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THREE-DIMENSIONAL PRINTING OF ORAL DOSAGE FORMS: CURRENT TECHNOLOGIES AND REGULATORY OUTLOOK

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Abstract

Three-dimensional printing builds a dosage form layer by layer from a digital design, which makes it attractive for personalised doses, complex release profiles and small-batch production. This mini review, which reports no new data, summarises published work on printing technologies used for oral products, namely extrusion-based, vat photopolymerisation, powder-bed and inkjet methods, together with materials, clinical applications, quality control and regulation. The literature shows that every major technology can yield tablets or printlets with controlled release, but most examples are laboratory demonstrations using a few model drugs. Regulatory pathways for point-of-care production are not settled, and analytical methods suited to individually produced doses remain under development.

1. INTRODUCTION

Most oral medicines are made by mixing, granulating and compressing powders on equipment designed to produce millions of identical units. That model is efficient, and it has served patients well. It is also rigid. A child who needs a fraction of an adult tablet, an older person taking several drugs who would benefit from a single combined unit, or a patient whose metabolism calls for a dose between the marketed strengths, must be accommodated by splitting, crushing or extemporaneous compounding. Each of these workarounds carries a risk of inaccurate dosing, and the evidence that tablet splitting leads to unequal portions is long-standing [1, 2, 3]. Additive manufacturing offers a

different logic, in which the dose and the geometry are specified digitally and the object is built on demand.

Dose individualisation is not a marginal issue. For drugs with a narrow therapeutic index, or those whose clearance varies widely between patients because of age, organ function or genetics, the gap between marketed strengths can matter clinically. Corticosteroids, anticoagulants, antiepileptics and immunosuppressants are familiar examples, and clinicians often handle them by combining tablets of different sizes, which adds complexity for patient and pharmacist alike. Reviews of printed medicines return repeatedly to such cases as the strongest argument for the technology, while acknowledging that few have been tested beyond the laboratory [1, 3, 4]. Printing is therefore best viewed as a tool for a defined set of unmet needs and not as a replacement for the conventional tablet.

The pharmaceutical interest in three-dimensional (3D) printing grew in the 2010s through academic groups that showed tablets could be printed with defined release behaviour, and it reached a milestone in 2015 when the United States Food and Drug Administration approved a levetiracetam tablet for oral suspension produced by a powder-bed printing process [5]. The approval showed that printed products could pass regulatory review, although it concerned a centrally manufactured, mass-produced product and not the personalised, point-of-care scenario that attracts most public attention [5, 6]. Since then the literature has expanded rapidly, with reviews counting dozens of formulations and several technologies [1, 2, 7, 8].

This mini review, which reports no new data, offers an overview of the printing technologies that have been used for oral dosage forms and the regulatory questions they raise. It begins with the principal printing methods and the materials each requires, then looks at clinical applications such as paediatric dosing, polypills and modified release, and finally examines quality control and the emerging regulatory framework. The central findings are collected in table 1, and the distribution of entries by technology and theme is shown in fig. 1. Because the field moves quickly and publication bias towards successful demonstrations is likely, the review attempts to separate what has been shown in the laboratory from what has been used with patients [3, 8, 9].

2. PRINTING TECHNOLOGIES

Standards bodies classify additive manufacturing processes into seven categories, of which four have been applied to oral dosage forms in a sustained way: material extrusion, vat photopolymerisation, powder bed fusion and binder jetting, with material jetting (inkjet) as a related approach [2, 6, 7]. Their differences matter because they determine the temperatures, solvents and excipients to which a drug is exposed, the resolution that can be achieved and the post-processing required. A technology that suits a robust drug in a polymer matrix may be unsuitable for a heat-labile peptide or a poorly soluble weakly stable compound, so no single process is likely to dominate every application [1, 3, 5].

Table 1: Printing technologies applied to oral dosage forms and representative published findings

Technology|study	Reported feature	Ref.
Fused deposition modelling Goyanes et al.	Drug loaded into filament by soaking, giving limited and variable loading	[10]
Hot-melt extrusion with FDM Zhang et al.	Controlled-release tablets from coupling extrusion and printing	[11]
Low-temperature FDM Okwuosa et al.	Immediate-release tablets printed at lower temperature with suitable polymer	[12]
Semi-solid extrusion Khaled et al.	Five-in-one polypill with distinct release profiles in separate compartments	[13]
Stereolithography Wang et al.	Modified-release tablets cured from photopolymer without heating	[14]
Stereolithography Robles-Martinez et al.	Multi-layered polypill containing six drugs	[15]
Selective laser sintering Fina et al.	Printlets with tunable release made from powder without solvent	[16]

Technology|study	Reported feature	Ref.
Selective laser sintering Fina et al.	Orally disintegrating printlets with rapid dissolution	[17]
Binder jetting Rowe et al.	Multimechanism oral dosage forms printed on a powder bed	[18]
Inkjet printing Kyobula et al.	Release tuned through complex printed geometry	[19]
Regulatory view Norman et al.	Printed drug products reviewed under existing frameworks with process validation	[5]

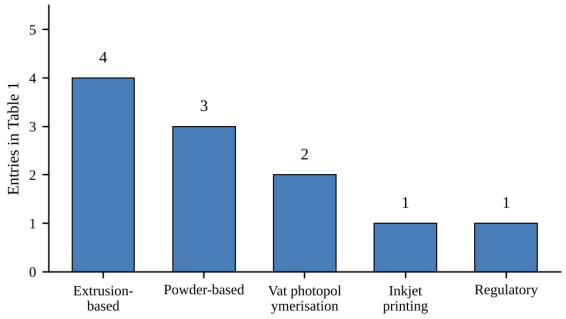


Fig. 1: Number of entries in table 1 by technology group

Fused deposition modelling (FDM) is the process most often used in academic work. A thermoplastic filament containing the drug is melted in a heated nozzle and deposited in layers that solidify on cooling. Early reports used commercial polyvinyl alcohol filament soaked in a drug solution, which gave low and variable loading [10]. The field moved on to filaments made by hot-melt extrusion, in which drug and polymer are blended at high temperature, producing higher loading and better uniformity [11, 20]. Printing then follows as a second thermal step. Coupling extrusion with printing has been used to prepare tablets with controlled release from polymers such as ethylcellulose and Eudragit grades, though the double heating raises stability concerns [11, 12].

Temperature is the central weakness of FDM. Printing generally requires nozzle temperatures above 150 °C for common pharmaceutical polymers, which can degrade labile drugs and produce impurities that would have to be controlled in a commercial setting. Researchers have responded by choosing lower-melting excipients and plasticisers. One group reported printing immediate-release tablets at a lower temperature by using a polymer grade that softened more readily, and another printed thermolabile drugs by adapting formulation and process conditions [12, 21]. These advances widen the range of candidates but do not remove the constraint, and every new drug-polymer pair must be evaluated individually for thermal stability and for solid-state form after printing [11, 20].

Semi-solid extrusion differs in that a paste or gel is forced through a syringe or nozzle at or near room temperature and then hardened by drying or cooling. This avoids high temperatures and suits thermolabile drugs, and the same principle has been used to print multi-compartment tablets. In an influential study, a five-in-one polypill with separate compartments containing different drugs and release profiles was produced by extrusion-based printing, which showed the potential of combination products with tailored kinetics [13]. A related report printed bilayer tablets with immediate and sustained release layers on a desktop printer [22]. The trade-offs are drying time, shape fidelity of soft materials and the effect of residual solvent on stability [9, 13, 22].

Vat photopolymerisation, which includes stereolithography (SLA), builds objects by selectively curing a liquid resin with light. Its resolution is high and no heat is needed, so drug degradation by temperature is not an issue. Stereolithography was used to print oral modified-release tablets containing paracetamol and 4-aminosalicylic acid, with release controlled by the drug loading and the geometry of the object [14]. A later study extended the method to a multi-layered polypill containing six drugs [15]. The principal concern here is the toxicity of the photopolymers and photoinitiators, and the need to remove unreacted monomer, together with the limited selection of pharmaceutically accepted resins [7, 14, 15].

Selective laser sintering (SLS) fuses powder particles with a laser and requires no solvent or support structure. For drugs it is attractive because the unfused powder acts as support and can be reused, and highly porous structures form that disintegrate quickly. Studies with paracetamol and other model drugs have shown that printlets (the term used

for printed tablets) with different release behaviour can be made by adjusting laser speed and powder composition [16]. Orally disintegrating printlets were also produced [17]. Drawbacks include the heat absorbed by the powder, which can degrade sensitive drugs, the need for laser-absorbing additives in some formulations and the difficulty of controlling surface roughness [7, 16, 17].

Binder jetting and inkjet approaches go back further than most of the newer methods. The first modern descriptions from the Massachusetts Institute of Technology used a printhead to deposit binder solution on a powder bed to make multi-mechanism oral dosage forms [18], and later groups printed tablets with linear release profiles and with fully customisable release profiles by changing internal architecture [23, 24]. Inkjet deposition of drug solutions onto edible substrates, including orodispersible films, offers precise dosing for low-dose potent drugs [25, 26]. A study using inkjet printing of complex geometries showed that release could be tuned through shape alone [19]. Binder jetting supports high throughput, which is why the first approved product relied on it [5, 18].

Throughput, resolution and scalability differ markedly between the methods and affect where each might be used. Binder jetting and powder-bed processes can produce many units in a single build and have a record of commercial-scale production, whereas FDM and semi-solid extrusion print one unit after another on a single nozzle and are better suited to small batches [5, 6, 18]. Stereolithography gives fine detail but depends on post-processing steps to wash and cure each object. More recent studies combine printing with advanced carriers, such as polymeric nanocapsules incorporated into printed tablets while retaining their release behaviour, which hints at functional possibilities beyond shape control [7, 27]. Speed, however, remains a limitation for any scenario in which hundreds of patients are to be served each day [8].

3. MATERIALS AND FORMULATION

Material selection constrains each technology, and a large part of the published work is formulation science in a new setting. FDM needs thermoplastic polymers with suitable rheology and mechanical strength, so that a filament feeds smoothly through the printer without breaking. Studies of hot-melt extruded filaments from pharmaceutical-grade polymers documented how composition influenced printability and mechanical behaviour, and showed that many standard excipients are too brittle or too soft without the addition of plasticisers [20]. This practical difficulty is easily overlooked in summaries that focus on release curves. A formulation that cannot be fed reliably cannot be printed, however good its dissolution profile.

Powder and paste systems use more familiar excipients, which helps regulatory acceptance. Binder jetting and SLS rely on powder blends of fillers, disintegrants and binders, while semi-solid extrusion uses gels from cellulose derivatives, starches and gelatin. In each case flow properties, particle size and wetting behaviour affect print quality, and the principles of pharmaceutical development apply as they would to conventional tablets [1, 13, 28]. A feature of printing is that structure becomes a formulation variable. Infill density, wall thickness and surface area-to-volume ratio determine dissolution as much as polymer type, and several groups have shown that identical formulations can release drug at different rates simply by changing shape [19, 29, 30].

Drug loading is a recurring constraint. Extrusion-based and photopolymerisation methods need a continuous matrix that carries the drug, and the proportion of drug that can be incorporated without compromising printability is limited, often to a modest share of the dosage form. High-dose drugs therefore pose a problem, because the printed object would become too large to swallow [11, 20]. Solubilisation of the drug in the polymer, whether as a molecular dispersion or as suspended crystals, depends on miscibility and processing temperature and determines whether the drug stays amorphous or recrystallises on storage. Work on thermolabile and low-melting drugs has shown that formulation design, rather than the

printer, usually decides whether a candidate can be printed successfully [12, 21].

Release profiles show where printing offers unusual control. Tablets with a hollow core or a porous lattice, bilayer designs and compartments with different polymers can deliver a pulsatile, delayed or sustained release that is hard to achieve with a single compression step [4, 22, 29]. A flexible-dose dispenser concept showed that the dose could be changed by altering the size of the printed object while keeping the formulation constant [31]. Prednisolone tablets printed with extended-release characteristics demonstrated how a patient-tailored product might be made for a drug with a narrow therapeutic need [4]. All these studies, however, concern a small number of model compounds, most often paracetamol, prednisolone, theophylline and caffeine [4, 10, 29].

4. CLINICAL AND PRACTICE APPLICATIONS

The most persuasive argument for printing is the patient who is poorly served by marketed strengths. Children are the standard example. Dose in paediatrics is usually based on weight or surface area, and marketed products are seldom available in the required strength or in a palatable, swallowable form. A focus-group study of healthcare professionals identified potential benefits of printed medicines for children, including accurate dosing, flavour and shape personalisation and the avoidance of liquid formulations with unstable or unpalatable ingredients, along with prerequisites such as validated processes and trained staff [32]. These perceptions are valuable, although they come from professionals and not from children or families, and no clinical trial has so far shown a paediatric outcome benefit.

Polypharmacy offers a second case. Combining several drugs in one printed unit could simplify regimens for people with cardiovascular disease, diabetes or HIV, where adherence suffers from pill burden. The five-in-one polypill and the six-drug stereolithographic printlet are proofs of concept in that direction, showing that separate compartments can release each drug on its own schedule [13, 15]. The challenge is to ensure that drug-drug interactions in the same dosage form do not compromise stability, and that the combination matches a clinically useful dosing scheme. Fixed-dose combinations already exist for many conditions, so the real advantage of printing would lie in individualised combinations that no manufacturer would make [3, 7, 9].

Hospital and community pharmacies may be where printed medicines first reach patients in a meaningful way. A Dutch hospital pharmacy study printed furosemide and sildenafil tablets, applied quality-control tests to them and discussed how the process could fit into compounding practice [33]. Compounding already involves preparing individualised doses under pharmacist responsibility, which provides a regulatory home for small-scale production, and printed doses would be more reproducible than manually prepared capsules in principle [8, 33]. The practical hurdles include capital cost, staff training, the need to validate each formulation and printer combination, and the limited printing speed compared with a conventional tablet press [8, 9, 26].

A printing workflow in practice has several links, and each is a place where errors or delays can occur. A prescription specifying the dose must be translated into a digital design, the design sliced for the specific printer, the feedstock selected and loaded, the print run executed and monitored, and the output checked, labelled and dispensed. Authors who have described this chain for hospital use emphasise that pharmacists, not engineers, should own it, because the steps correspond to the dispensing and compounding responsibilities that pharmacists already hold [8, 33]. Training, standard operating procedures and electronic prescribing links are all prerequisites, and published pilot descriptions suggest that these organisational elements are as demanding as the technology [8, 9].

Sensory and adherence-related features of printed products have received attention too. Shapes such as stars, animals or letters have been proposed for children, and colour or embossing can distinguish strengths and help patients with visual impairment or cognitive difficulties [3, 9, 32]. Orally disintegrating

printlets and printed films may suit patients with dysphagia, who struggle with conventional tablets [17, 25]. The assumption that these features improve adherence is plausible but largely untested. Evidence from properly designed studies with patient-reported outcomes would be needed before such claims are used in product development or in policy discussions [8, 32].

A final application worth noting is the incorporation of drugs that are hard to formulate conventionally. Poorly soluble compounds can be dispersed in a polymer matrix during hot-melt extrusion and printed as amorphous solid dispersions, which may improve dissolution, while controlled architectures can protect acid-labile drugs from gastric fluid [11, 21, 30]. Whether printing offers an advantage over spray-drying or conventional hot-melt extrusion for this purpose is not established, since the same enabling chemistry is available upstream of the printer. Printing contributes shape and dose control and not solubility enhancement as such, a distinction that is sometimes blurred in promotional accounts [1, 3, 11].

5. QUALITY CONTROL AND ANALYTICS

Conventional batch release depends on testing representative samples from large lots. Printing at the point of care reverses the situation: each batch may be a handful of units, perhaps a single patient's supply, so destructive tests on a sample are impractical. The quality attributes remain the familiar ones, namely identity, strength, content uniformity, dissolution, disintegration, hardness or friability, and microbial quality, but the way they are verified has to change [33, 34]. Analytical reviews of printed oral dosage forms discuss non-destructive methods, such as near-infrared and Raman spectroscopy, and imaging techniques to check composition and structure without destroying the unit [30, 34].

The hospital pharmacy study mentioned above is instructive here because it combined printing with an explicit quality-control programme, testing weight, dimensions, content and dissolution of printed tablets against pharmacopoeial expectations [33]. Mass uniformity of printed units varied with formulation and printer settings, and the authors stressed that each product-printer pair needs its own validation. This agrees with the general experience in the field that printed tablets can meet compendial requirements but only after process parameters have been optimised, and that repeatability across printers has been little studied [30, 33, 34].

The pharmaceutical quality by design framework supplies a ready vocabulary. Critical quality attributes are defined from the patient's perspective, critical process parameters identified, and a control strategy built from understanding and not from end-product testing alone [28, 35]. For printing, the process parameters include nozzle temperature, layer height, print speed, infill pattern, laser power and curing time, depending on the technology. Risk-based thinking can be applied to rank which parameters most threaten product quality, and the shift towards continuous and digitally controlled manufacturing described in the literature offers a route for integrating printing into an existing hospital or manufacturing environment [36, 37].

Dissolution and disintegration testing raise their own difficulties for printed objects. Standard apparatus was designed for compressed tablets of conventional shapes, whereas printed units may be hollow, lattice-like or irregular, and the way they sit in the vessel can affect hydrodynamics and apparent release rate [19, 29]. Studies that varied geometry while holding composition constant found marked differences in release, so the reporting of shape, orientation in the test and sinker use becomes necessary for results to be reproducible [30, 34]. Analysts have called for method development specific to printed dosage forms, and for pharmacopoeial attention to the question whether current general chapters are adequate for individually produced units [34].

6. REGULATORY OUTLOOK

Regulators have approached 3D printing mainly through existing frameworks. The first approved product was reviewed as a conventional new drug application, and FDA

scientists have described the considerations that apply to printed drug products, including the formulation, process control, in-process testing and the importance of validating the process and software [5]. The agency also issued a guidance on technical considerations for additively manufactured medical devices, which addresses design, validation and testing for devices and does not govern medicines, but its approach to process validation and digital workflows has been read across by pharmaceutical developers [38]. Together, these texts indicate that regulators see the technology as a manufacturing method rather than a distinct product category.

Centralised manufacturing of printed products is, in regulatory terms, the easiest case. A company that prints at scale operates under good manufacturing practice, files a marketing application, validates its process and releases batches, just as for any other dosage form. The harder scenario is distributed production, where printers in hospital pharmacies or clinics make patient-specific doses. Here questions arise about who holds the marketing authorisation, who is the manufacturer, how the drug substance or pre-formulated feedstock is supplied and controlled, and how quality is assured across many sites [5, 6, 8]. Several authors have suggested that a pharmacy-based model could rely on regulated feedstocks and validated printer settings issued by a central authority holder [8, 9].

Published work on quality by design, continuous manufacturing and the future of manufacturing sciences provides a common foundation that applies regardless of the manufacturing technology [35, 36, 37]. Developers of printed products are expected to describe the design space, justify the choice of process and show control over variability. For personalised dose products, the question is how to define a design space that spans a range of doses and geometries, and how much of the validation can be generic and how much must be repeated for each dose. Stability testing, container closure and labelling follow established principles, though a product made on request for a named patient raises new labelling and traceability questions [28, 30, 35].

Labelling and traceability are practical aspects that regulators will need to settle. A conventional pack carries a batch number, expiry date and storage conditions, and these allow recall and investigation of problems. A printed unit made for one patient from a digital file and a stock of feedstock requires equivalent information: the feedstock lot, the file version, the printer and settings used, and the date of printing [8]. Pharmacovigilance depends on linking adverse events to products, so this record-keeping matters beyond compliance. Published discussions suggest that existing electronic dispensing records could carry the information if designed accordingly, but harmonised requirements do not yet exist and practice would vary between countries [3, 6, 8].

Compounding law presents another route. Many jurisdictions allow pharmacists to prepare individualised medicines for patients under defined conditions, and printed doses could in principle be made under such provisions if the process is validated and documented. The attraction is that no new legal framework is needed. The difficulty is that compounding rules were written with manual preparation in mind, and they typically limit quantities and prohibit anything resembling manufacture at scale, so the boundary between compounding and manufacturing must be redrawn with care [8, 33]. Policy debate in recent years has focused on this boundary and on whether a dedicated point-of-care pathway would serve patients better than stretching existing categories [6, 8, 9].

Intellectual property, liability and data protection complete the regulatory picture. A digital file describing a dosage form is a transferable asset that can be copied, modified and shared, which raises questions about authorised use and responsibility if a modified file causes harm. Patient data used to personalise doses must be protected under health data law, and electronic prescriptions that drive printers need secure integration with pharmacy systems [6, 8]. None of these issues is unique to printing, but their combination in a single workflow is unusual and has hardly been addressed in published

guidance, which is a gap that regulators, professional bodies and manufacturers will need to close together [3, 9].

7. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations affect how confidently the literature can be read. Most published studies are laboratory demonstrations with a few model drugs and small numbers of printed units, and many report only dissolution against a reference. Clinical studies of printed oral medicines are rare, and there is no randomised evidence that printed products improve outcomes over conventional alternatives [3, 8, 9]. Reports of failures are scarce, so publication bias is likely. Direct comparison between technologies is difficult because drugs, doses and test conditions differ. As a mini review, this article is selective and cannot claim to be exhaustive, and the technologies discussed are changing quickly [1, 2, 7].

The next steps are fairly clear. Studies should test a wider range of drugs, including those with narrow therapeutic indices, using validated analytical methods and reporting reproducibility across printers and operators [30, 34]. Clinical pilot studies in paediatric or geriatric populations, comparing printed doses with standard care for accuracy, acceptability and adherence, would show whether the benefits claimed in principle appear in practice [32, 33]. Regulators and pharmacists would benefit from shared reference frameworks for point-of-care production, and for harmonised terminology that avoids confusion between mass-produced, compounded and patient-specific products [5, 8]. Progress along these lines would turn a promising technique into a dependable part of pharmaceutical practice.

Economic questions also deserve study. A printer is cheap compared with a tablet press, but a validated process, trained staff, regulated feedstocks and quality testing add expense, and the savings from avoiding waste or from improved adherence have not been quantified. Models that compare printed doses with compounded capsules or splitting of marketed tablets, in terms of cost per correct dose delivered, would help hospitals decide where printing makes sense [8, 9, 33]. Environmental aspects, including material waste, energy use and disposal of photopolymer residues, are rarely discussed in the pharmaceutical literature, though they will be asked about as the technology moves from the laboratory to routine use [7, 14].

8. CONCLUSION

Three-dimensional printing has been shown, in the laboratory, to produce oral dosage forms with controlled geometry, combined drugs and tailored release by extrusion, photopolymerisation, powder-bed and inkjet methods, and each of these has particular strengths and risks (fig. 1) [1, 5, 13, 14, 16, 18]. Thermal exposure limits fused deposition modelling, photopolymer safety limits vat processes, and powder methods demand careful control of surface and porosity. Applications in paediatric dosing, polypills, dysphagia and hospital compounding are plausible, yet clinical evidence remains thin, and the models used are dominated by a few familiar drugs [3, 4, 32, 33].

The regulatory outlook is cautiously positive for centrally manufactured products, which fit established pathways, and unsettled for point-of-care production, where responsibility, feedstock control and release testing must be defined [5, 8, 38]. Quality by design, risk management and non-destructive analytics offer a workable basis for control, but standards specific to printed doses are still taking shape [34, 35, 36, 37]. For pharmacists and formulation scientists, the immediate task is to evaluate each technology against a clinical need, validate carefully, and publish negative as well as positive results so that the field advances on evidence and not on enthusiasm [7, 9].

9. ABBREVIATIONS

3D-Three-dimensional, FDA-Food and Drug Administration, FDM-Fused deposition modelling, SLA-Stereolithography, SLS-Selective laser sintering, HME-Hot-melt extrusion, QbD-Quality by design

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Nil

11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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