	No manufacturing step; accuracy depends on tablet and score design
Printed by size scaling (FDM, SLS)	Caffeine 25 to 100 mg: 99.0% to 103.6% of target [2]; prednisone 5 to 25 mg: mean 97.8% of design [12]	Compared qualitatively or by model fitting; no f_2 between strengths	Lowest strength can be fragile (5 mg prednisone below 10 N)
Printed by SSE, hospital setting	Metoprolol 6.25 and 12.5 mg: 98.0% to 103.4%; acceptance value 14 or below [1]	Not examined	One batch per condition; industry-funded
Printed by number of minitablets	0.19 to 3.91 mg with a linear dose-count relation [11]	Units 5 to 20 similar by bootstrap f_2; single 1% unit differed	Counting and administration errors; acceptability to be shown

6.3 Use discriminatory and analytically adequate dissolution methods

A claim of preserved release depends on the test being able to detect a meaningful change. A method that dissolves every variant quickly in highly solubilising medium can hide structural effects. Non-sink conditions, by contrast, can produce an apparent dependence on strength because the larger dose approaches saturation of the medium. Comparisons across pH, ionic strength and agitation illustrate how much the test environment can alter interpretation [20].

Analytical sensitivity needs explicit attention at the lowest strength. The validated range should cover early time points, not only the final concentration. Sampling losses, adsorption, filter recovery and volume corrections matter more for small doses, and insufficient sensitivity can be mistaken for delayed release or higher unit variability. Raising the unit count improves detectability but changes the question, since the result for a composite dose does not verify the behaviour of one minitablet. For modified-release products, early, middle and late release all need coverage, and delayed-release systems need evaluation of both the barrier and the subsequent release stage [21].

6.4 Assess similarity with a prespecified method

The regulatory benchmark most often used for profile comparison is ICH M13B, which addresses additional-strength biowaivers for immediate-release solid oral dosage forms where appropriate in vivo evidence exists for at least one strength [22]. Its dissolution criteria are therefore presented here as a useful benchmark for thinking about profile comparison, and not as a directly applicable validation pathway for an unrestricted continuum of personalised 3D printed doses. ICH Step 4 adoption (August 2026), regional implementation (for the EU, the EMA implementation document of October 2026) and the EU effective date (17 March 2027) are separate events, as set out in Section 9 [22, 33].

The conventional similarity factor is

$$f_2 = 50 \times \log_{10} \{ [1 + (1/N) \Sigma (R_i - T_i)^2]^{-0.5} \times 100 \}$$

where R_i and T_i are the mean percentages released at the same sampling time and N is the number of times included. A value of 50 or more is commonly used within regulatory comparison procedures.

Four points define the role and limits of f_2 under this benchmark. First, when both profiles show very rapid dissolution (85% or more within 15 min), further mathematical comparison is generally unnecessary under ICH M13B. Second, when variability is sufficiently low (a standard deviation of 8% or below at every time point), conventional f_2 can be used, with at least 12 units per strength [22]. Third, when variability is high, the appropriate bootstrap approach is required, using a 90% confidence interval whose lower bound is at least 46 and a median of at least 50 [22]. Fourth, an acceptable f_2 result indicates similarity of the tested in vitro dissolution profiles. It does not demonstrate bioequivalence or therapeutic equivalence, and the numerical threshold alone does not define acceptable similarity. These provisions concern immediate-release products and should not be transferred to modified-release families.

A high coefficient of determination between dose and printed volume does not establish dissolution similarity. A non-significant difference from an underpowered test does not establish equivalence either. Authors should report the prespecified comparison, the individual profiles, the variability, the sample sizes and the basis for any interval or bootstrap procedure. Exploratory experiments with a few replicates can show feasibility, but their inferential weight should not be equated with a completed regulatory comparison. Averages can also hide unit-level failure, because a mixture of units that release too quickly and too slowly can still give an acceptable mean, so individual results should be examined alongside the mean profile.

6.5 Show that the intended mechanism persists

Measured mass and geometry should be linked to internal structure and material state. Depending on the formulation, useful methods include microscopy or computed tomography, solid-state analysis, mechanical testing, moisture measurement and assessment of swelling or erosion. Each experiment should test a hypothesis about the mechanism. Controlled deviations help: deliberately altering wall thickness or drying conditions shows whether the dissolution method detects the expected failure. A comparison of FDM printing with conventional tableting for ibuprofen amorphous solid

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dispersions is a reminder that the shaping route is part of the product definition, even when the feedstock is shared [23]. **Table 6** summarises the verification tasks across the strength family.

Table 6. Proposed verification tasks across a strength family. These are development recommendations and not a regulatory checklist.

Question	Suggested challenge	Evidence to retain
Is the prescribed amount present?	Lowest and highest dose; relevant run positions	Individual content, recovery, uniformity and variability
Does the design rule describe the real object?	Smallest walls or openings; structural transition points	Measured geometry, density and relevant internal structure
Is release preserved?	Justified strengths and comparison conditions	Individual and mean mass and percentage release profiles
Can the test detect failure?	Deliberate material or process deviations	Discriminatory dissolution response and analytical recovery
Is the mechanism stable over time?	Feedstock storage and finished-product storage	Assay, impurities, physical changes and release performance
Does transfer preserve performance?	Intended equipment or site change	Confirmatory manufacturing and relevant analytical revalidation

6.6 Bridge dissolution to clinical performance

Preserved fractional dissolution can reduce uncertainty about a change in strength, but it does not establish proportional absorption or therapeutic effect. Gastrointestinal transit, food, solubility limits and patient physiology can all affect exposure, and a printed design does not guarantee that the patient takes it intact or with the intended vehicle. A volunteer MRI study of printed tablets reported that in vitro disintegration tests did not clearly correlate with the disintegration times seen in vivo [24]. Imaging measures a different endpoint from plasma exposure, but it cautions against assuming that laboratory behaviour predicts the corresponding physiological event.

Physiologically based pharmacokinetic modelling can explore the consequences of release variation. A ropinirole study combined printed formulations with virtual bioequivalence simulations, a model-based approach and not a human equivalence result [25]. A separate study reported the development and bioequivalence of a point-of-care printed medication [26]. Neither result validates arbitrary additional strengths, and the clinical bridge should match the product, the proposed change and the intended population.

7. MATERIAL AND PROCESS CONTROLS

7.1 Feedstock and deposition consistency

An architectural rule works only if the material is deposited consistently. In filament printing, diameter variation and mechanical behaviour affect delivered mass, and hot-melt extrusion fluctuations have been shown to propagate into filament properties and the mass uniformity of printed dosage forms [27]. Storage matters even when assay stays constant: a filament study found polymer-dependent changes in dimensions, flexibility and printability during storage [28]. A strength family developed on fresh feedstock should therefore be challenged with material near the justified storage limit.

Semi-solid extrusion has different dependencies. Drying changes dimensions, pores, mechanical behaviour and release, and post-printing drying conditions have been optimised specifically for point-of-care SSE manufacture [10]. Dose and release validation should refer to the finished, conditioned product, with the drying endpoint defined, and not to the freshly deposited object.

7.2 Content measurement and performance prediction are different claims

Non-destructive methods can lighten the testing burden for small personalised batches, but a content claim and a performance claim need different evidence. Near-infrared (NIR) spectroscopy has been used to predict density and release for laser-sintered tablets [13], and transmission Raman spectroscopy has been proposed as a rapid quality-control tool for personalised extended-release printlets [18]. More recently, NIR spectra combined with geometric and temporal inputs were used to predict dissolution profiles of extended-release printlets [19]. A content model alone cannot show that a malformed pore or barrier still performs its function.

For a family of strengths, predictive models should be validated by separating familiar units from new configurations. An intermediate size made from the same formulation is a different test from a new drug, printer or laboratory. A model should state which changes it covers, how out-of-domain units are identified and which manufacturing changes trigger new dissolution experiments. Machine learning has so far been applied mainly to printability, as in the M3DISEEN approach [29], and its use for predicting release across strengths needs the same domain definition. Prediction should support a justified control strategy and not replace product understanding.

8. CLINICAL TRANSLATION AND MARKETED PRODUCTS

The first 3D printed drug product to receive US approval was levetiracetam (Spritam), announced in August 2015 and made by

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powder-bed printing [14] (a manufacturer press release, cited only to document the milestone). Triastek has taken melt-extrusion-deposition products into clinical development, and one of them, a gastric-retention product, received FDA investigational new drug clearance in 2025 [30] (company press release; development information and not peer-reviewed evidence). Neither case is a dose-scaling strategy of the kind reviewed here, and both are industrial products made centrally in fixed strengths.

The personalisation evidence comes mostly from hospitals and small clinical studies. A paediatric study in rare metabolic disorders used printed personalised medicines in a clinical setting [9], the metoprolol study compared printed and split doses in pharmacy practice [1], and a case study examined transfer of feedstock and in-line NIR measurement between sites for decentralised manufacture [31]. These studies show feasibility and, in some cases, dose accuracy. They do not answer whether release is preserved across a range of strengths, which is why the clinical value of any family should be tied to a defined indication. Where dose flexibility offers a clear benefit, product performance can be established and outcomes relevant to that decision measured. **Table 7** lists the translation examples discussed in this section and what each does and does not show.

Table 7. Marketed products and clinical or hospital studies of printed oral medicines. The source type of each entry is indicated in italics.

Example	Status or setting	Relevance to dose and release control
Spritam (levetiracetam) [14] *Manufacturer press release*	First 3D printed drug product approved in the United States, announced August 2015; powder-bed printing	Industrial product in fixed strengths; not a dose-scaling design
Triastek T20G [30] *Company press release*	Gastric-retention product made by melt-extrusion deposition; FDA investigational new drug clearance, March 2025	Clinical development of a fixed design; not a dose-scaling design
Paediatric rare metabolic disorders [9] *Clinical study*	Hospital clinical study of printed personalised medicines	Shows feasibility in practice; does not test release across strengths
Metoprolol in hospital pharmacy [1] *Hospital pharmacy study*	Printed and split doses compared in pharmacy practice	Dose accuracy only; manufacturer-funded
Point-of-care printed medication [26] *Clinical study*	Development and bioequivalence reported for a printed medication	One product; does not validate other strengths
Decentralised manufacturing case study [31] *Primary experimental case study*	Transfer of feedstock and in-line NIR between sites	Feasibility of inter-site control; dose-release rule not tested

9. REGULATORY INTERPRETATION

Regulators have started to address the quality questions raised here **(Table 8)**. The European Medicines Agency (EMA) published questions and answers in 2026 on implementing 3D printing technology for solid oral dosage forms, covering material attributes, process understanding, conventional finished-product quality attributes, the possible role of non-destructive measurement, and responsibilities in technology transfer [32]. For a strength family, the relevant reading is that digital customisation has to operate within demonstrated material, manufacturing and product controls.

Table 8. Regulatory texts relevant to strength families of printed oral medicines. All entries are regulatory documents.

Document	Scope	Relevance to this review
EMA questions and answers on 3D printing technology, 2026 [32]	Solid oral dosage forms made by additive manufacturing	Material attributes, process understanding, non-destructive measurement, technology transfer
ICH M13B, Step 4 adoption, August 2026 [22]; EMA implementation [33]	Additional-strength biowaivers for immediate-release oral products	Dissolution comparison benchmark for immediate-release products only; EU effective date 17 March 2027
EMA guideline on oral modified-release products, 2014 [21]	Quality of modified-release oral products	Governs modified-release families; M13B does not apply
UK Statutory Instrument 2025 No. 87 [34]	Modular manufacture and point-of-care manufacture	In force 23 July 2025; framework for products made near the patient

ICH M13B covers additional strengths of immediate-release oral products where in vivo bioequivalence has been shown for at least one strength. It asks for a prospective dissolution comparison plan and individual and mean results from at least 12 replicates per strength [22]. It cannot be read as authorising an unlimited personalised dose range, and it does not govern modified-release medicines. The EMA implementation document, adopted on 15 October 2026 with an EU effective date of 17 March 2027, identifies the sections of the existing European bioequivalence guideline that it replaces, namely those on the strength to be investigated and on in vitro dissolution in support of strength biowaivers [33]. Adoption by ICH and regional implementation are separate events, and a

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development programme should identify which text applies in each region.

The United Kingdom has gone furthest in creating a route for products made at the point of care. Regulations that came into force on 23 July 2025 introduced a framework for point-of-care and modular manufacture, and the government overview names 3D printed products that can only be printed at the point of care as one example [34]. Requirements in other jurisdictions, including the United States, were not reviewed here and should be checked before a programme is planned. The intended dispensing workflow should set the scope of personalisation. A prescriber-selected dose can map to a verified configuration library or to a validated design rule. The second option is more flexible and carries a larger validation domain, and the manufacturer should be able to explain how a given configuration was generated, which family it belongs to and how its critical attributes were verified.

10. RESEARCH PRIORITIES AND LIMITATIONS OF THIS REVIEW

Table 9 lists the gaps that most limit confident use of dose-scaling designs and the study design that would address them. A favourable coefficient of determination or a single dissolution endpoint does not allow a central claim of preserved fractional release across strengths to be assessed, and a design rule should remain interpretable when it fails. Knowing whether failure came from analytical sensitivity, an altered material state, a new hydration pathway or a manufacturing limit transfers better than a report that several geometries passed one test.

Table 9. Research gaps and suggested study designs.

Gap	Why it matters	Suggested study design
Incomplete release reporting	Percentage release alone hides absolute differences, and the reverse	Report measured dose, composition, actual dimensions, and both absolute and fractional release; name the dose interval, media, variability and number of units
Untested failure boundaries	Mean trends conceal the lowest and highest strengths	Include the smallest practical dose, the largest architecture, concentration changes and feedstock ageing
Analytical sensitivity at low dose	Poor recovery mimics delayed release or unit variability	Validate early time points; report recovery, adsorption and filter effects
Similarity without prespecification	Post hoc methods can favour the result	Prespecify the method; use at least 12 units where guidance requires; plan a bootstrap when variability is high
Equipment and site transfer	Release control may not survive a change of printer or site	Inter-site demonstration of a dose-release design rule, building on feasibility work [31]
Predictive models without a stated domain	Models fail silently on new configurations	Define covered changes, detect out-of-domain units, and set triggers for new dissolution testing
Missing clinical link	Dissolution does not guarantee exposure	Choose an indication where flexibility has clear benefit; use PBPK or pharmacokinetic bridging suited to the product

This review has limits. The search was narrative and single-team, without screening counts or formal risk-of-bias assessment. Vat photopolymerisation and inkjet printing were not covered, and regulatory sources outside Europe and the United Kingdom were not examined. Several primary studies tested one drug and polymer pair at small replicate numbers, and conclusions about them are bounded by what the original authors reported. The classification of evidence strength in **Table 4** reflects the authors' reading of each report, and the search description in the Introduction is not a PRISMA-style systematic methodology.

11. CONCLUSIONS

3D printing can vary the oral dose while preserving a predefined fractional release profile within the studied design range, but the evidence supports bounded, formulation-specific solutions. Holding the surface-area-to-volume relationship, repeating identical units and allocating drug within a fixed architecture all work under stated conditions. Their success depends on preserving the effective release mechanism across the intended strengths and not on reproducing a nominal shape or an accurate drug amount.

The lowest strength is the clearest practical boundary to emerge independently from several parts of the reviewed evidence. It carried mechanical weakness in the prednisone tablets (breaking force below 10 N at 5 mg) [12], a variable profile in the single 1% griseofulvin minitablet that held roughly 190 µg [11], and the greatest demands on analytical recovery and early-time-point sensitivity. These observations should not all be read as failure of the formulation or design concept. Some reflect inadequate analytical sensitivity at very low dose, which can mimic delayed release or higher unit variability, and the two explanations need to be separated by validating recovery, adsorption and filter effects at the lowest strength before a design rule is judged to have failed. Programmes should therefore justify and test the lowest strength explicitly and report it separately from the rest of the family.

The next step is validation across a defined family of strengths. That needs independent content verification, discriminatory dissolution

testing with adequate analytical sensitivity, a prespecified similarity assessment, and control of material and process changes. Predictive spectroscopy can contribute once its domain is demonstrated, and clinical bridging remains necessary where the product and the proposed change require it. A clear statement of the operating limits will make personalised dosing more useful than an unqualified claim that release is independent of dose, because similarity has been shown only under specified experimental conditions.

ABBREVIATIONS

3D, three-dimensional; API, active pharmaceutical ingredient; APF, Arburg Plastic Freeforming; EMA, European Medicines Agency;

EVA, ethylene-vinyl acetate; FDM, fused deposition modelling; HPC, hydroxypropyl cellulose; ICH, International Council for Harmonisation; NIR, near-infrared; PBPK, physiologically based pharmacokinetic; PVA, polyvinyl alcohol; PVP-VA, vinylpyrrolidone-vinyl acetate; SA/V, surface-area-to-volume ratio; SLS, selective laser sintering; SSE, semi-solid extrusion.

DECLARATIONS

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this review.

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