Trends in Pharmacological Sciences

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Review

Advancing non-destructive analysis of 3D printed medicines

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Pharmaceutical 3D printing (3DP) has attracted significant interest over the past decade for its ability to produce personalised medicines on demand. However, current quality control (QC) requirements for traditional large-scale pharmaceutical manufacturing are irreconcilable with the production offered by 3DP. The US Food and Drug Administration (FDA) and the UK Medicines and Healthcare Products Regulatory Agency (MHRA) have recently published documents supporting the implementation of 3DP for point-of-care (PoC) manufacturing along with regulatory hurdles. The importance of process analytical technology (PAT) and non-destructive analytical tools in translating pharmaceutical 3DP has experienced a surge in recognition. This review seeks to highlight the most recent research on non-destructive pharmaceutical 3DP analysis, while also proposing plausible QC systems that complement the pharmaceutical 3DP workflow. In closing, outstanding challenges in integrating these analytical tools into pharmaceutical 3DP workflows are discussed.

Highlights

3D printing of medicines holds the potential to revolutionise therapeutic regimens and manufacture by offering tuneable, personalised, and on-demand manufacture at a small scale and at the PoC.

Regulatory authorities have established expert working groups and have called for stakeholder feedback to develop new, additional regulatory guidelines concerning implementation and QC for decentralised and PoC manufacturing.

Recent research has demonstrated the applications of non-destructive analytical techniques (herein PATs) as measures to assess the quality of the printed therapeutics. In particular, spectroscopic and chemical imaging techniques have been highlighted.

Moreover, some research has demonstrated the feasibility of implementing process control monitoring tools to assure the quality of 3D printed drug products.

QC challenges for pharmaceutical 3D printing

Pharmaceutical 3DP has experienced significant interest and advances over the past decade for its potential to produce highly versatile drug products that in turn afford enhanced clinical outcomes [1]. There are numerous applications, and one that has garnered considerable research interest is individualised on-demand manufacturing at the PoC [2–4]. Despite growing research efforts, PoC manufacturing of medicines by 3DP has struggled to reach large-scale adoption owing to QC challenges. QC measures are integral in assuring the safety and efficacy of marketed medicines. The existing regulatory framework for pharmaceutical manufacture has been adapted over decades for large-scale batch manufacturing platforms. Conversely, pharmaceutical 3DP of personalised dosage forms involve on-demand and small-scale manufacture wherein minimal to no time or excess finished products are available for QC tests. Therefore, owing to their inherently destructive and time-consuming nature, traditional end-product testing is unsuitable for personalised manufacture by 3DP.

Several medicines regulatory agencies have recently taken tangible steps to support implementation of PoC manufacture. The UK MHRA published the *Consultation on Point of Care Manufacturing* in August 2021, outlining challenges for PoC manufacture and a potential regulatory framework [5]. Feedback and government responses were published in January 2023 that highlighted the overwhelming support for a new or supplementary regulatory framework for PoC manufacture [6]. Similarly, in October 2022, the US FDA published a discussion paper that outlined the advantages of PoC and distributed manufacturing (DM) platforms, and sought feedback from external stakeholders to develop feasible regulatory guidelines [7]. Responses are anticipated to be published soon. Common to both publications was emphasis on the need for new assurance measures during manufacture, such as **in-line** (see Glossary) PAT

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tools, to safeguard patient safety and ensure product efficacy. In addition, in late November 2022, the European Medicines Agency (EMA) established a Quality Innovation Expert Group to support translation of novel strategies for manufacture and QC of medicines [8]. Their first focus group meeting was held in March 2023 and focused on decentralised manufacturing.

Given the regulatory tailwind, there is strong motivation for further research into PAT and non-destructive analytical tools for safeguarding the quality of 3DP medicines. Therefore, we first highlight 3DP technologies of most relevance to the pharmaceutical space before briefly outlining existing QC frameworks. The latter, coupled with insights from discussions with regulatory authorities, form the basis of our proposed QC systems for 3DP medicines. Recent advances in PAT and non-destructive analytical tools for pharmaceutical 3DP QC are subsequently reviewed, with suggestions for how they may fit into the proposed QC workflows. Finally, outstanding challenges are discussed to allow readers to appreciate the steps necessary to realise PoC pharmaceutical 3DP.

Principles of pharmaceutical 3DP

3DP, or additive manufacturing, is a manufacturing technology characterised by a layer-by-layer approach for constructing the final product based on computer-aided design [9]. Additive manufacturing technologies are divided into seven categories based on their underlying working principles, and their terminology has been standardised by the American Society for Testing and Materials (ASTM) (Box 1) [10]. While almost every 3DP technology has received comparable research attention in the pharmaceutical space, some have not reached the same **technology**

Box 1. Working principles of selected 3DP technologies

The ASTM classified 3DP (or additive manufacturing) technologies into seven different categories according to the mechanism by which the 3D geometry is built. These are vat photopolymerisation, material jetting, binder jetting, material extrusion, powder bed fusion, sheet lamination, and directed energy deposition. In medicines, subtechnologies that have gained notable traction belong to the binder jetting, powder bed fusion, material extrusion, and material jetting categories (Figure I). As such, focus will be on these categories; interested readers may refer to the following reviews for detailed explanation on other 3DP technologies [84–86].

Material extrusion technologies

These extrude and deposit a continuous filament through a nozzle to build the desired 3D geometry. Material extrusion subtechnologies that have been explored in pharmaceutical research are fused deposition modelling (FDM), direct powder extrusion (DPE), and semi-solid extrusion (SSE). In FDM, thermoplastic filaments are heated through an extrusion head and nozzle, where they melt to form thin strands that are subsequently deposited onto a build plate where they cool, and solidify. In medicines, these thermoplastic filaments are prepared through a preliminary process known as hot melt extrusion, where a mixture of powder is blended, melted, and extruded through a nozzle. DPE streamlines this process by obviating the need to prepare filaments. Instead, the powder formulation is directly fed into the extruder, where it is mixed, melted, and extruded as thin strands through a nozzle. In SSE, semi-solid material (e.g., gels and pastes) are loaded into syringes and extruded through a nozzle by applying pressure [87].

Powder bed fusion technologies

These melt or sinter and fuse layers of material powder, deposited on a powder-bed, using a laser or electron beam. The sole powder bed fusion technology that has been used for pharmaceutical applications is selective laser sintering (SLS). A diode laser is used to sinter a drug-loaded powder bed layer-by-layer. After each layer is sintered, a roller spreads a fresh layer of powder above the sintered object [88].

Binder jetting technologies

These involve depositing a liquid binding agent onto a powder bed to 'glue' the particles together, and works similarly to SLS. Binder jetting was used to produce the first FDA-approved 3DP medicine (Spritam®) [89].

Material jetting technologies

These involve dispensing droplets through a printhead. The feedstock for these technologies is liquid inks. For medicines production, inkjet printing (IJP) has been explored for fabricating both drug-loaded films and tablets. Ink droplets are dispensed either through rapid vaporisation by heating (thermal inkjet) or through pressure exerted by piezoelectric mechanical deformation (piezoelectric inkjet) [90].

Glossary

At-line: scenario in which samples are removed from the process stream, and are analysed within the processing area, but are not returned to the process stream.
Classical least squares: linear mixture model relating final spectrum to weighted component contributions from individual reference spectra.
Cytotoxicity: the damage that a substance can cause to cells.
Differential scanning calorimetry (DSC): a thermoanalytical technique that measures the heat absorbed or released by an analyte as it undergoes thermal transitions over a range of temperatures.
Gas chromatography (GC): a technique used to separate and analyse constituents of an analyte that can be vaporised without decomposition.
High-performance liquid chromatography (HPLC): a technique to separate, identify, and quantify constituents of a liquid analyte under high pressure.
International Council for Harmonisation: an organisation that aims to achieve greater unification and harmonisation of pharmaceutical development and manufacturing processes in the quest of safe and efficacious medicines through collaboration between regulatory bodies and pharmaceutical industries.
In-line: scenario in which the analytical probe head is directly inserted into the process stream.
Liquid chromatography–mass spectrometry (LC-MS): an analytical technique that combines liquid chromatography (HPLC) with MS. The latter is a technique used to measure the molecular mass of constituents of an analyte.
Medicines adherence: the extent to which the actions or behaviour of a patient conforms to their prescribed medication regime.
Multivariate curve resolution-alternating least squares: iterative algorithm used to separate and quantify individual components in mixtures by bilinear models.
Off-line: scenario in which samples are removed from the process stream and are taken to a separate laboratory located outside the processing area for analysis.
On-line: scenario in which samples are removed from the process stream,

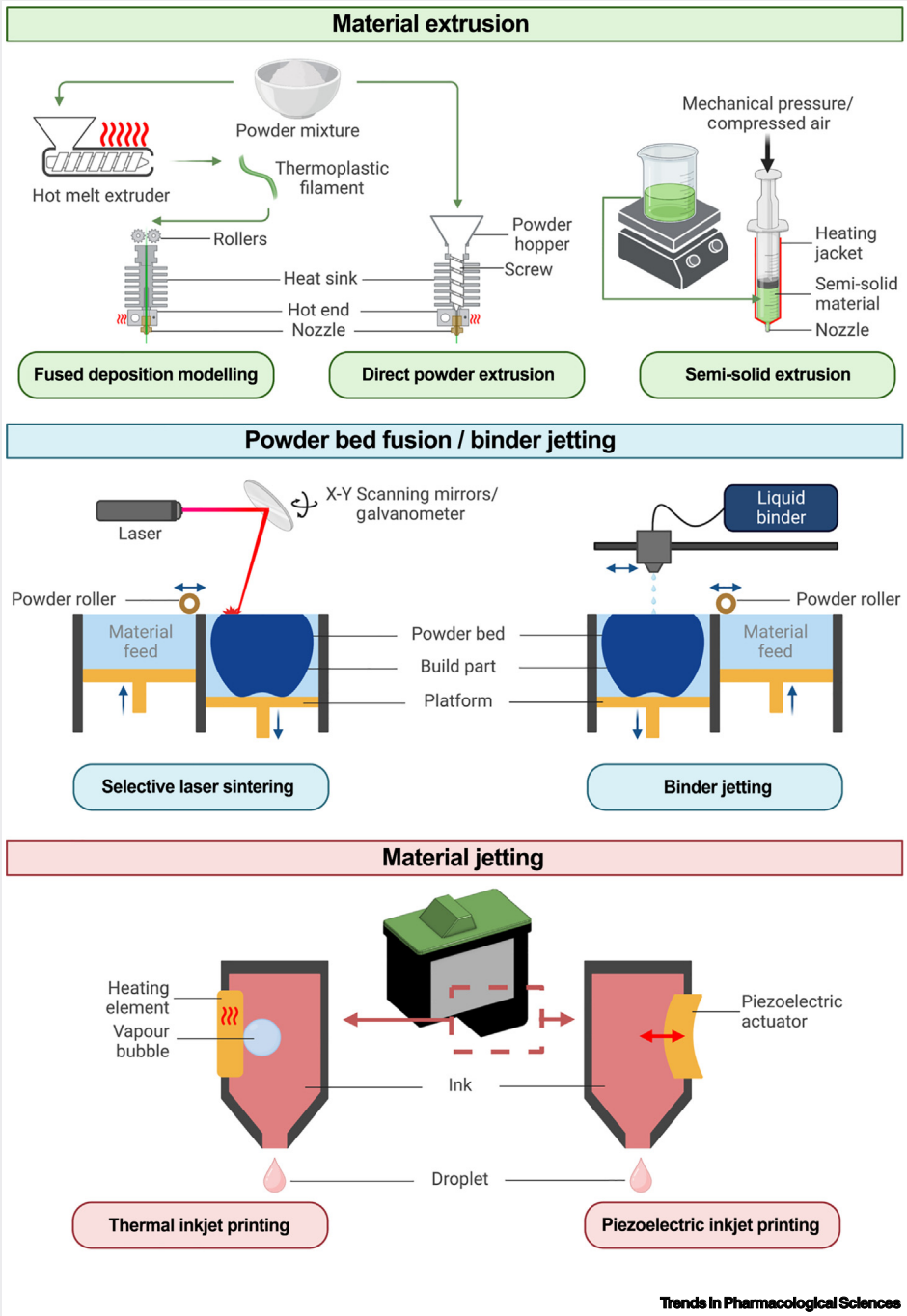

Figure I. Schematic representation of working principles of material extrusion, powder bed fusion, and material jetting 3D printing. Figure created with BioRender.com.

are analysed within the processing area, and are returned to the process stream.

Partial least squares regression: multivariate model based on covariance, working by reducing variables to create predictors for regression.

Principal component analysis: model reducing dimensionality of dataset to new, fewer variables with largest possible variance.

Printlet: a 3D printed oral dosage form, such as a tablet or a capsule.

Technology readiness levels (TRLs): a measure of the maturity of a given technology. There are nine TRLs, where TRL 1 is the least mature.

Unit operation: a basic step involving a physical or chemical change in a multistep process.

UV/vis spectroscopy: a quantitative technique used to measure the amount of light an analyte absorbs across the UV and visible ranges of the electromagnetic spectrum.

X-ray powder diffraction: a non-destructive analytical technique used to characterise the physical properties, such as crystal structure and unit cell dimensions, of powder materials.

readiness level (TRL) owing to issues such as the **cytotoxicity** of the feedstock [11]. This review focuses on 3DP technologies that, in our opinion, are on the cusp of transitioning from TRL 4 to TRL 5 – defined as the transition from validation in laboratory settings to relevant (in

this case clinical) environments [12]. These are namely binder jetting, powder bed fusion (selective laser sintering, SLS), material extrusion (fused deposition modelling, FDM), semi-solid extrusion (SSE), direct powder extrusion (DPE), and material jetting (inkjet printing, IJP). Their principles are briefly outlined in Box 1.

Research in personalised 3D printed medicines has introduced a model of decentralised pharmaceutical manufacture and distribution, in contrast to conventional centralised factory-based manufacture. This model of personalised medicines affords numerous clinical benefits, such as producing patient-friendly formulations to improve **medicines adherence** (e.g., chewables for paediatrics [13,14], unique geometries [15,16], and personalised polypills [17,18]), and reducing adverse drug reactions through tailored dosages and release behaviours [19,20]. Despite significant research efforts, only one 3DP pharmaceutical product (Spritam®) has been commercialised to date [21]. Furthermore, until recently, most 3DP medicines in clinical trials were produced in masses (notably T19, T20, and T21 from Triastek) [22]. Although this highlights the potential of 3DP as a pharmaceutical manufacturing technology, it is still merely used for mass production and therefore conforms to existing regulatory frameworks. Instead, to achieve widespread deployment of PoC pharmaceutical 3DP, present-day QC systems and regulatory frameworks must be readapted.

Current state of pharmaceutical QC

Adopting PAT and non-destructive analytical tools as replacements for traditional end-product testing first requires an understanding of the product specifications that existing QC measures assess. Specified pharmacopeial tests for finished products, often referred to as the quality by testing (QbT) regime, constitute the conventional QC workflow for drug products [23]. These include, but are not limited to, content uniformity, uniformity of mass, friability, and dissolution testing. Most prescribed assessments are destructive in nature, and rely on analysis through labour-intensive techniques such as **high-performance liquid chromatography (HPLC)**, **liquid chromatography–mass spectrometry (LC-MS)**, **gas chromatography (GC)**, and **UV/vis spectroscopy** [24–27]. Solid-state analysis may be performed destructively via **differential scanning calorimetry (DSC)** and non-destructively through **X-ray powder diffraction (XRPD)** [26].

Recently, the emergence of an alternative approach to pharmaceutical quality assurance, termed quality by design (QbD), underpins the importance of understanding the interplay between

Table 1. Examples of CQAs according to unit operation for the manufacture of oral drug products.

Unit operation	CQAs	Importance
Mixing	Particle size distribution	May influence dissolution behaviour and extent of compaction
	Content uniformity	Ensures homogeneity of blend, which influences content uniformity
	Flow characteristics	Influences mass and content uniformity
Tablet compaction	Content uniformity	Ensures that every product contains the marketed amount of active pharmaceutical ingredient, thereby assuring the therapeutic performance of the batch of products
	Uniformity of mass	Surrogate of content uniformity – assures that every product contains the marketed amount of the active pharmaceutical ingredient
	Porosity	Influences the exposed surface area and consequently affects the rates of disintegration, dissolution, and drug release
Tablet coating	Coating thickness	Influences the rates of dissolution and drug release
	Friability	Tablets with high friability cannot be easily handled by patients, and breakage before administration could lead to inaccurate dosing
	Uniformity of weight gain	Ensures equal coating of the entire batch

Abbreviation: CQAs, critical quality attributes.

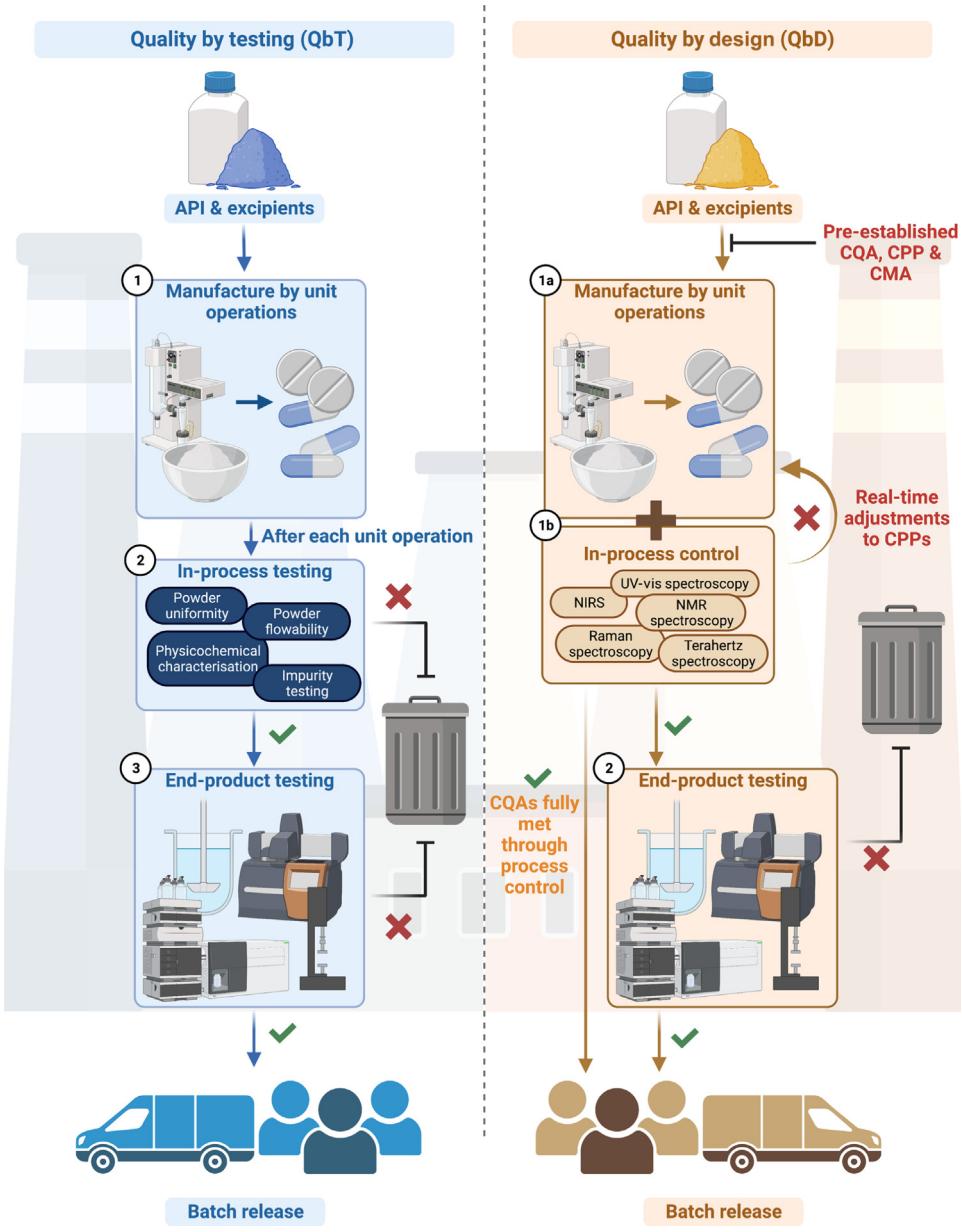

Figure 1. Pharmaceutical quality control workflows through quality by testing (QbT) and quality by design (QbD). In QbT (blue), the drug product quality is assured through extensive end-product testing according to pharmacopeial tests and analytical methods before release of the batch (part 3). The manufacturing process is monitored through in-line testing after each unit operation to assess various characteristics (part 2). Produce is discarded at any stage of the production line upon failed tests. In QbD (yellow), drug product quality is assured through the monitoring of predefined critical quality attributes (CQAs) throughout the manufacturing process by process analytical technologies (PATs) (1a and 1b). Understanding CQAs as the results of critical processing parameters (CPPs) and critical material attributes (CMAs) allows for real-time processing adjustments to obtain desired CQA readouts. Full understanding and control of CQAs, CPPs, and CMAs enable real-time release of batches. End-product testing is required in cases of partial employment of QbD manufacturing workflows (2) where test failures lead to discarded produce. Depicted end-product tests are dissolution testing, differential scanning calorimetry (DSC), high-performance liquid chromatography (HPLC), mass spectrometry (MS), and hardness tests. Abbreviations: API, active pharmaceutical ingredient; NIRS, near-IR spectroscopy; NMR, nuclear magnetic resonance. Figure created with BioRender.com.

materials and process for attaining desired product quality, with general guidelines issued by the **International Council for Harmonisation** [28]. Identifying the critical quality attributes (CQAs) for each **unit operation** in the process stream, and understanding these as functions of the critical process parameters (CPPs) and critical material attributes (CMAs), are of high importance in QbD [23,29]. Examples of CQAs for oral drug product manufacturing, stratified according to examples of unit operations, are listed in Table 1.

PATs are analytical instruments used to monitor and analyse the defined CQAs and CPPs, allowing control of the pharmaceutical manufacturing process [30]. Commonly used PATs include spectroscopic techniques such as near-IR spectroscopy (NIRS), IR spectroscopy, Raman spectroscopy (RS), nuclear magnetic resonance (NMR) spectroscopy, and UV/vis spectroscopy [31–34]. These may be installed **off-line**, **at-line**, **on-line**, or in-line, and can provide quantitative and qualitative information. Direct measurements of CQAs via PAT tools are not always possible, and modelling of CQAs based on PAT readouts is necessary [35].

One of the major aims of QbD and PAT implementation is to enable real-time release testing (RTRT), assuring pharmaceutical product quality without destructive end-product testing by having a comprehensive understanding of process and product through CQAs, CMAs, and CPPs [28,36]. Although RTRT is considered to be the optimal workflow for pharmaceutical quality assurance, and there are cases of industrial use, the extent of its full implementation in industry remains limited [23,30,37,38]. Extensive end-product testing is still obligated in cases where QbD and PAT tools are only partially used for process control. Figure 1 depicts current QC workflows in pharmaceutical manufacturing through both QbT and QbD.

Given the need for non-destructive QC measures, adoption of QbD principles for pharmaceutical 3DP would be highly sensible for practical and successful clinical implementations [39,40].

Proposed QC systems for pharmaceutical 3DP

Recognition by national regulatory agencies of 3DP as a decentralised manufacturing strategy warrants rethinking of applicable QC measures [5–7,41,42]. However, the most suitable QC technology and workflow to implement are likely dependent on the distribution model for personalised PoC **printlets** (3D printed tablets) [43]. Following numerous consultations with regulatory authorities, we anticipate three possible distribution models that differ in their workflows from manufacture of the intermediary pharmaceutical feedstock formulation through to dispensing (Figure 2). Briefly, route A emphasises the PoC manufacturing model in its entirety, where raw materials are shipped directly to PoC facilities for on-site feedstock formulation and manufacture of printlets that are directly dispensed to patients. On the other hand, in routes B and C, feedstock is formulated at a DM site, for example a specialised pharmaceutical company. The pharmaceutical feedstock is then used in 3DP manufacture at either the PoC facility for subsequent dispensing (route B) or at the DM facility before being sent to the patient (route C) [44,45]. Through route C, off-line QC testing may also be performed onsite (within the same manufacturing facility) or offsite (in a separate specialised QC lab). Undoubtedly, the different routes from formulation to dispensing will require, and be amenable to, different QC measures. For instance, batch manufacture of pharmaceutical feedstock (via route B/C) could be amenable to testing via both emerging non-destructive and conventional destructive methods, whereas non-destructive QC is an absolute necessity for on-demand feedstock formulation (route A) and post-printing QC.

Application of non-destructive analytical and PAT tools in pharmaceutical 3DP

Recently, PAT and non-destructive analytical tools for quality assessment of 3DP drug products have gained increasing research interest. Most work has involved the use of NIRS and RS, with

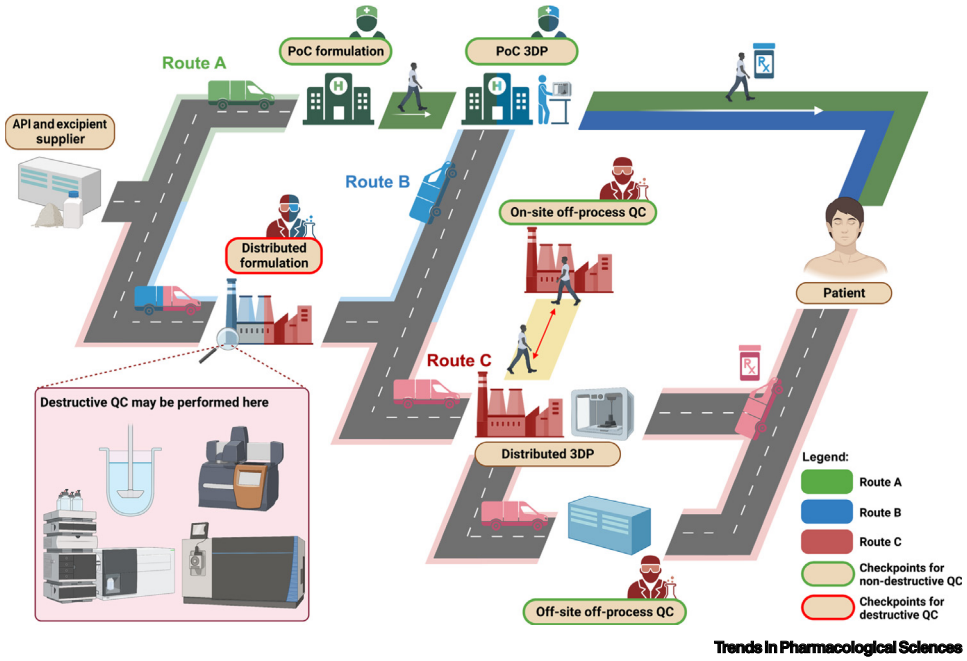

Figure 2. Plausible supply chain and distribution models for pharmaceutical 3D printing (3DP) personalised medicines. Three different routes for dispensing personalised 3DP pharmaceuticals to patients are envisaged. Route A (green icons) outlines the full point-of-care (PoC) route with feedstock formulation, pharmaceutical 3DP, and quality control (QC) all taking place at the PoC with subsequent dispensing. Route B (blue icons) outlines a partial PoC route where feedstock formulation and QC thereof are performed at a distributed manufacturing (DM) site that is amenable to mass produce QC workflows. Feedstocks are then shipped to the PoC for pharmaceutical 3DP and QC followed by dispensing. Route C (red icons) details a model relying on production fully located at DM sites. Feedstock formulation, 3DP, and all QC are undertaken at or for the DM sites, followed by delivery of the medicines to the patient. Red borders indicate that destructive, conventional QC measures [the red box depicts, from upper left to right, dissolution bath, differential scanning calorimetry (DSC), liquid chromatography–mass spectrometry (LC-MS), and mass spectrometry (MS)] may be performed at this stage, whereas non-destructive QC measures are vital in scenarios with green borders. Vans are indicative of shipment processes. Abbreviation: API, active pharmaceutical ingredient. Figure created with BioRender.com

some also examining hyperspectral imaging. Their working principles are briefly introduced in Box 2, and a review of these analytical tools for 3DP medicines is presented in the following section (Figure 3, Key figure).

Near-IR spectroscopy

Both transmittance NIRS (tNIRS) and reflectance NIRS (rNIRS) are suitable for the quantification and qualification of samples with limited to no sample preparation. To obtain a comprehensive spectrum of the sample through all its layers, tNIRS will be advantageous. However, a sample that is too thick or densely packed may lead to minimal to no signal at the detector. Conversely, rNIRS signals are often prominent, though its major disadvantage is that signals arise only from the shallowest layers of the sample, preventing appreciation of inhomogeneity through the entire sample. Consequently, use of rNIRS in pharmaceutical 3DP may require analysis to be performed on a layer-by-layer basis. Therefore, the thickness of the printed product needs to be considered when determining the appropriate format of NIRS to use.

Most applications of NIRS in pharmaceutical 3DP have centred around drug quantification. A comparative study of tNIRS and rNIRS for the quantification of three distinct drugs (propranolol, montelukast, and haloperidol) deposited onto porous substrates via IJP was published by Edinger *et al.* [46]. Interestingly, in all three cases, tNIRS failed to produce reliable predictive

Box 2. Principles of selected process analytical technologies (PATs)

Near-IR spectroscopy (NIRS) and Raman spectroscopy (RS) are both vibrational spectroscopic techniques. NIRS works based on absorption of light due to vibrational bending and stretching of intramolecular bonds across the wavelengths 780–2500 nm [91]. Each physical or chemical entity has a unique NIR spectrum, making it useful for identifying components either stand-alone or within a sample matrix [92]. Absorbances in NIR spectra are broad, necessitating proper model development for analysis, and the presence of water can mask absorption peaks characteristic of the analyte. NIRS can be configured in two modes; transmission mode (tNIRS) and reflectance mode (rNIRS), the difference being that the light source and the detector are located on either the opposite or the same side of the sample, respectively. Portable and handheld NIRS devices are typically only capable of the latter [76].

An extension to NIRS is near-IR hyperspectral imaging (NIR-HSI), which is a chemical imaging technique. The data in the hyperspectral image is constructed by a 3D data array in which two of the dimensions represent the spatially resolved information and the third dimension carries the spectral information. Each pixel in the hyperspectral image thus has a corresponding NIR spectrum, thereby providing spatially resolved chemical and physical sample information [54,93].

On the other hand, RS works by sample irradiation through a monochromatic laser which causes either Rayleigh scattering (light scattered at the same frequency as the incident light and constitutes the bulk of sample scattering) or through Raman scattering (occurring at frequencies below or above that of the incident light) [94]. RS may be configured in either transmittance or backscattering modes. Compared to NIRS, RS scattering signals tend to be weaker; however, active pharmaceutical ingredients (APIs) are usually stronger Raman scatterers than pharmaceutical excipients, and Raman scattering also produces a fingerprint that directly relates to analyte concentration, highlighting its applications in pharmaceutical analyses [95–97]. RS may also be beneficial for samples containing water or in the aqueous state because water is a very weak Raman scatterer. The downsides of RS include induced sample fluorescence from incident laser light and potential sample degradation from the use of high-intensity lasers [98].

Both NIRS and RS can deliver quantitative and qualitative sample information on the foundation of properly built models. Spectral preprocessing is necessary before statistical and mathematical modelling of chemical data can be performed, collectively known as chemometrics, which is crucial for model development [99,100]. Multivariate and classification modelling methods are frequently utilised, and selection of the appropriate chemometric method is imperative for model performance.

models by **partial least squares regression** (PLSR), and this was hypothesised to be due to detector oversaturation from the highly porous samples. On the other hand, rNIRS resulted in high-correlation PLSR models for propranolol and montelukast ($R^2 \geq 0.98$) and haloperidol ($R^2 \geq 0.96$) [46]. High porosity of 3DP pharmaceuticals may be a desired property, and this study demonstrated that rNIRS could be the optimal configuration for quantification of samples with this physical characteristic.

The first investigation of NIRS for quantitative analysis in SLS printlets, containing paracetamol, achieved a highly linear quantitative model ($R^2 = 0.996$) [47]. Likewise, NIRS has also been used to quantify the drug content of IJP printed products: Pollard *et al.* demonstrated that NIRS can accurately quantify timolol loading onto contact lenses ($R^2 = 0.9120$) through iterative IJP cycles [48]. The former was obtained through a portable device covering more spectral wavelengths than the latter (accomplished through a handheld sensor), potentially leading to better model performance. In addition, presence of water in the contact lenses may have had negative effects on timolol quantification because peaks arising from water in NIRS spectra are large and broad, potentially leading to distorted spectral interpretation of signals originating from the drug. Both cases utilised PLSR for model development.

One way to potentially overcome spectral noise (i.e., from water) may be to develop the model using subareas of the acquired absorbance spectra intrinsic to the analyte of interest. This approach was demonstrated for SLS printlets containing two distinct drugs, amlodipine and lisinopril, with quantitative PLSR models ($R^2 = 0.997$ and $R^2 = 0.991$) developed from data acquired by rNIRS [49]. Overall, high linearity was observed for both drugs, although important spectral information captured outside of the respective zones may have been neglected. Nonetheless, studies comparing full- and subset spectral approaches for pharmaceutical 3DP, particularly for multiple drugs, have not been published.

Key figure

Principles and applications of selected analytical technologies for pharmaceutical point of care (PoC) 3D printing (3DP)

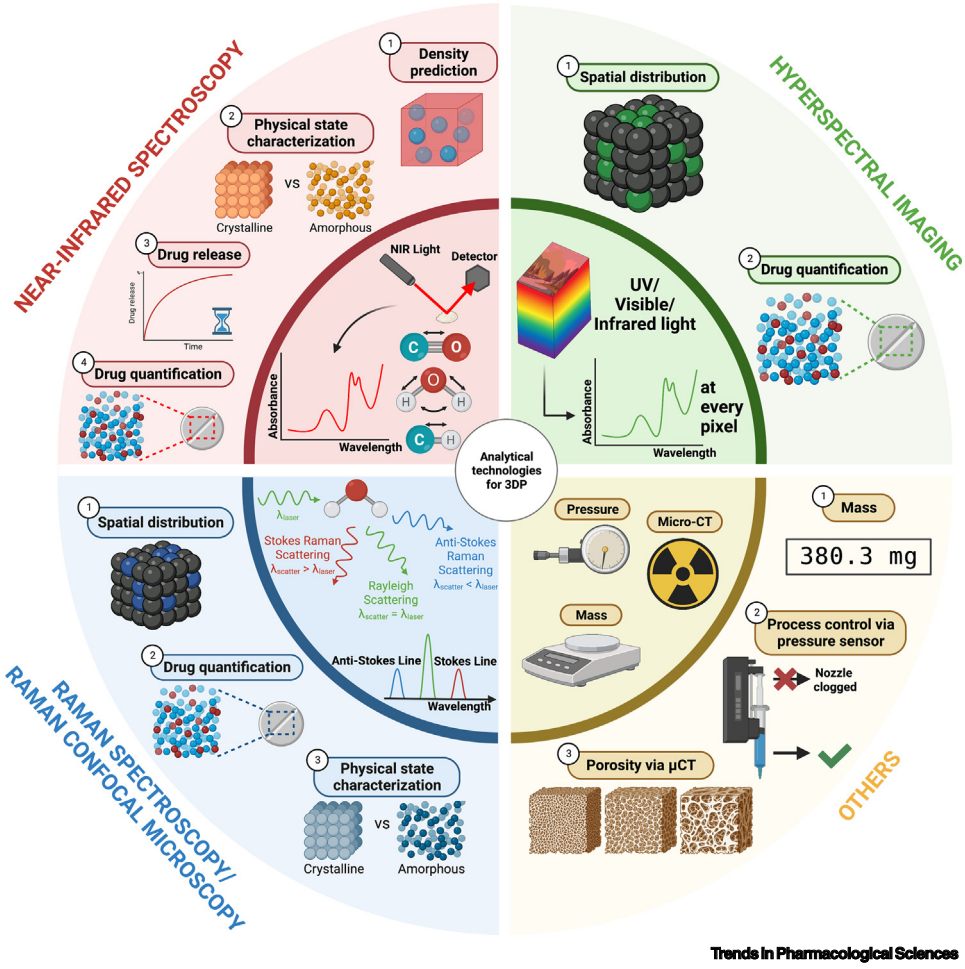

Figure 3. Selected analytical technologies applied as quality control (QC) measures for 3DP pharmaceuticals stratified by technology. Schematics captured within the inner circle depict working principles of the technologies, and the outer ring highlights the applications of the technique for 3DP of pharmaceuticals. Near-IR (NIR) spectroscopy (NIRS) (red section) has been applied for drug quantification and qualification of both crystalline and amorphous substances, as well as density and drug release predictions. Hyperspectral imaging (green section) has been coupled with NIRS for drug quantification and spatial distribution in the printed drug products. Raman spectroscopy and Raman confocal microscopy (blue section) have been utilised for drug quantification and qualification of crystalline and amorphous contents, as well as the spatial distribution of drugs in the printed pharmaceuticals. Other techniques (yellow section) include X-ray microtomography (µCT/micro-CT) for porosity evaluation, mass uniformity by weight analysis, and pressure sensor incorporation for process control of extrusion-based 3DP pharmaceutical processes. Figure created with BioRender.com

The 3DP process can induce changes in the solid state of the drug, either as a desired or an unwanted property, making this an important attribute to analyse [50,51]. Physical information retained within NIRS spectra can be used for this, as shown for SLS by Trenfield and colleagues. They applied Fourier transform NIRS (FT-NIRS) to both detect the presence and quantify the level

of amorphous itraconazole in printlets with PLSR models (R^2 = 0.998), where amorphisation was induced by laser sintering [52].

As previously mentioned, some quality attributes and product characteristics require modelling from data acquired from analytical instrument or surrogate data. An example is dissolution behaviour, which can be tunable via 3DP. Trenfield *et al.* recently utilised FT-NIRS to create models for predicting the density of SLS theophylline printlets and drug release at 2 and 4 h under simulated biorelevant conditions [53]. Density correlation showed high linearity, whereas linearity to a lesser degree was observed for the drug dissolution models, presumably because the limited sample sizes were ineffective in capturing all the variability arising from materials and processing parameters.

NIRS hyperspectral imaging

Hyperspectral imaging (HSI) coupled to NIRS (NIRS-HSI) is capable of acquiring signals containing both spectral and spatial data [54]. Quantitative applications of NIRS-HSI have been applied to FDM and IJP 3DP. A semi-quantitative approach was developed for FDM by **multivariate curve resolution-alternative least squares**, building on the assumption that multicomponent spectra are the sum of weighted individual component spectra. Reflectance NIRS-HSI chemical images were obtained from FDM feedstocks to assess transformation of nitrofurantoin from its monohydrate to the anhydrous form, and inhomogeneity due to the heat applied during printing [55]. Although good predictions of anhydrous nitrofurantoin concentration in printlets were obtained, the data were not validated against other analytical techniques. A full quantitative NIRS-HSI model with chemical mapping was developed through both PLSR and **principal component analysis** (PCA) for IJP of metformin hydrochloride onto gelatin films with validation through HPLC and Raman chemical imaging [56]. The model displayed a good linear correlation, particularly at lower drug concentrations deposited onto the films. Reduced model performance at higher concentrations (i.e., films with more printed layers) was partly attributed to limited depth-sensing of the equipment. Limitations of NIRS-HSI include scanning across narrower parts of the NIR spectra and the lack of depth information.

Raman spectroscopy and Raman confocal microscopy (RCM)

In the aforementioned publication by Edinger *et al.* [46], IJP of three active pharmaceutical ingredients (APIs) onto porous substrates was also quantitatively assessed by PLSR models from RS in backscattering and transmission modes. The polymer and porous substrate only showed weak Raman scattering signals, supporting the use of RS for API quantification. However, RS quantification was only feasible for montelukast (R^2 = 0.99 and R^2 = 0.96) and for haloperidol in backscatter mode (R^2 = 0.98). Propranolol, the third API, could not be reliably quantified owing to fluorescence induction. RS, in backscatter mode, has also been used to quantify amorphous content in SLS itraconazole printlets through PLSR modelling (R^2 = 0.998) [52].

Referring to the first published study on non-destructive analysis of SLS printed pharmaceuticals the spatial distributions of paracetamol and polymer were successfully obtained by RCM modelled through **classical least squares** [47]. RCM is a chemical imaging technique that combines spatial resolution, sometimes in conjunction with depth resolution, with spectral information [57,58]. RCM has also been used to map the spatial distribution of amorphous paracetamol in FDM printed buccal films [59] and theophylline in FDM printlets [60]. FDM printlets containing one of three forms of dexamethasone were also successfully analysed via RCM for homogeneity in the distributions of drug and mannitol on the printlet surface [61]. Moreover, RCM was recently used for solid-state analysis of lumefantrine in FDM printlets, and the authors were able to fully detect amorphous lumefantrine present in printed dosage forms [62]. In addition, RCM was more sensitive than XRPD for detecting amorphicity in filaments with lower drug loading, whereas

amorphicity could not be detected in higher drug-loaded filaments via RCM owing to strong Raman scattering of crystalline materials. Solid-state characteristics of final dosage forms are integral; although RCM may be more sensitive than conventional techniques, it may be insufficient for amorphous detection in a highly crystalline bulk.

Other techniques

For extrusion-based methods such as SSE and FDM, monitoring the extrusion pressure could be useful to assure material characteristics and processing conditions. Díaz-Torres *et al.* developed an in-line pressure sensor integrated within an SSE printer [63]. This allowed precise monitoring of feedstock material attributes such as rheology, plasticity, and viscoelasticity, while also providing real-time process information (e.g., on nozzle blockage). Pressure sensors may be a valuable PAT tool for extrusion-based 3DP techniques for process and material evaluation.

For homogeneous feedstocks and proper process control, uniformity of mass and content should be proportionally related. Mass uniformity testing was investigated as a surrogate method for assessing drug content uniformity for SSE tablets containing furosemide and sildenafil, validated through HPLC [64]. In this case, the masses correlated well with API contents. However, this indirect quantification approach should be fully validated against the printing process and feedstock uniformity, and supplementary techniques may be necessary to support the quantification.

The porosity of a solid dosage form may affect other important quality aspects such as dissolution rate [65]. Fanous and colleagues assessed the porosity of FDM lumefantrine printlets by using X-ray microtomography (μCT) [62]. Lower printlet infill levels were statistically correlated with faster *in vitro* dissolution rates that were considered to be a consequence of higher porosity and thus exposed surface area. However, no model for this relationship was constructed. Similar findings were reported by dos Santos *et al.* who correlated lower infills of dexamethasone-loaded FDM printlets with faster dissolution rates [66]. Interestingly, in a separate study, the same authors found that increasing the surface area by varying infill levels had no significant effect on dexamethasone release from an inert 3DP polymeric carrier [61]. μCT has also been used to conduct morphological assessments of FDM printlets on several occasions [67–70], as well as quantitative applications [71].

Terahertz spectroscopy was recently utilised for crystalline detection in amorphous dispersions prepared by SLS 3DP [72]. Previous studies have shown that terahertz spectroscopy can be used for porosity measurements [73] and colorimetry for drug quantification in 3DP medicines [74,75], but no further work has been reported in recent years.

Potential challenges for implementation of novel QC methods for 3DP pharmaceuticals

Given the nascency of QC in pharmaceutical 3DP, there inevitably remain several facets that challenge the complete integration of PAT-enabled QC into 3DP workflows.

Hardware considerations

Foremost, implementation of analytical equipment for RTRT entails specific hardware requirements. For in- and on-line operations, handheld or portable instruments will be essential, whereas at- or off-line applications may be accomplished with benchtop and larger equipment. However, reducing the footprint of an analytical instrument often comes at the cost of sensitivity and resolution, necessitating a tradeoff between feasible physical integration into 3DP systems and the quality of readouts [76,77]. Moreover, to keep 3DP medicines accessible, technological advances and engineering efforts to reduce the size of PAT tools while minimizing performance tradeoffs, such as using higher-grade materials, must be balanced against implications for the

cost of the final medicines. Due consideration should also be given to the placement of analytical instruments within 3DP systems for in- and on-line analysis. This may be achieved in two ways: firstly, the probe or miniaturized analytical tool is attached to the side of the printer head and vertically aligned with the nozzle. This would be suitable for periodic analysis of each layer during the printing process, but inappropriate for real-time monitoring. Alternatively, it may be integrated within the printing chamber in a stationary location a distance away from the printing head. This could be more amenable to continuous monitoring throughout the printing process, but readouts may be negatively impacted by the angle of scanning, distance from the sample, and ambient light.

In addition, no single analytical tool will plausibly be sufficient as a stand-alone QC measure for analysing all CQAs and CPPs. Therefore, the incorporation of analytical tools into 3DP workflows is further complicated by challenges associated with physical integration of multiple analytical tools, data extraction and ingestion from different formats, and multimodal analysis to provide comprehensive insights [78]. When considering combinations of analytical tools, it is also important to be cognizant that different 3DP technologies may require and be amenable to different analytical equipment. For instance, the mechanism of printing may hinder or even preclude the use of some sensor-based analytical tools. This could particularly be a challenge for laser-based 3DP systems such as SLS, where a laser is responsible for the sintering of the layers to construct the final product. SLS printers typically use lasers at 455 nm, which may induce fluorescence that could interfere with numerous spectroscopic techniques such as NIRS and Raman spectroscopy. Light scattering could also occur as the laser strikes the powder surface, which could result in signal noise. While there is currently no data published on this potential issue, the theoretical risk warrants due consideration.

Software considerations

Instrument and operator requirements of analytical instruments may also differ depending on the intended 3DP distribution model. In cases where healthcare professionals (HCPs) would be solely or partially responsible for QC (Figure 2), the equipment should be easy to operate with user-friendly software for automated data processing and analysis. On the other hand, where DM sites would be responsible, highly specialised employees may be able to operate equipment of higher complexity, allowing more flexibility in analytical systems and software [79]. The chosen 3DP distribution model will also have implications for data custody and protection. Notably, route C (Figure 2) would require exchange of patient health data (e.g., prescriptions) between HCPs and a DM site with commercial interests. Aspects that require consideration include removal of identifying values in patient records, establishing appropriate data security infrastructure for the data controller, and the data retention period [80,81]. Given the sensitivity of health records, the challenges associated with sharing of patient data are inevitably complex and beyond the scope of this review, although interested readers may find the following review informative [82].

Building and evaluating chemometric models is essential for generating readable and reliable outputs from the analytical instruments. Current conventions rely on pre-established chemometric models that are evaluated for accuracy and reliability prior to deployment and periodically post-deployment. Metrics to evaluate these include root mean square error of calibration (RMSEC), which measures the goodness of fit between the model and the data used to derive it, and root mean square error of prediction (RMSEP), which measures the goodness of fit between data from real samples and the reference values. However, given the sheer diversity of combinations of drug, excipient, 3DP technology, and printing parameters (e.g., number of layers, layer height, nozzle size), creating and maintaining a database of chemometric models that represents all possible formulation printed by every 3DP technique is a gargantuan and unfeasible task. Admittedly, this also would warrant changes to the way models are evaluated. Given the nascency of the field, this requires further discussion and is out of the scope of this review.

Regulatory considerations

An integral aspect of pharmaceutical QC is routine and *ad hoc* inspections of manufacturing facilities by regulatory agencies [83]. Decentralising and thus multiplying the number of manufacturing locales by several fold (some of which may even be mobile) will inadvertently complicate inspections. To address this, the MHRA has proposed in their 2021 consultation a regulatory system based on Control Sites [akin to the Pharmaceutical Quality System (PQS) in the FDA discussion paper] [5,7]. These would serve as semi-centralised facilities that will be responsible for the management and control of all activities for DM or PoC manufacturing sites in a given region. The responsibilities of Control Sites include process monitoring, product quality assurance, equipment maintenance, and recording of all relevant information for routine inspections.

In addition, there is ambiguity over how QC criteria for 3DP products will be reflected in national pharmacopoeias. Currently, every drug product has a monograph in pharmacopoeia national formularies, which includes its CQA, CPP, and end-product testing criteria. Because 3DP products are individually unique, it is not possible to have a monograph for every product. A possible scenario would be the addition of a pharmacopoeia chapter dedicated to 3DP, which specifies technology-specific CPPs for each 3DP technology and general CQAs for each product type.

Concluding remarks

Personalised medicine gained significant momentum following the launch of the Precision Medicine Initiative by the Obama administration in 2015. The goal of transitioning from a 'one-size-fits-all' model to a tailored approach is being realised through various strategies, among which pharmaceutical 3DP has been touted to potentially play a significant role. A decade of academic research has allowed the field to arguably reach its next inflection point, underlined by the regulatory tailwind. Although regulatory authorities have shared insights on the envisaged regulatory framework for PoC manufacture, details on the appropriate QC measures remain ambiguous. Instead, pharmaceutical 3DP QC workflows may be modelled based on the existing QbD approach. This review has highlighted emerging non-destructive analytical tools that have been explored for pharmaceutical 3DP QC, with emphasis on the CQAs that each technique may respectively quantify or qualify. Continued engineering efforts will focus on miniaturising the analytical equipment while preserving resolution and sensitivity, and on physically integrating the devices together and into 3DP systems (see Outstanding questions). Software development efforts will need to include building comprehensive data-ingestion pipelines capable of handling information stored in different formats, machine learning algorithms for multimodal analysis, and intuitive user interfaces. Infrastructural and data governance hurdles also remain to be resolved. Nonetheless, the impending legislation offers much optimism that pharmaceutical 3DP QC is poised for accelerated research and development, allowing pharmaceutical 3DP to take its next leap towards translation.

Outstanding questions

What other CQAs and CPPs should be monitored in pharmaceutical 3DP processes, other than those currently being explored, to safeguard patient safety and therapeutic efficacy?

What other unexplored analytical tools may offer valuable readouts for non-destructive analysis of 3DP pharmaceutical products?

How could the physical integration of multiple analytical tools within 3DP systems potentially influence the read-outs of each analytical instrument, and how can these be mitigated?

How can data obtained from different analytical tools, potentially in different formats, be ingested and structured in a manner that can be analysed by computer or machine-learning algorithms?

How should chemometric models be built and maintained to assure accuracy and reliability of read-outs?

How should patient data be shared with DM sites to assure data privacy and security?

In scenarios where healthcare professionals are tasked to perform QC for 3DP drug products, who is responsible for conducting, certifying, and auditing their training?

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