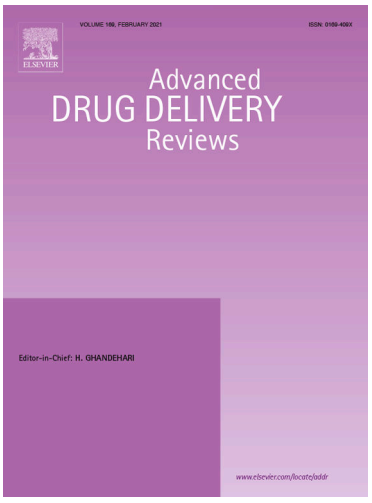
Journal Pre-proofs



Harnessing Artificial Intelligence for the Next Generation of 3D Printed Medicines

Moe Elbadawi, Laura E. McCoubrey, Francesca K.H. Gavins, Jun Jie Ong, Alvaro Goyanes, Simon Gaisford, Abdul W. Basit

PII: S0169-409X(21)00179-4
DOI: https://doi.org/10.1016/j.addr.2021.05.015
Reference: ADR 13805

To appear in: *Advanced Drug Delivery Reviews*

Received Date: 19 February 2021
Revised Date: 2 May 2021
Accepted Date: 13 May 2021

Please cite this article as: M. Elbadawi, L.E. McCoubrey, F.K.H. Gavins, J. Jie Ong, A. Goyanes, S. Gaisford, A.W. Basit, Harnessing Artificial Intelligence for the Next Generation of 3D Printed Medicines, *Advanced Drug Delivery Reviews* (2021), doi: https://doi.org/10.1016/j.addr.2021.05.015

Harnessing Artificial Intelligence for the Next Generation of 3D Printed Medicines

Moe Elbadawi[1], Laura E. McCoubrey[1], Francesca K.H. Gavins[1], Jun Jie Ong[1], Alvaro Goyanes[2,3], Simon Gaisford[1,2], Abdul W. Basit[1,2*]

[1]Department of Pharmaceutics, UCL School of Pharmacy, University College London, 29-39 Brunswick Square, London WC1N 1AX, UK.

[2]FabRx Ltd., 3 Romney Road, Ashford, Kent, TN24 0RW, UK.

[3]Departamento de Farmacología, Farmacia y Tecnología Farmacéutica, I+D Farma Group (GI-1645), Universidade de Santiago de Compostela, 15782, Spain.

[*] Corresponding authors: Basit, A.W (a.basit@ucl.ac.uk); Goyanes, A. (a.goyanes@fabrx.co.uk)

Abstract

Artificial intelligence (AI) is redefining how we exist in the world. In almost every sector of society, AI is performing tasks with super-human speed and intellect; from the prediction of stock market trends to driverless vehicles, diagnosis of disease, and robotic surgery. Despite this growing success, the pharmaceutical field is yet to truly harness AI. Development and manufacture of medicines remains largely in a 'one size fits all' paradigm, in which mass-produced, identical formulations are expected to meet individual patient needs. Recently, 3D printing (3DP) has illuminated a path for on-demand production of fully customisable medicines. Due to its flexibility, pharmaceutical 3DP presents innumerable options during formulation development that generally require expert navigation. Leveraging AI within pharmaceutical 3DP removes the need for human expertise, as optimal process parameters can be accurately predicted by machine learning. AI can also be incorporated into a pharmaceutical 3DP 'Internet of Things', moving the personalised production of medicines into an intelligent, streamlined, and autonomous pipeline. Supportive infrastructure, such as The Cloud and blockchain, will also play a vital role. Crucially, these technologies will expedite the use of pharmaceutical 3DP in clinical settings and drive the global movement towards personalised medicine and Industry 4.0.

Keywords: Additive Manufacturing; Digital pharmaceutics and pharmaceutical sciences; Digital therapeutics and healthcare; Drug product design and development; Computer aided design of printlets; Computational modeling and finite element analysis; Fabricating gastrointestinal drug delivery systems and dosage forms; Personalized pharmaceuticals and medical devices; Mass customization and machine learning; Falsified and counterfeit oral pharmaceutical products.

1 Intelligent 3D Printing of Personalised Medicines

The last 25 years have experienced a digital revolution: from the naissance of wireless internet access to global smart phone uptake, widespread use of cloud storage, and the permeation of social media into everyday life. At first, it was human intelligence that conceived and utilised these transformative technologies. Now, we find that technology is being hardwired for intelligence far beyond human capacity; allowing it to entertain us, highlight lucrative financial investments, and maintain our health, to name just a few applications [1-5]. The language of data is fast surpassing traditional spoken or written languages on the stage of global communication and connectivity. As data storage and capacity steadily mount with each passing year, systems are fed increasing information, allowing them to become smarter [6].

Artificial intelligence (AI) encompasses a plethora of technologies driving the current data revolution [7]. Applications of AI can be narrow, whereby intelligence is directed at single tasks, such as smartphone personal assistants, the discovery of novel drugs, or diagnosis of disease from medical images [8-10]. Alternatively, AI applications can be afforded cognitive ability similar to the human brain, by which robust AI systems retain memory and apply knowledge across different domains. The latter form of AI is growing in momentum, exemplified by the development of driverless cars that autonomously recognise unexpected obstructions, monitor exact lane position, and govern optimal vehicle functioning simultaneously [11]. An even more recent application of AI is its unification with networks of interconnected hardware, known as the 'Internet of Things' (IoT). In an IoT, devices with distinct capabilities are wirelessly connected to perform integrated functions. IoT has conceived the concept of smart houses, in which a network of sensors and control devices fully automate tasks of daily living: from the management of heating, lighting, and security, to ordering groceries and synchronising a morning alarm with breakfast [12]. Combined, AI and IoT permit the intelligent automation of limitless processes.

The Food and Drug Administration (FDA) has placed emphasis on innovation through utilising digital health technologies and developing novel analytical approaches to advance healthcare [13], which was answered by diagnostic companies, where recently the FDA has approved AI-based software for diagnostics [14, 15]. Compared to other fields, the development and supply of pharmaceuticals sits behind the forefront of modern technology, who employ *in silico* tools to expedite discoveries. BASF released Zoomlab™ for predicting the properties of formulations, such as tabletability. The software is based on the SEDEM system that was developed 15 years ago but is yet to be widely adopted by

pharmaceutical researchers. It requires users to input 12 properties of the API, which include flowability, hygroscopicity, particle size and the homogeneity index [16, 17]. F-CAD is another software used in the industry to guide formulation development. Similar to Zoomlab™, the physical-chemical properties of the API are required, but in addition, so are the physical-chemical properties of the excipients [18]. The drawback with these software is that they can be difficult to readily incorporate into the current workflow and are exhaustive, costing both time and materials in order to gather the input data. Hence, these optimisation methodologies have not been widely adopted by pharmaceutical researchers. This lack of an *in silico* tool consequently positions the pharmaceutical field behind others in harnessing their capabilities to expedite discoveries.

Medicine largely remains in a 'one size fits all' paradigm, in which patients are administered mass-produced pharmaceutical products with very little flexibility on dose or formulation. The last decade has witnessed an awakening to the shortcomings of this inflexible treatment model, with a push for personalised medicines that meet individual patient needs [19, 20]. 3D printing (3DP) promises a nexus for personalised medicine [21-27]. The FDA approval of Spritam, and the more investigation new drug (IND) clearance for Triastek's T19 – indicated for rheumatoid arthritis [28] – has set the precedence for 3DP as a viable manufacturing technology, demonstrating that they are viable fabrication technologies. However, both these examples do not capitalise on 3DP ability to produce personalised dose. The modern catalogue of 3DP technologies provide the ability to produce medicines with fully customisable drug contents, morphology, release kinetics, aesthetics, and taste profiles: on-demand at the point of patient need [29-31]. Notable examples of patient-centred 3DP medicines include tablets with braille designs for the visually impaired; multi drug-loaded hearing aids with anti-biofilm properties; microdevices with stimuli-responsive release mechanisms; and abuse-deterrent opioid tablets [32-37]. The first clinical study demonstrating the benefits of pharmaceutical 3DP over traditional manufacturing methods published its results in 2019, accelerating the transition of 3DP of medicines to mainstream clinical practice [38].

As a fully automated and digitalised technology, pharmaceutical 3DP is a natural partner to AI. In numerous fields, AI and physical devices are being united to create intelligent robots. Indeed, robotics is one of the most explored applications of AI. In medicine, intelligent robots are being increasingly applied to perform surgical procedures and aid remote patient assessment; their use spurred on by the COVID-19 pandemic [39, 40]. Within manufacturing technology, robotics and AI are predicted to come to the frontier of industry – permitting streamlined, autonomous production 24 hours a day with minimal

human intervention [41]. AI is likely to be a key facilitator in pharmaceutical 3DP's translation to the clinic. Machine learning (ML), a powerful subset of AI, can aid the formulation development process within pharmaceutical 3DP. Because 3DP of medicines offers a large number of possibilities over the final product, such as the different compositions of the starting materials, design considerations (e.g. shape and dimensions), and printing parameters (e.g. speed, temperature), the process of designing a formulation presents an innumerable number of options that ordinarily require expert navigation. Here, ML can be leveraged to learn from the large volume of pre-existing data to predict new outcomes, irrespective of the number of variables that need to be analysed. Consequently, the need for expert formulation scientists is reduced from the clinical setting, and ML can manage the formulation of 3DP medicines for any given scenario. ML can also guide the printing process by calculating ideal processing parameters, such as printing temperature, nozzle diameter, laser speed, or light exposure time. In contrast to Zoomlab™ and F-CAD, ML does not require specific material properties to make the prediction, and hence does not require the user to expend time and money collecting further data, although the option is there should the researcher wishes to include the properties. Moreover, continuous maintenance of printers can be AI-managed, ensuring that supply of medicines is not interrupted due to machine failures [42, 43]. An advanced goal of pharmaceutical 3DP is to achieve a fully autonomous and intelligent pipeline of personalised medicines supply in the healthcare setting. IoT-based technology can realise this vision: a network of robots will be connected to 3D printers to support formulation compounding, post-processing, quality control (QC), and packaging. As such, human resources, error, and bias will be almost entirely removed from pharmaceutical 3DP and patients will gain 24/7 access to quality, personalised medicines.

This review will focus on the next era of pharmaceutical 3DP, in which AI is harnessed to achieve the streamlined and autonomous production of 3DP medicines. As methods of pharmaceutical 3DP are manifold, we begin by providing an overview of technologies available, with consideration of challenges within each. Non-AI industrial techniques for process optimisation will then be discussed, namely design of experiments; mechanistic models; pharmacokinetic modelling; and finite element analysis. Next, a background on AI and ML will be covered, followed by how they overcome the pitfalls of traditional unintelligent techniques, and an in-depth analysis of how they can be leveraged for 3DP of medicines. Finally, an overview of IoT and an evaluation of the trajectory of the pharmaceutical 3DP field will be provided.

2 The Modern Catalogue of Pharmaceutical 3D Printing Technologies

Pharmaceutical 3DP represents a collection of distinct technologies that together allow the printing of almost any conceivable medicine. To understand where AI can align with pharmaceutical 3DP, it is first necessary to recognise the heterogeneity and the challenges within the various techniques. Each 3DP method contains its own unique features, advantages, and limitations, suited to the use of different excipients and drugs. An overview of contemporary pharmaceutical 3DP techniques is presented in ***Table 1***.

Table 1. An overview of pharmaceutical 3D printing technologies.

3D printing technology	Material	Mode of fusion	Advantages	Limitations
Material Extrusion				
Fused Deposition Modelling (FDM)	Thermoplastic polymers	Heat	• Ease of use • Inexpensive • Different materials can be printed together	• Not suitable for heat-labile molecules • Relatively low resolution • Complex structures require support.
Direct powder extrusion (DPE)	Thermoplastic polymers	Heat	• Ease of use • Inexpensive • Different materials can be printed together • Single-step process	• Relatively low resolution • Complex structures require support
Semi-solid Extrusion (SSE)	Gels, pastes		• Suitable for heat-labile drugs, and biomaterials • Conducted at room temperature	• Relatively low resolution • Requires post-processing steps
VAT photopolymerization				

Stereolithography (SLA)	Liquid photopolymer	Laser beam	• High resolution • Relatively fast • Suitable for heat-labile drugs	• No FDA approved excipient suitable for oral delivery applications • Post-processing (curing) necessary • Overhangs require support
Digital Light Processing (DLP)	Liquid photopolymer	Light	• High resolution • Smooth finishing • Relatively fast • Suitable for heat-labile drugs	• No FDA approved excipient suitable for oral delivery applications • Overhangs require support • Post-processing required
Continuous Liquid Interface Production (CLIP)	Liquid photopolymer	Light and oxygen	• High resolution • Objects can be easily removed • Fast • Suitable for heat-labile drugs	• Expensive • No FDA approaved excipient suitable for oral delivery applications
Material Jetting				
Ink Jet Printing (IJP)	Liquid solvent	Evaporation, UV curing, reactive jetting	• High resolution • Suitable for heat-labile drugs (only for piezoelectric ink jet printers)	• Performance dependent on formulation properties • Chemical stability of drugs in solvent
Powder Bed Fusion				
Selective Laser Sintering (SLS)	Thermoplastic polymer, metal & ceramic	Laser beam	• Does not require supports • High resolution	• Potential thermal degradation of drug due to short term exposure to heat

			• Feed material can be recycled and reused • Able to confer rapid disintegration	• Objects can be too friable
Binder Jetting				
Binder Jetting	Polymer powder	Liquid binder	• Does not require support • Suitable for heat-labile drugs	• Potential drug hydrolysis due to presence of solvent • Time consuming

2.1 Material Extrusion

2.1.1 Fused Deposition Modelling (FDM)

FDM, a thermal material extrusion technology, is one of the most explored 3DP technologies within pharmaceutical research [44]. Its popularity is mostly attributed to its low costs, versatility, and its ability to produce products with high mechanical strength. A diverse range of drug delivery systems have been fabricated by FDM to meet patient-specific needs [24], including tablets [45, 46] (also referred to as Printlets™ [47]), capsules [48], beads and catheters [49], topical masks [50], orodispersible films [51, 52], mouthguards [53], implants, transdermal microneedles [54], vaginal rings [55], scaffolds for tissue engineering [56], and subcutaneous devices [57, 58].

FDM 3DP is a two-step process, which can be achieved by coupling hot-melt extrusion (HME) with FDM 3DP [59]. In HME, raw pharmaceutical materials are fed into a hopper and are subject to heat and pressure whilst moving through a rotating screw, which produces long strands of filaments of solid dispersions. With HME, high drug loading of filaments can be achieved, as opposed to the alternative of impregnating filaments with a drug-containing solution [45, 46]. The balance of brittleness and stiffness of filaments are assessed, as well as softness, diameter, and uniformity. Subsequently, filament feedstocks are fed into the FDM printer, where molten material is deposited, layer-by-layer, onto a platform creating a 3D object. The resolution of the object is dependent upon the thickness of the extruded filament, typically 100 μm.

In general, excipients used are thermoplastic polymers, which include polylactic acid (PLA), polyvinyl alcohol (PVA) and hydroxypropyl methylcellulose (HPMC). By selecting specific polymers or blends of polymers [60, 61], desired quality attributes can be achieved. Drug release properties can be modified by tuning the infill percentage [62], polymer matrix composition [59], compartmentation [63], structural shape [64] and shell thickness. 'Polypills' have been fabricated using FDM, allowing the combination of several drugs in a single capsule with bespoke release patterns [65, 66]. FDM is also capable of fabricating complex structures like microneedles for parental delivery [67] and implants [57, 68, 69].

Despite its versatility, a key limitation of FDM 3DP is its incompatibility with heat-labile drugs. While selected polymers have been deemed suitable for low-temperature printing (i.e. 70 ºC), the majority of conventional polymers used for FDM printing necessitates high temperatures to be extruded [70]. Additionally, other 3DP technologies discussed below can achieve products with higher resolutions. A challenge common to every present-day pharmaceutical 3DP technology is the largely empirical process of selecting the appropriate process parameters and composition of drug product. The 3DP scientist must consider the parameter space for formulation, HME, and FDM particulars. Within each space there are numerous considerations, such as proportion of starting materials, use of excipients (such as lubricants, binders, plasticisers, disintegrant, antioxidant, and solubiliser), extrusion temperature, printing temperature, printing speed, horizontal and vertical resolution [44]. A more comprehensive list of parameters vital to FDM are enumerated in ref. [71].

2.1.2 Direct powder extrusion (DPE)

Direct powder extrusion is a material extrusion technology akin to FDM, wherein a powder mix containing the active pharmaceutical ingredient is directly extruded through the nozzle of the printer [72, 73]. Like in FDM, the powder mix is fused together through the application of heat and pressure as the particles flow through a rotating screw. However, unlike FDM, DPE obviates the HME step in FDM 3D printing. In this way, DPE permits the fabrication of pharmaceutical powder mixtures that might have been unsuitable for FDM printing due to inadequate mechanical characteristics of the HME filaments. While it shares several drawbacks with FDM 3DP, the one-step fabrication process of DPE confers simpler and faster manufacturing. Most of the reported DPE papers are single-screw, and hence face the same challenges as single-screw HME, such as poor mixing [74, 75]; expanding the system to twin-screw would require consideration on the effect of the travel speed, since more load will be carried.

2.1.3 Semi-solid Extrusion (SSE)

SSE is an extrusion-based 3DP technique involving the deposition of viscoelastic 'ink' onto a build plate [76]. Here, gels or pastes containing the active pharmaceutical ingredient are extruded through a syringe-based tool-head nozzle and deposited layer-by-layer on a platform to form a 3D object [77]. Unlike other aforementioned material extrusion-based technologies, SSE can be achieved at room temperature, making it ideal for heat-labile compounds. It is for this feature that SSE is extensively used in bioprinting, where living cells are printed to form tissues and complex structures. Examples of SSE applications in the pharmaceutical sphere include the fabrication of rectal suppositories [78, 79], paediatric-friendly tablets [80], orodispersible tablets [81], and implants [82].

SSE is a technique that would benefit greatly from an optimised and automated means of formulation development. The quality of the final product is heavily influenced by numerous process parameters and physicochemical properties of the mixture. These include the rheological properties and miscibility of the mixture, the flow rate, the processing temperature, and the printing speed [83]. Furthermore, as the diameter of nozzles used in SSE is often larger than that in FDM, the printing resolution achieved by SSE 3DP can be relatively lower than FDM 3DP. Post-processing steps, such as drying or cooling, are also necessary, during which the product might be distorted if the mechanical properties have not been optimised.

2.2 Vat Photopolymerisation (SLA, DLP, CLIP)

Vat polymerisation 3DP cures liquid photopolymerisable resins using light, sequentially building a desired solid object layer by layer [31, 84]. There are three main types of vat photopolymerisation 3DP: stereolithography (SLA), digital light processing (DLP), and continuous liquid interface production (CLIP) [85]. The three methods vary subtly. SLA employs a concentrated beam of ultraviolet (UV) light or a laser, to selectively sketch and harden layers of liquid photopolymer [86]. DLP projects light images, composed of square pixels, onto resin from a digital projector screen. CLIP shines UV light through an oxygen permeable window, which hardens the resin above. A key advantage of CLIP over SLA and DLP is that the bottom hardened layer of the printed product does not adhere to the printer, due to 'inert space' created by the oxygen permeable membrane. This means that products can be easily removed from the printer without mechanical force after 3DP. In terms of manufacturing speed, DLP printing briefly projects each resin layer with whole images, rather than drawing them with a UV beam or laser, thus is a significantly faster fabrication method than SLA. When first released, CLIP claimed to print

items 25 to 100 times faster than SLA and DLP, however, this was later proven to be generally unfounded for 3DP items that are not composed of thin lattice-like structures [85].

Together with material jetting 3DP, vat polymerisation printing has the advantage of producing items with the best surface resolutions of all additive manufacturing technologies. This is because the UV, visible, and laser light sources can be shone at resolutions as low as 5 µm, allowing the production of highly intricate structures [87]. Moreover, the light curing methods of vat polymerisation are especially suited to the production of medicines, as avoidance of excess heat in the printing process evades the thermal degradation of susceptible drugs. Fast photopolymerisation also makes SLA, DLP, and CLIP some of the quickest 3DP methods, an important feature for printing medicines in a clinical setting, where demand may be urgent [33]. The unique properties of vat polymerisation have been successfully exploited for several pharmaceutical applications. Polypills containing several drugs in distinct layers, with tuneable release profiles, have been printed using SLA [33, 88]. Such methods are well suited to reducing tablet burden for patients with polypharmacy. Elsewhere, SLA has been employed to fabricate drug-loaded tablets with modified release characteristics, and drug-loaded hydrogels [89, 90]. DLP is similarly capable of printing modified release tablets and has also been used to fabricate antibacterial dental devices [91-93]. Interesting applications of CLIP in pharmaceutics include anti-cancer drug loaded devices, and microneedles for the delivery of biotherapeutics over skin [94, 95].

As with all manufacturing processes, vat polymerisation has several disadvantages and challenges. A prominent issue is the biocompatibility of the uncured resin, which if not addressed has been reported to be toxic. Photopolymerisation reactions, initiated by free radicals, also have the propensity to react with drugs, potentially altering the drug release profile [88]. Depending on the materials used, reactive monomers in resin may be toxic or irritant, necessitating post-processing of printed products. Post-processing involves exposing a finished 3DP object to UV or visible light, to ensure all liquid resin monomers are polymerised and hardened. Without this step, harmful monomers may remain on or within the item, and the risk of post-printing conformational warping is increased [96]. Attention should also be paid to the compatibility of API with the photopolymer, as a recent study revealed the occurrence of a Michael addition reaction between amlodipine and PEGDA [88]. Vat polymerisation might also be unsuitable for heat labile drugs, as the temperature of the system might inadvertently increase as a result of the exothermic photopolymerisation reaction [31]. Lastly, any unsupported overhanging parts of structures must be supported by removable scaffolding in the vat polymerisation process, increasing production time and steps [85].

2.3 Material Jetting

2.3.1 Inkjet Printing

Inkjet printing (IJP) is a material jetting-based 3DP techniques involving the deposition of viscoelastic 'ink' onto a build plate. Here, droplets of solvent are generated either through vaporisation of ink within the printer nozzle, or through the use of a piezoelectric material that vibrates and ejects droplets upon the application of a voltage [97]. Droplets are commonly deposited onto an edible substrate, but studies have also explored the fabrication of complete tablets obviating the need for a substrate [98]. Deposited droplets are subsequently solidified through various means, including solvent evaporation, UV curing, or reactive jetting. Apart from flexible dosing, IJP enables the fabrication of high-resolution patterns through the precise control of droplet extrusion rate and positioning. Various studies have exploited this unique feature to fabricate 2D QR encoded dosage forms, either through the deposition of drug-loaded ink into the pattern of the QR code [99], or by printing QR codes and data matrices onto the surface of FDM-produced tablets [100]. These studies support ongoing efforts to combat counterfeit medicines, ensuring safe transport of medicines through the supply chain and safeguarding patient safety [101]. With the aid of UV curing, 3D structures can be obtained using IJP [102-104].

Formulation development is a key challenge within IJP. Satisfactory printing performance is highly dependent on the combined physical properties of the formulation, such as surface tension, viscosity, and density [105]. Suboptimal physical properties can cause issues such as splashing of the droplet upon impact with the substrate and nozzle blockage. While the carrier fluid forms the bulk component and largely drives the formulation's physical properties, drugs and excipients will nevertheless influence viscosity, surface tension, and therefore printability. Beyond physical considerations, the stability of drugs and excipients is critical in such solvent-based systems. While thermal degradation can be avoided by using a piezoelectric inkjet printer, chemical stability is primarily determined by the choice of carrier fluid and drug. The most commonly reported carrier fluid in pharmaceutical inkjet printing is water; alternative solvents must be developed for drugs prone to hydrolysis. Clearly, novel means of formulation development will greatly alleviate time and labour investment within inkjet printing and other 3DP technologies.

2.3.2 Powder Bed Fusion (SLS, DMLS, EBM, SLM)

In powder bed fusion, heat is used to bind powder particles that are deposited in a build area or bed to build up the 3D object. These include Selective Laser Sintering (SLS), Direct Metal Laser Sintering (DMLS), Electron Bean Melting (EBM) and Selective Laser Melting (SLM) [30, 106]. To date, only SLS has been

explored for the manufacture of pharmaceuticals. Here, a laser traces a pattern and fuses powder particles on the surface of the build plate. The process is repeated each time a fresh layer of powder is deposited by a roller until the entire 3D object is printed. SLS offers unique advantages for printing orally administered medicines, such as intricate and complex geometries [32, 107], and orally disintegrating structures [108, 109]. A recent review has provided a comprehensive overview on the principles and applications of SLS [110].

Though heat is applied only momentarily during powder bed fusion, thermal degradation of the active pharmaceutical ingredient (API) can be a limitation with some types of SLS printers, especially when printing heat-labile compounds [110]. Additionally, SLS and other powder bed fusion technologies produce powder waste, causing its cost-effectiveness to suffer. Finally, while the porosity of SLS-printed tablets can confer rapid oral disintegration properties, it can also lead to unacceptable friability. Consequently, there is a need to optimise manufacturing parameters, such as temperature and powder composition, for the production of tablets with satisfactory mechanical properties, disintegration properties, and thermal stability.

2.3.3 Binder Jetting

Similar to powder bed fusion technologies, binder jetting involves the layer-by-layer build-up of a 3D object through the binding of powder particles [111]. However, unlike powder bed fusion technologies, thermal energy is not used to fuse the particles together. Instead, a liquid binder is selectively extruded and deposited across the powder bed. Notably, the licensed 3DP medicine Spritam® is fabricated using binder jetting. Though heat is not applied during printing, drug stability remains a concern as the application of the liquid binder may result in hydrolysis. In addition, binder jetting tends to be time-consuming as the printed object must be left for up to 48 hours to allow solvent evaporation. In addition to general 3DP features, binder jetting also requires consideration of factors concerning the liquid binder, including its viscosity and stability.

2.3.4 Electrohydrodyamic Printing

Electrohydrodynamic Printing (EHDP) is another material jetting technology that is distinct from other 3DP technologies in that an external electric field is used to jet the material [112]. It is this feature that has allowed EHDP to garner attention, which provides EHDP with the ability to achieve smaller printing resolutions and faster printing times compared to similar 3DP setups where an electric field is not incorporated [113-115]. EHDP has been applied in pharmaceutics to primarily fabricate films [116-120].

However, EHDP has been reported to produce unstable jets, which can result in large batch-to-batch variation, as well as limited thus far to vertically small products [121, 122].

3 Alternative Optimisation Techniques to Machine Learning in 3D Printing

Due to the complexity of pharmaceutical 3DP, a trial-and-error approach to the development of new medicines often wastes time, money, materials, and importantly may not result in an optimal product. There are many choices to be made when developing a novel 3DP medicine, ranging from the macro: such as printing technology and formulation components; to the micro: including printer settings and fine morphological features. Whilst the experience of experts is often sought for research projects, this is less feasible in clinical settings where printing demand far outstrips the availability of experienced 3DP practitioners. Moreover, the knowledge-led approach is not standardised or structured. For this reason, predictive tools are useful in identifying optimal process parameters as they apply existing scientific knowledge to the production of new medicines. Several optimisation techniques are already established in industry, with varying scopes of utility. These techniques can be used to ascertain pharmaceutical 3DP 'rules' that may be applied to print medicines without the presence of an expert, to achieve desired medicine characteristics. Optimisation techniques are key tools in multiple sectors owing to their ability to minimise both cost and resource wastage, whilst accelerating innovation. The pharmaceutical industry has come to rely on traditional methods of process optimisation for various formulation development tasks [86, 87]. Recent work has demonstrated how such tools can accelerate project timelines from years to months [85]. In some cases, techniques can predict how medicines will behave *in vivo*, thus reducing requirements for animal experiments. To fully recognise where AI can provide benefit to pharmaceutical 3DP, it is important to recognise the modalities of existing tools and their limitations. The applications of four non-AI optimisation techniques within pharmaceutical 3DP will henceforth be discussed.

3.1 Design of Experiment

Design of experiments (DoE) is a non-learning mathematical technique extensively used in pharmaceutics. DoE is a systematic model for process optimisation that studies how input parameters (e.g. drug loading) relate to each other and the desired output (e.g. tablet strength) [123]. For example, variables that could impact tablet breaking force include binder content and excipient porosity and

friability [124]. DoE allows mapping of the extent that variables affect the experimental outcome, alone and in combination. DoE projects generally follow a similar structure. Firstly, the research objective is defined, such as 'optimise the strength of 3DP tablets'. Next, researchers must consider what process variables are likely to have a considerable impact on the outcome [125]. This step requires specialist process knowledge, careful consideration of all possibilities, and elimination of bias. Once all significant process variables have been agreed upon, researchers must select which to investigate in their DoE model. If researchers choose to investigate many variables, then greater time, money, and consumables will be required to build an accurate and robust model. Following variable selection, levels of variables to investigate need to be chosen. Two-level DoE models are very common, though more levels can be investigated if researchers are comfortable in building larger, more complicated models. In a two-level design with numerical variables, a 'low' and 'high' point are selected for each (**Figure *1***). This selection will define the range over which the model can be used. For example, if printing temperatures of 50 °C and 100 °C are chosen as the two levels, then researchers would not be able to use the resulting DoE model to predict printing outcomes outside 50 – 100 °C [123]. Once experiment variables and their levels are decided upon, then model design can be determined. DoE model design can be a complex task, and other sources go into substantial depth on this process [126]. These decisions will be influenced by available resources, statistical power, and operational considerations. If a full-factorial design is chosen, then all possible experimental permutations are performed. Fractional factorial designs sample a subset of the full-factorial, which can be used to reduce the number of experiments required, albeit at the expense of reduced statistical power. In this way, the experimental space is covered without having to perform all possible iterations. DoE designs are followed by performing experiments that sequentially alter variables' levels, testing how individual variables affect the outcome, and often whether there are compounding effects between variables. Once data collection is complete, then statistical methods such as ANOVA are used to analyse how variable levels relate to the outcome. Researchers can then use the model to predict what variable settings will result in an optimal outcome. To date, DoE in 3DP of pharmaceuticals has been applied to evaluate structure–function relationships of various parameters for FDM, SLS and SSE [127-131].

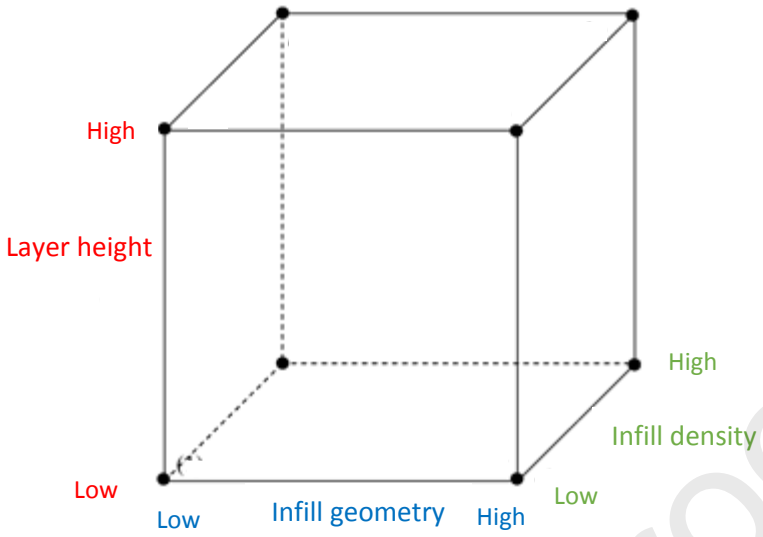


Figure 1 Two-level full-factorial DoE design considering three numerical independent variables implicated in 3D printing.

3.2 Finite Element Analysis and Computational Fluid Dynamics

Similar to DoE, finite element analysis (FEA) and computational fluid dynamics (CFD) are another standard optimisation techniques used in both academia and industry, applied in fields such as aerospace, electronics and biomechanics. In fact, the FDA is actively investing in CFD for medical devices and biological fluids [132]. The wide adoption of both techniques can be attributed to the high degree of accuracy that can be achieved, which in some instances has been found to be more accurate than results obtained from experimental measurements [133, 134]. An additional appeal is that simulations can be performed that are experimentally challenging to conduct [135]. Both modelling techniques are able to simulate a range of forces that products are subjected to, including mechanical stress, heat and fluid dynamics, which seamlessly allows researchers to optimise their design thereafter. The process involves loading the design of interest and applying stresses that are anticipated for the design, factoring in both magnitude and direction. The results of the stresses on the design can be observed by the user, and hence provides a 'white-box' effect. This has been leveraged by pharmaceutical researchers in 3DP to visualise the stress distribution in microneedles, thermodynamic behaviours in FDM filaments, air flow in inhalers, and rupture behaviour of coated capsules [136-139].

3.3 Mechanistic Modelling

Mechanistic models are mathematical models built using physical laws to explain process variables, and have been applied to 3DP [140]. These types of models require domain expertise, which depending on the model developed, will require knowledge of thermodynamics, particle physics, and fluid dynamics [141]. A salient advantage of mechanistic models is that they can be regarded as 'white-box' modelling since the dependent variable is clearly explainable [142]. Mechanistic modelling has been explored for 3DP, with relevant models covering filler impregnation, predicting mechanical properties, photopolymerisation kinetics, and heat absorption in powder-bed technologies [140, 143-146]. However, for pharmaceutical 3DP mechanistic modelling has not been thoroughly employed. Unlike other techniques (DoE and FEA), there are no readily available software to simulate mechanistic models for 3DP. Two notable studies incorporating mechanistic models within pharmaceutical 3DP have been conducted by Zidan et al. (2019), whereby rheological characteristics of formulations were modelled. Rheology is an invaluable tool to understanding processing conditions [147], which in the study ultimately led to improving the flow rate of pastes during printing [148, 149].

4 Artificial Intelligence and Fundamentals of Machine Learning

ML is one of the main AI technologies [150]. The goal of AI is to achieve super-human intelligence. Classic AI, also referred to as symbolic AI, was able to achieve this through a rule-based system, whereby rules were hard-coded into models through human intervention. Hence, symbolic AI requires researchers to first learn the rules and then code the relationship into an algorithm. This is a drawback because time and resources are needed to first identify relationships. Moreover, rules will need to be revised if new rules are identified, which consequently makes symbolic AI difficult to scale-up. ML AI on the other hand uses statistical learning techniques that allow a machine to establish its own relationship between explanatory and response variables. Therefore, ML is able to adapt as the training data changes (**Figure *2***). ML algorithms can work at speeds well beyond human intellect, with a much lower risk of error, therefore it is unsurprising how ML has come to transform so many contemporary disciplines and processes [8, 151-154].

The ML process involves a series of stages that combine to form an overall pipeline (**Figure *3***). Typically, data must be pre-processed and possibly vectorised prior to any learning taking place. The pre-processing stage is to ensure the data is cleaned and ML-friendly. In a survey conducted, it was found that ML practitioners spend most of their time, up to 60-80%, on cleaning data and pre-

processing [155]. For one, datasets are rarely ML compatible, with issues encountered include missing data, incorrect data, and outliers. Such anomalies can impact the performance of a ML model and in some cases, lead to invalid predictions. In addition, pre-processing can enrich data, which in turn can facilitate the ML technique in discerning patterns. Such methodologies include removing noisy variables or reducing the number of features considered by an algorithm. Although ML can be approached in a *plug-and-play* manner, whereby unprocessed data is directly fed to an algorithm, taking the additional steps to clean and pre-process data can significantly improve prediction performance. An adage used within physical experimentation also applies to ML: by taking the additional steps to ensure the starting materials are properly pre-treated, one can improve the consistency of the end product.

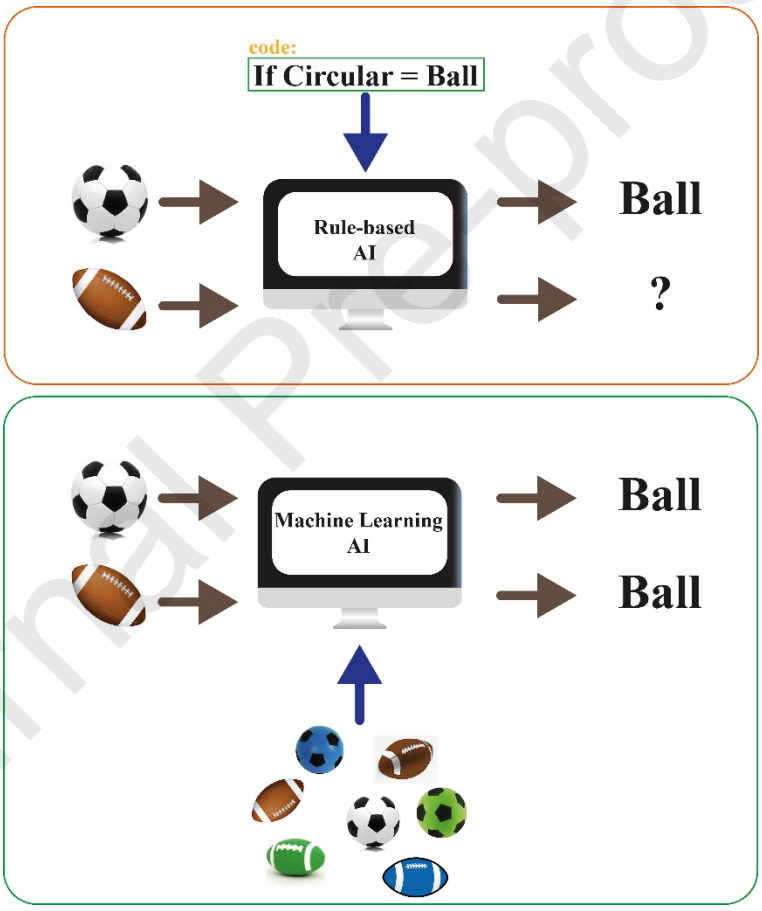


Figure 2. The difference between rule-based and machine learning AI. The former requires a user to explicitly code, in this example, the definition of a ball; whereas the latter is given images of the target and asked to learn from the dataset.

Once data is clean, learning can begin. Mode of learning varies depending on the specific ML technique used and is discussed in more depth in **Sections 4.1.1-4.1.5**. Generally, algorithms are trained to recognise patterns in data, which they can then attach rules to, hence 'learning' how data features map to outcomes. Once data has been fed into a ML algorithm, and a model is formed, then predictions for new data can be made. There are various metrics that are used to evaluate the performance of ML techniques since there is no one metric that holistically describes predictive performance. Thus, a frequent practice is to evaluate the performance using several metrics. For classification techniques, metrics include accuracy, precision, recall, specificity, Cohen's kappa, and Matthew's correlation coefficient. For regression analysis, common metrics include the root mean squared error, mean absolute error and coefficient of determinations (r^2). Metrics can be additionally useful for comparing the performance of different ML techniques or different pre-processing strategies [156].

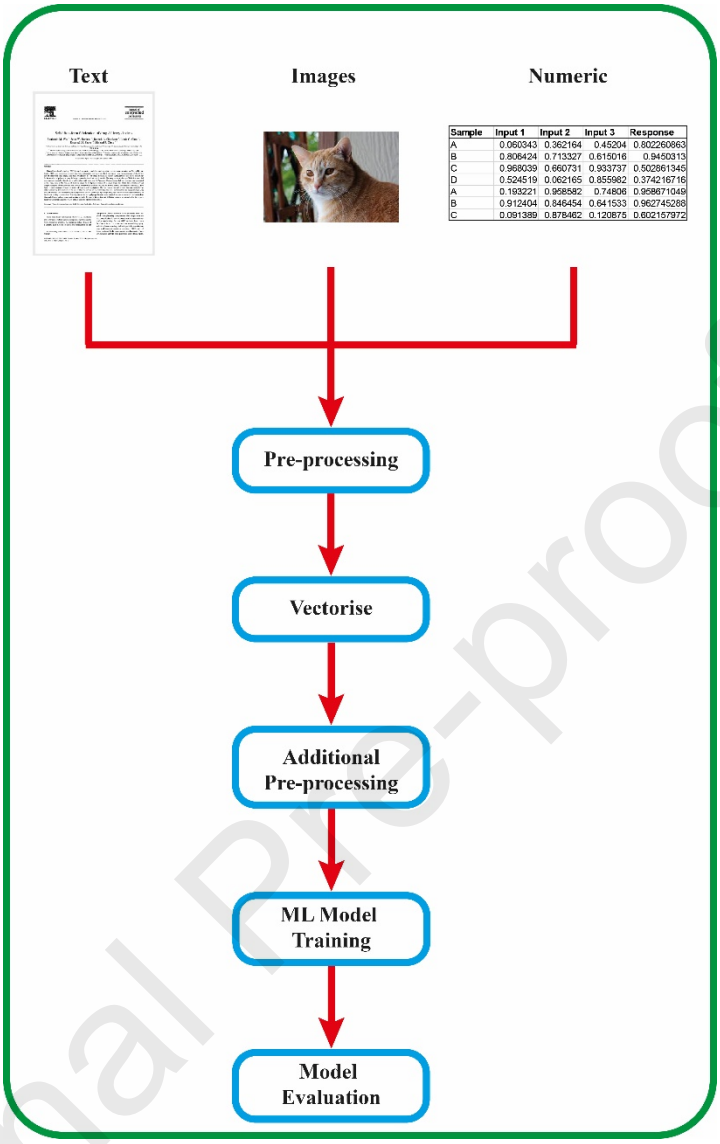


Figure 3. Overview of a typical ML pipeline. ML can handle text, images and numeric data formats. Though a 'plug-and-play' approach can be taken with ML, pre-processing can help enrich input data and ultimately improve model performance.

4.1 Machine Learning Techniques

4.1.1 Supervised learning

There are several subclasses of ML, of which supervised learning is one. Supervised learning involves directing an algorithm to solve a specific question. The algorithm is presented with data that has been labelled, describing the question of interest. For example, labels could be medicine 3D printability, or optimum 3DP temperature [156]. The former label in this example illustrates a classification ML task, as

medicines are classified as being 3D printable, or alternatively, not 3D printable. The latter exemplifies a regression task, because a specific printing temperature is given from a continuous range (**Figure *4***). A supervised ML algorithm takes a subset of the labelled data, known as the training data, and uses it to learn how dataset features relate to labels; e.g. how the physical properties of a medicine affect its 3D printability. After learning how data features relate to data labels, the ML algorithm can use a second subset of the data, known as testing data, which is unseen to the machine, to verify how accurate its predictions are. Supervised learning has been used to classify gene-disease association, pattern recognition of pharmaceutical raw ingredients [157, 158].

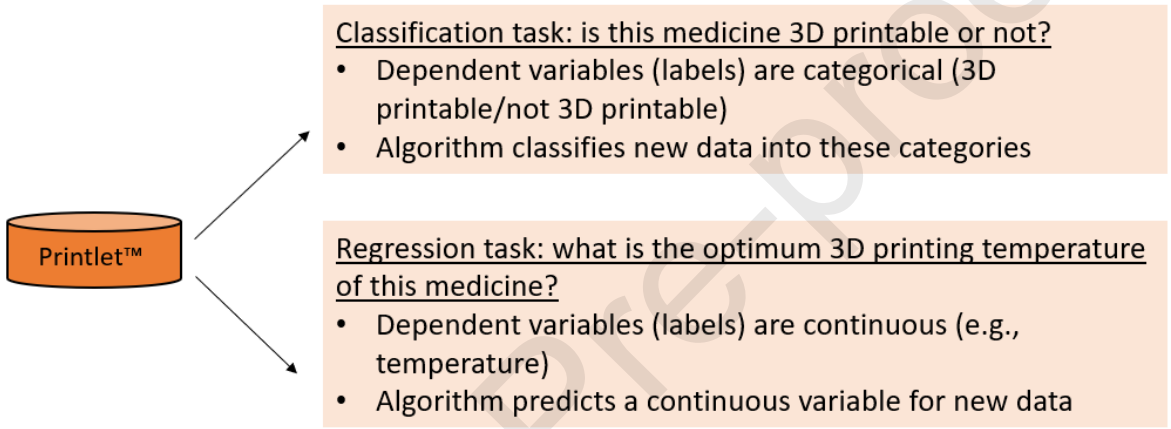


Figure 4. Difference between classification and regression ML tasks.

Frequently used supervised algorithms include multilinear regression, decision trees, random forest, support vector machine, and artificial neural networks (ANN). Multilinear regression is a series of linear regression calculations, seeking to fit a regression line through a multi-dimensional space [159]. As the name suggests, decision trees make their predictions by learning classification rules within data based on the dataset features (**Figure 5**). A decision tree consists of nodes and branches, where each node splits into further nodes until the terminal node. The user can define how each node splits. For classification tasks, a popular splitting decision is based on probability, where the algorithm learns the split with the greatest probability of obtaining the correctly labelled class [160]. Multiple decision trees can be used to establish the best prediction, which are referred to as random forest. Essentially, random forests are a collection of decision trees that are randomly divided, learning random subsets of

explanatory variables. The final step is then to pool the results together, and depending on the user-defined method, random forest can then obtain an average or the majority vote [160].

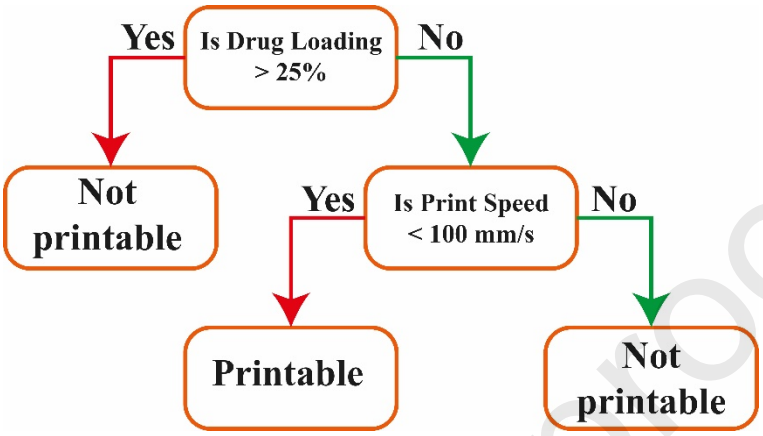


Figure 5. A schematic depicting an example of a simple decision tree. In this example, a decision tree is learning the rules for determining printability based on drug loading and print speed.

Support vector machines create a decision boundary seeking to separate the different classes. The decision boundary consists of a linear hyperplane and support vectors, where the latter determines the margin of the decision boundary [161] (**Figure *6* (A)**). Hence, the input data needs to possess a linear relationship. For non-linear datasets, the *kernel trick* can be employed for SVM, whereby the data is projected onto a high-dimensional feature space, and subsequently a linear hyperplane is fitted (**Figure *6* (B)**). With the *kernel trick,* SVM is an attractive ML technique for both linear and non-linear datasets. Artificial neural networks are another commonly used algorithm, first modelled in 1943. Inspired by biological neurons, an ANN consists of interconnected nodes, which are connected by edges. Each node performs a calculation, factoring in the weighted values received from preceding nodes, where if a given threshold is reached, then the node is activated, and the signal is propagated to the next layer (**Figure *7***) [162].

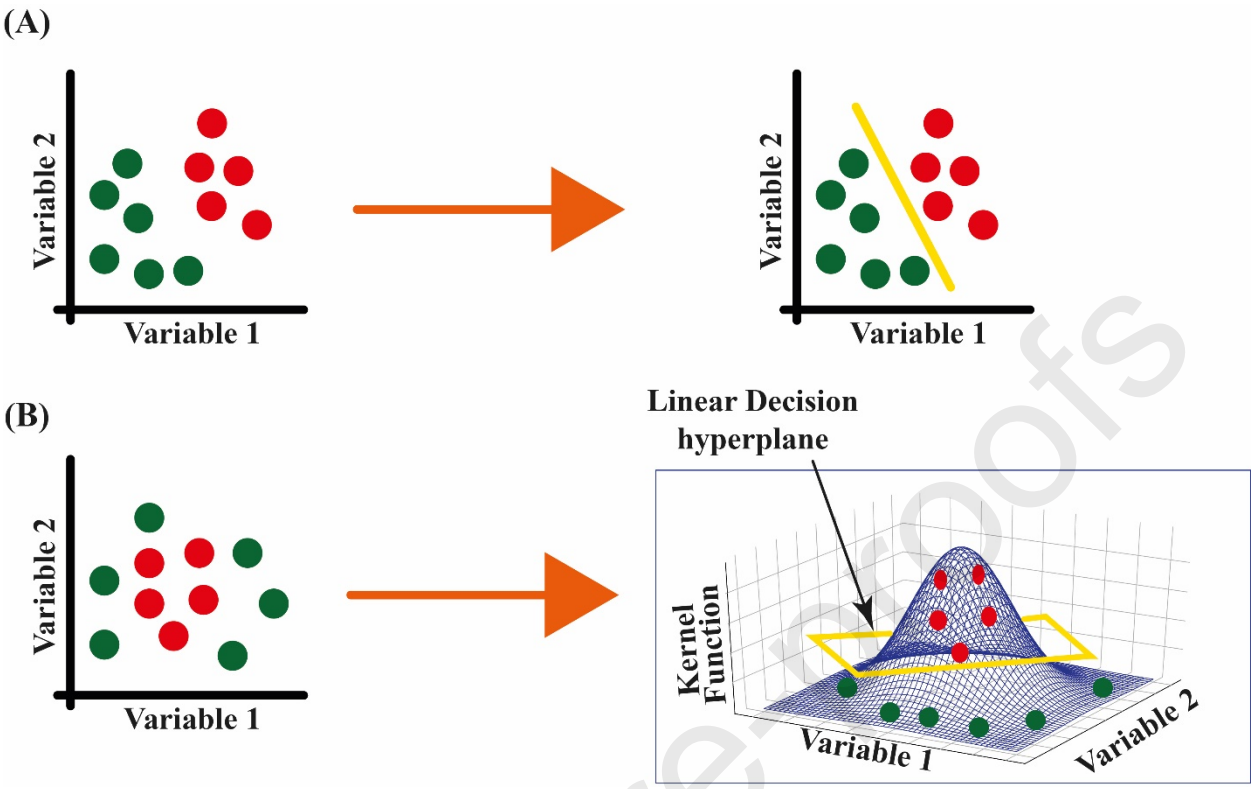


Figure 6. Schematic illustrating the classification principle behind SVM. This algorithm learns through creating hyperplanes in order to separate different classes. If the input data is non-linear, then the '*kernel trick*' is used to find linearly separable hyperplanes between different classes.

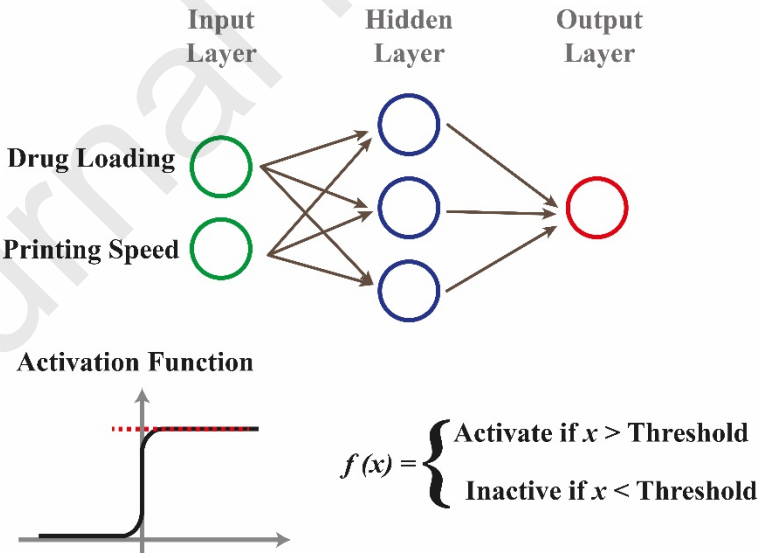


Figure 7. Schematic of ANN. Inspired by biological neurons, the algorithm consists of nodes (coloured circles) and edges (arrows) that communicate together provided the threshold for the activation function has been reached. ANN is inspired by the workings of a biological neurone.

4.1.2 Unsupervised learning

Unsupervised learning involves the identification of patterns in data, without access to labels. For this reason, no predefined questions are asked of the algorithm; the algorithm identifies differences in data without being told what differences to look for [163, 164]. For example, an unsupervised algorithm could be supplied with the pharmaceutical properties of thousands of 3D printed tablets, and of its own accord find if there is a relationship between tablet porosity and disintegration speed. Unsupervised learning provides researchers with a powerful tool to analyse data without human bias [165]. By choosing to not ask specific questions, algorithms may find patterns in data that researchers had not previously considered. A common unsupervised ML technique is clustering, in which a model learns differences between data points, and clusters them into groups for visualisation of a data trends [166]. Key clustering algorithms include hierarchical clustering, k-means, and divisive analysis [167]. Unsupervised learning has been used to classify P-glycoprotein inhibitors [168]. The difference between supervised and unsupervised learning is portrayed in **Figure 8**.

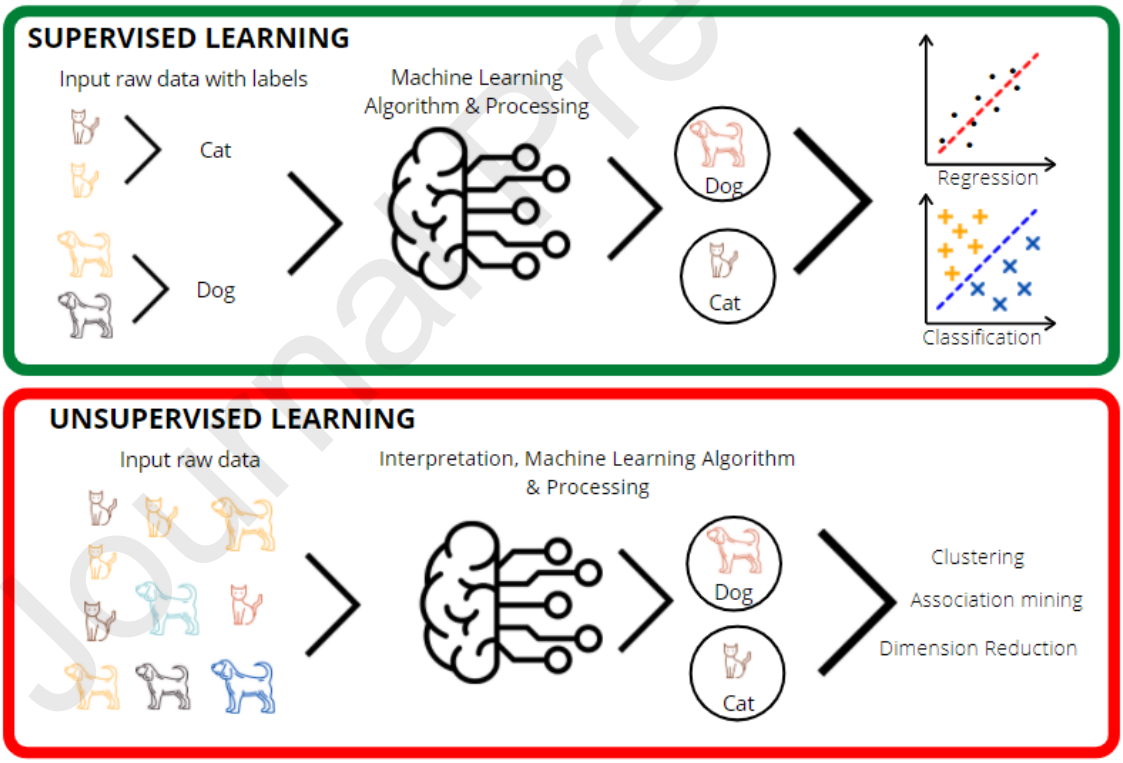


Figure 8. Illustration depicting the difference between supervised and unsupervised learning. Supervised learning requires the input data to be annotated by the user, and can perform both regression and classification tasks. Unsupervised learning does not require the data to be annotated, and thereby saving time. Instead, unsupervised learning requires the algorithm to

inherently identify difference between groups. Unsupervised learning is generally used for clustering, association mining and dimension reduction.

4.1.3 Semi-supervised learning

Semi-supervised learning, as its name suggests, sits at the intersection between supervised and unsupervised methods [169]. Semi-supervised projects begin with a dataset that is partially labelled. In the modern world of big data, partially labelled datasets are a common occurrence [170]. Unsupervised learning techniques are used to label unlabelled data by drawing inferences from data with labels [171]. Subsequently, supervised techniques are then used to identify relationships between data features and their labels. Semi-supervised learning is a useful approach for increasing the quantity of useable data in a set. Increasing the amount of data is often sought after to increase the external validity of a ML model. As with all experiments, increased sampling typically leads to more reliable and transferable results. Labelling of data by humans can require significant time, money, and is prone to mistakes. In juxtaposition, the same task carried out by unsupervised ML methods is often fast, efficient, and fastidious.

4.1.4 Reinforcement learning

Reinforcement learning is a goal-directed technique applied to unlabelled data [172]. Reinforcement algorithms are set a goal and then the ML model works towards accomplishing this in an iterative, self-teaching manner. For example, a reinforcement algorithm has mastered the boardgame Go through self-teaching alone, achieving super-human performance [173]. During reinforcement learning actions are applied, and their success is judged based on how close they bring the algorithm to its end goal. For example, a 3D printer with in-built reinforcement learning would tweak printing parameters and quantify what effect they have on tablet hardness. If a chosen parameter results in an outcome that deviates from the end goal, the algorithm experiences ‘punishment’, and learns not to carry out such an operation again. Conversely, if a parameter moves the system closer to the goal, then the algorithm will experience ‘reward’, and will learn that this is a positive action. With time reinforcement algorithms learn how to avoid punishment and maximise reward, eventually leading them to achieve their goal [174].

4.1.5 Deep Learning

Deep learning is a subset of ML that is garnering increasing attention in recent years [175]. Deep learning is an extension of artificial neural networks, whereby networks extend more deeply and thus interact at higher complexities [176]. ANN typically have three layers: an input, a hidden layer, and an

output layer. In deep learning, the number of hidden layers can extend into the 100s [177]. This has resulted in deep learning being able to outperform other ML algorithms for large datasets, and to easily model complex interactions between features [176, 178]. Additionally, the neural architecture can be made such that deep learning can be used for either supervised, unsupervised or reinforcement learning, and thus expands deep learning's application.

5 Applications of ML in Pharmaceutical 3D Printing

Both 3DP and ML are enabling features of the fourth industrial revolution, Industry 4.0, whereby traditional manufacturing methods are advanced and automated [179]. Despite both technologies existing for decades, it was only recently that the two began to merge (***Figure 9***). ML has the potential to drastically change how research in 3DP is approached in both research and clinical settings. Recently, Gongora et al. found that ML can reduce the number of FDM experiments by 60-fold [180], whilst Ruberu et al. reported that process optimisation through ML can considerably reduce the number of bioprinting experiments to below 50, out of a possible 6,000 to 10,000 [181]. Evidently, these will expedite research discoveries and facilitate personalised, on-demand printing of medicines. ML has been applied to different stages of the 3DP pipeline, which here are categorised as pre-printing, in-situ or real-time printing, and post-printing.

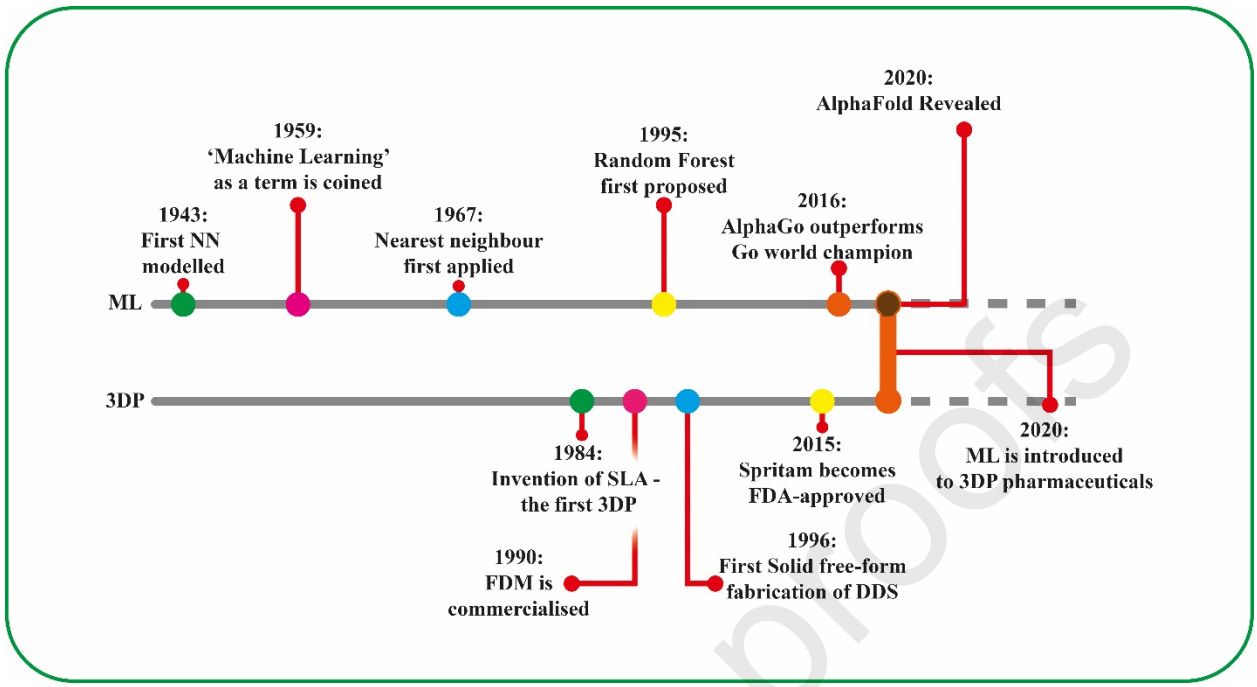
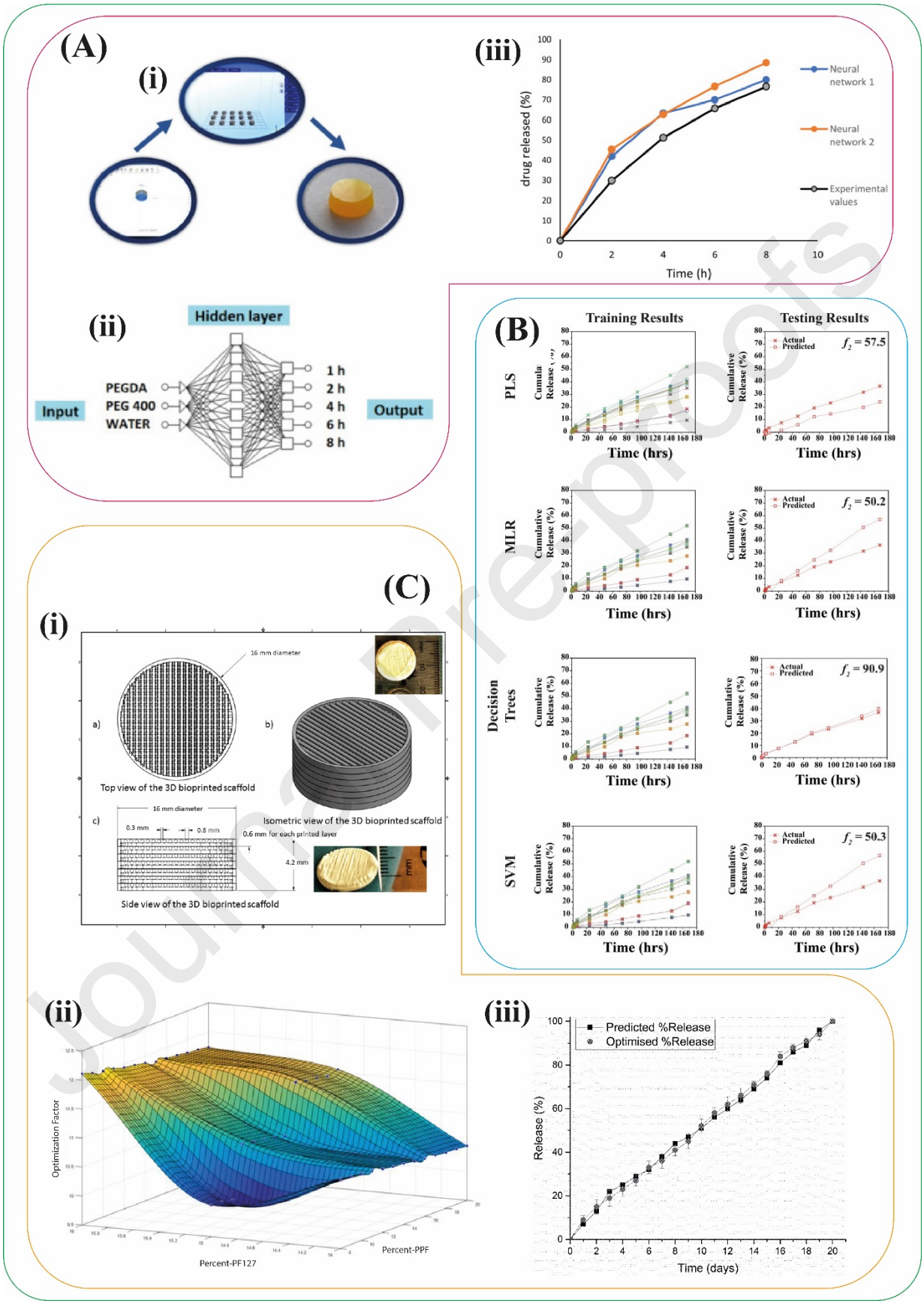


Figure 9. Side-by-side timeline depicting key landmarks in ML and 3DP research until 2020. Although both technologies align with Industry 4.0, they have been mostly researched independently to one another. In 2020 articles combining ML and 3DP of pharmaceuticals begin to be published. (NN: neural network).

5.1 Machine Learning in the Pre-Printing Stage

Pharmaceutical formulation is a complex task ordinarily requiring expert experience. Even seemingly insignificant changes to formulation design can significantly affect the final medicine characteristics and *in vivo* behaviour. For example, tablet geometry can considerably affect drug dissolution rate, and the choice of excipients can affect bioavailability [182, 183]. In pharmaceutical 3DP, formulations are often personalised and thus different from one batch to the next. Thus, specialists in the field must rely on their knowledge to adapt formulations to suit the pharmaceutical needs of the individual [50]. There are many factors to consider during personalised formulation design, some include: patient's swallowing capacity, flavour preferences, required drug dose, required drug release kinetics, presence of disease, sex, age, motor skills, and coadministered medications [184-199]. ML has the capacity to consider all these factors and predict optimal formulation design features based on an individual's requirements [154, 200-202]. Within the pharmaceutical formulation field, ML has been used to predict medicines' stability, drug loading capacity, drug release kinetics, and clinical patient response, to name a few applications [203-208]. These are all directly applicable to formulation of 3DP medicines.

In the pharmaceutical world, ML has mostly been used to predict and optimise drug release [209-220]. Medicines' drug dissolution profiles are a fundamental characterisation technique in pharmaceutics [221]. Traditional evaluation of drug dissolution is time-consuming, expending large quantities of consumables, such as buffers, and requiring apparatuses with high capital costs, such as UV-Vis spectrophotometers and dissolution baths. Therefore, ML prediction of medicines' dissolution behaviour could allow researchers to experimentally screen only the formulations predicted to have the best results (i.e. formulations of interest); hence allowing scientists to redirect time and resources to other aspects of the formulation process. Several studies have used ML to predict dissolution profiles of 3DP medicines (***Figure 10***). ANN has been used to predict the dissolution behaviour of DLP-fabricated Printlets™ [222]. Two ANN were compared, where one model only used the material composition as an input, and the second ANN model used both the material composition and the DLP exposure time. It was revealed that the ANN architecture using solely the material composition obtained an R^2 of 0.981 when compared to the experimental data, whereas the ANN architecture factoring exposure time yielded an R^2 of 0.996, thus inferring the exposure time to be a pertinent input. Another study compared the performance of four different ML techniques to predict the dissolution profiles of FDM products, using rheological properties as inputs [210]. The study revealed that a non-linear technique, decision trees, outperformed other linear techniques in predicting drug release profiles. A third study investigating ML for prediction of drug release using the material composition as input found ANN to achieve near perfect predictions, as depicted in **Figure 10** (**Ciii**), thus highlighting the utility of ML in such applications [223]. These studies have shown that ML models can learn how drug release works, in that drug concentration, at succeeding time points, will be equal to or greater than preceding time points.



1

Figure 10. Machine learning applied to predict 3DP medicines' drug release profiles. **(A)** The inputs for **(i)** SLA formulated printlet were processed using **(ii)** ANN to **(iii)** predict the dissolution profile [222]. **(B)** Several MLTs were compared, where it was determined decision tree produced the most accurate predicted dissolution profile [210]. **(C)** ANN were also used on (i) bioprinted scaffold to determine (ii) the correlation between inputs and outputs, to (iii) ultimately determine the release profile [223].

ML has also been used to predict the printability of formulations: a key consideration of 3DP formulation design [156]. In the first study using big pharmaceutical 3DP data with ML, researchers built a dataset comprised of 614 drug-loaded formulations for FDM filaments produced by HME, incorporating 145 distinct excipients. Each formulation was labelled according to the filament mechanical characteristics (e.g. good, brittle, flexible), printability (i.e. printable or not), and both extrusion and printing temperatures. With this labelled dataset it was possible to employ supervised learning to predict filaments' printability (**Figure *11***). The study investigated several methods of supervised learning. The model was able to predict the qualitative filament mechanical properties, such as whether the filament was flexible, brittle or good. Solely using the weighted fraction of the materials in a formulation as inputs, a printability accuracy of 76% was obtained.

As mentioned in **Section 4**, pre-processing of data prior to ML can help improve the performance of a model. With this in mind, the authors of [156] created an additional four feature sets using their pharmaceutical domain expertise. One of the limitations of using material names as an input is it means predictions cannot be made for materials not existing within the training dataset. Hence, the rationale for engineering new feature sets was to improve the generalisability of the model. A feature set called Physical Properties was engineered. This feature sought to use weighted physical properties of a formulation as inputs; the glass transition temperature (T_g), melting temperature, and molecular weight. Hence, if a material did not exist in the dataset, or if the material was used as a primary polymer rather than a plasticiser (e,g, PEG), then this was not a problem for the ML model as it could consider the weighted properties of the formulation. Although the model accuracy when using Physical Properties decreased to 70%, it afforded the ability to apply ML models to formulations with new materials without having to re-train the model using new materials. As a transparency check to ensure the ML models were learning the correct information, random forest was used to rank the importance of materials in formulations on response variables. It was subsequently discovered that the concentration of the primary polymer was the main determinant for predicting printability, followed by

plasticiser concentration, which are formulations variables that experienced 3DP practitioners would agree influence the printability of a formulation.

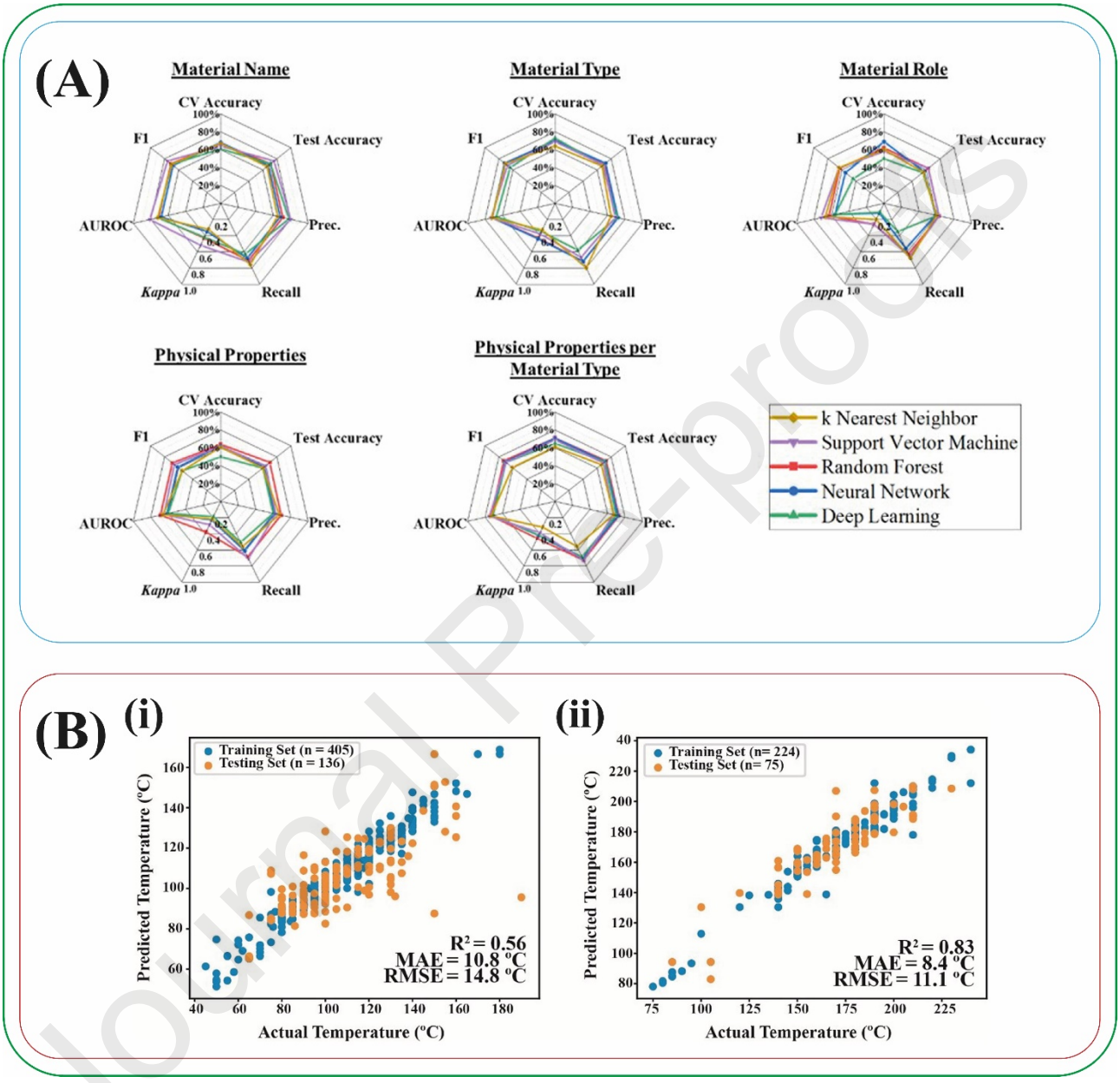


Figure 11. (A) Machine learning performances for determining the printability of FDM formulations using five different feature sets. **(B)** Random Forest predictions for the **(i)** extrusion and **(ii)** printing temperature [156].

Further to supervised learning, unsupervised learning has also been applied to support the pre-printing stage. As mentioned, unsupervised learning does not require labelling of data with explanatory

variables. An advantage is that models are not influenced by subjective or erroneous human labelling, allowing algorithms to naturally establish patterns in the dataset. An unsupervised ML technique that has been widely used is principal component analysis (PCA). PCA learns a transformation that maps high-dimensional data to low-dimensional representations, capturing the variation in the data [224, 225]. As well as being used as a ML technique is its own right, PCA's powerful dimensionality reduction can also be applied to the pre-processing stage of ML to reduce dataset noise. PCA has been used to predict the feedability of filaments for FDM pharmaceutical printing (**Figure *12* (A)**) [226]. By measuring mechanical properties of filaments, and generating a force-distance profile, PCA was found to cluster similar filaments together, which were termed as 'feedable', 'tunable' or 'non-feedable'. Here PCA shows that complex mechanical plots can be made more interpretable with ML, allowing the discernment of patterns. As illustrated in **Figure *12*(A)**, it is visually easier to interpret PCA results than raw data. Alternatively, PCA can be paired with another unsupervised technique, k-means, to further streamline ML [227]. K-means seeks to cluster neighbouring points, which in the example in **Figure *12*(A)** would have been able to distinguish between feedable and non-feedable filaments. With this combination the raw data could have been directly fed to a k-means algorithm, outputting a filament's feedability without needing to visually inspect the PCA plot (**Figure *12* (A iii)**).

Clearly, ML has many applications in the pre-printing stage of medicines manufacture. Researchers can harness computer intelligence to streamline formulation development, producing 3D printable formulations that will result in products personalised to individual patients. Whereas manual compounding and testing of many iterations of formulations could take weeks to find a suitable product, AI can dramatically reduce this timeline. Ultimately, this will mean that development of personalised 3DP medicines will be accelerated; granting patients access to bespoke pharmaceuticals with shorter lead times. This will be particularly useful in time-sensitive clinical situations.

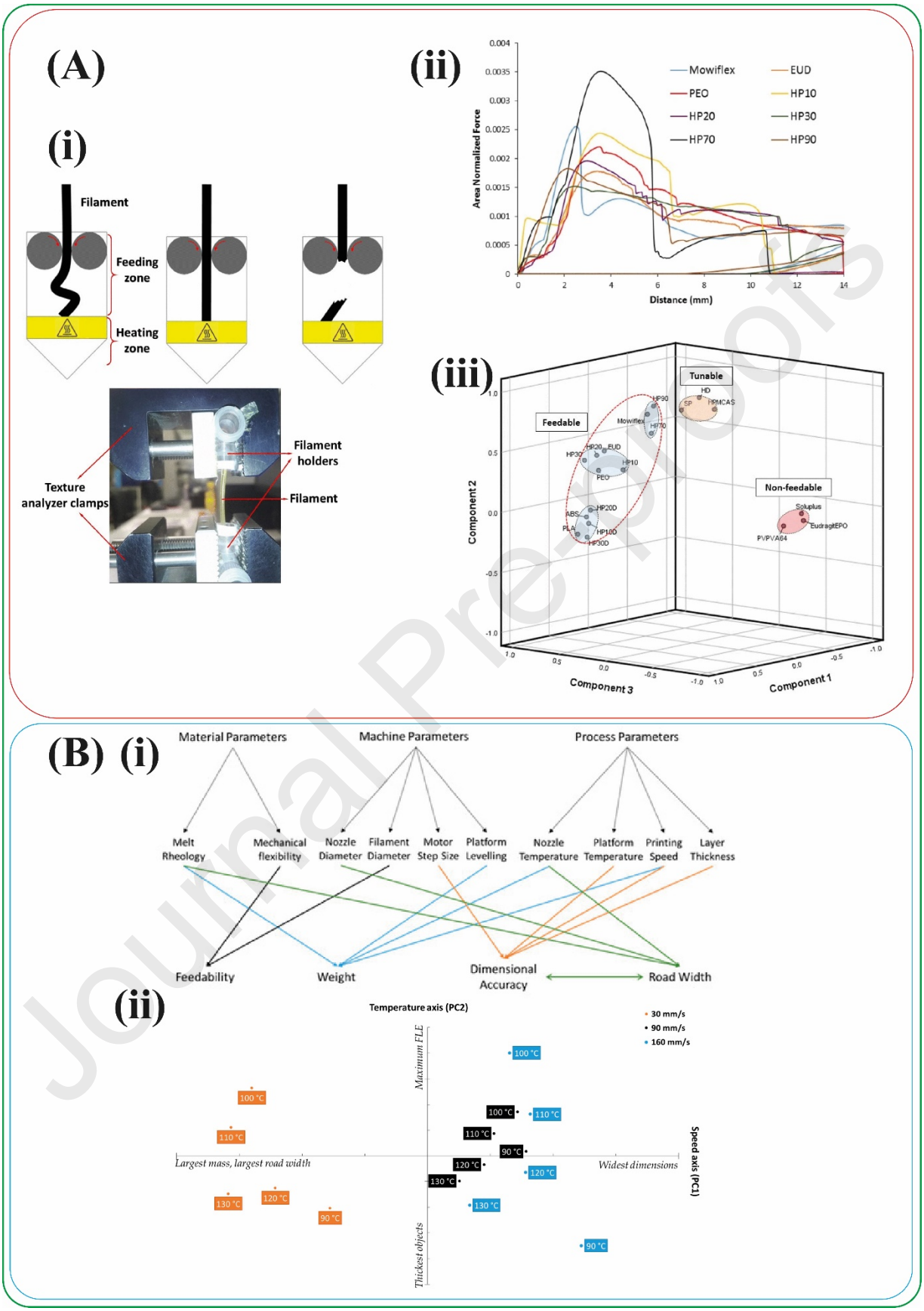

(A)
(i)
Filament
Feeding zone
Heating zone
Texture analyzer clamps
Filament holders
Filament
(ii)
Area Normalized Force
Distance (mm)
Mowiflex
EUD
PEO
HP10
HP20
HP30
HP70
HP90
(iii)
Tunable
Feedable
Non-feedable
Component 1
Component 2
Component 3
(B) (i)
Material Parameters
Machine Parameters
Process Parameters
Melt Rheology
Mechanical flexibility
Nozzle Diameter
Filament Diameter
Motor Step Size
Platform Levelling
Nozzle Temperature
Platform Temperature
Printing Speed
Layer Thickness
Feedability
Weight
Dimensional Accuracy
Road Width
(ii)
Temperature axis (PC2)
30 mm/s
90 mm/s
160 mm/s
Maximum FLE
Largest mass, largest road width
Widest dimensions
Thickest objects
Speed axis (PC1)

Figure 12. Models developed using PCA, an unsupervised learner, to predict the printability of formulations. **(A) (i)** An in-house tester was made to replicate the feeding behaviour of filaments during FDM. **(ii)** A force-distance plot was generated from the tester, which was **(iii)** subsequently analysed by PCA to determine the 'feedability' of filaments [226]. **(B) (i)** Summary of the interaction between material properties and processing parameters. **(ii)** A biplot generated using PCA depicting the relationship between processing parameters and print properties [228].

5.2 Automated 3D Printing of Medicines

A key goal of pharmaceutical 3DP is to leverage AI to create a seamless, autonomous 3DP process. Currently, researchers are required to input printing process parameters before each batch of medicines is produced. Setting fixed parameters is not an option in the production of personalised pharmaceuticals, as printer settings can directly affect the performance of an end product. For example, printing temperature will need to be controlled when printing heat-labile drugs. Moreover, light exposure time in DLP printing can affect the mechanical properties of a product, consequently affecting drug release profile [229]. ML algorithms have the capability to transform 3DP into an autonomous process, facilitating the printing of medicines without the need for on-hand expert advice.

Both supervised and unsupervised methods of ML have begun to be used to predict optimal printing conditions for medicines. One study demonstrated how PCA can determine how FDM printing parameters such as printing speed and temperature will affect the final product quality [228]. The analysis allowed rapid interpretation of the relationship between multiple variables. For example, using a PCA biplot, it was observed that printing speed was negatively correlated with product road width and product mass. **Figure *12* (Bii)** illustrates that samples printed with the same printing speed clustered together. Besides these categorical features, another key dependent variable are the processing temperatures. Historically, recommended starting HME temperature for formulations is guided by a *rule of thumb*, which recommends starting with anywhere between 15-60 °C above the T_g of the formulation. Recently, supervised ML techniques were used to predict optimal HME and FDM printing temperatures, where accuracies of ± 8.9 and ± 8.9 °C, respectively, were achieved (**Figure *11* (B)**) [156]. The benefit with this approach over the *rule of thumb* is it obviates the need to perform time-consuming differential scanning calorimetry measurements to determine the T_g. In addition, the recommended starting temperature output by ML is narrower than the *rule of thumb* [230]. Hence, ML offers a rapid and cheaper alternative to recommending the HME extrusion temperature. To date, there are no *rule of thumbs* or standardised predictive algorithms for the FDM temperature, and thus the study was the first

to establish the ideal printing temperature. The ML techniques were combined to produce a web-based software, which allows users to take advantage of predicting both the extrusion and printing temperature, as well as filament aspect and printability (http://www.m3diseen.com/predictions/).

Another application of AI during pharmaceutical 3DP is the automatic *in situ* detection of manufacturing defects. Intelligent recognition of deviations from optimal printing would allow researchers to leave pharmaceutical 3DP to work autonomously, thus facilitating 24/7 supply of personalised medicines in healthcare settings. One approach to achieving *in situ* printing correction is to pair ML with computer vision, another subset of AI. Computer vision, also referred to as machine vision, seeks to achieve super-human interpretation of images or videos [231]. A recent example of merging ML with computer vision was developed for detecting anomalies during laser powder bed additive manufacturing [232]. The printer was fitted with a camera to take images and monitor the printing process. The algorithm was then trained to detect multiple anomalies through algorithm adaptation, a feature superior to traditional computer vision algorithms that are used to detect one event per image. The algorithm was trained on a dataset containing pixels that were classed as either anomaly-free, or one of the six potential anomalies frequented during the printing process (**Figure *13***). Positively, the algorithm was found to achieve 100% accuracy in detecting absence of anomalies and 89% accuracy for detecting an anomaly.

Aside from photographic images, videos can also be processed by ML techniques, made possible by advancements in deep learning, namely handling of copious and complex information. Pairing deep learning with live video monitoring was demonstrated to autonomously correct FDM printing for both over- and under-extrusion [233]. Prior to achieving autonomy, a training procedure was performed off-line to train the model, which was used to classify ‘over-extrusion’, ‘under-extrusion’, or ‘good-quality’ printing. The model was then applied real-time, whereupon detecting irregular extrusion, the FDM printer was able to adjust the printing speed, flow rate or nozzle height. Deep learning was discovered to achieve an accuracy of above 98% in predicting the quality of the part, and predictions were made at times considerably faster than human reactions permit.

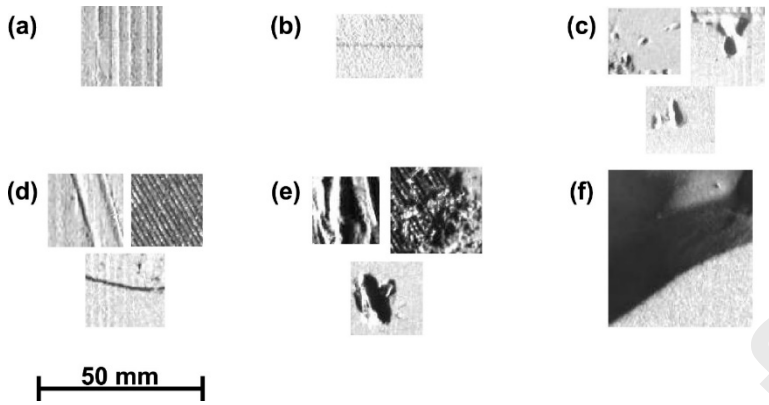


Figure 13. For detecting anomalies during laser powder bed additive manufacturing, an algorithm was trained on pixels containing one of six anomalies presented in figures (**a-f**) [232].

Building advanced modalities into application of *in situ* monitoring results in cutting-edge 3DP applications. One case was demonstrated by Zhu et al. (2020), where ML was leveraged to print directly on live organs [234]. A schematic of the process is illustrated in **Figure *14***. The challenge of 3DP on live organs is that the surface is non-planar and dynamic, which is in contrast to 3DP on build-plates that have a flat surface and the movement thereof is encoded and known via the .gcode (i.e. the command code for the printer). The study recognised these issues for printing on porcine lungs, and exploited ML to predict tissue surface deformation occurring during the lung breathing. The potential primary advantages of ML-guided *in situ* 3DP, like robotic surgery, include higher precision, better safety profiles, and a reduction in invasiveness [235]. In the context of pharmaceutics, *in situ* printing can be exploited to fabricate intricate drug-eluting devices or sensors for therapeutic drug monitoring inside the body [236, 237].

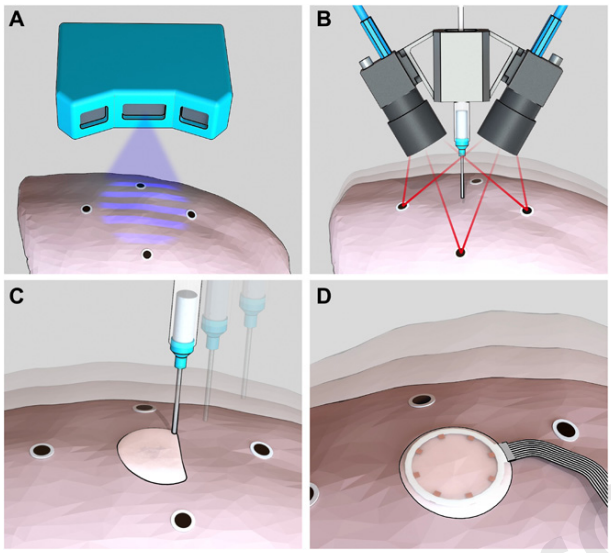


Figure 14. Schematic depicting the steps of printing hydrogels on lungs. The process begins by (A) scanning the lung surface, combined with (B) live tracking of the lung breathing. This allows the printer to predict the changes in lung deformation and (C) print accordingly. (D) Depicts the final print, which was an electrical impedance tomography sensor [234].

5.3 Machine Learning in the Post-Printing Stage

Building machine intelligence into the post-printing phase of pharmaceutical 3DP would facilitate the timely release of medicines to patients. ML has been used after printing as a quality control (QC) measure for 3DP drug products, which irrespective of the fabrication technique, is an important issue [238, 239]. ML can be leveraged to support process analytical technology (PAT), a mechanism designed to control the quality production of pharmaceuticals. PAT has been widely implemented by the pharmaceutical industry, motivated by regulatory guidelines such as the FDA *Pharmaceutical Quality for the 21st Century Initiative* [240]. Such guidelines were proposed to achieve maximum efficiency, flexibility, and agile pharmaceutical manufacturing that reliably produces high-quality medicines without extensive regulatory oversight [241]. In pharmaceutical 3DP, intelligent PAT systems could be employed as a QC measure to enable real-time approval of 3DP medicines, facilitating pharmaceutical 3DP's transition to widespread clinical use. For such applications, non-destructive analysers are required, due to their ability to preserve the integrity of the final product, as well as requiring minimal sample preparation. Widely used non-destructive tools are vibrational spectroscopy technologies, such as Raman or near-infrared (NIR) spectroscopy. Vibrational spectroscopy spectra can be processed using

multivariate analysis to build a predictive model relating the spectra with different parameters e.g. the concentration of drugs [242]. In other words, vibrational spectroscopy and multivariate analysis can be combined to quantify the drug concentration in formulations.

A popular ML technique used for multivariate analysis is partial least square (PLS) , a supervised learning technique [243]. Similar to PCA, PLS is a dimension reduction method that first identifies the latent variables from the explanatory data, then fits a linear model using least squares. In contrast to PCA, PLS determines these new features in a supervised manner, as well as computing the covariance between variables [243]. The use of NIR with PLS was recently exploited for dose verification of two separate drugs in a single SLS-printed product (***Figure 15*** **(A)**) [244]. The authors noted that the QC measure was able to provide rapid dose prediction in 10 seconds per tablet. In a separate study by the same research group, a portable NIR device was used to predict drug concentration in tablets across a range of 4 to 40 w/w% (***Figure 15*** **(B)**) [245]. The model developed, again using PLS, was able to achieve high accuracies for tablets of different geometries and formulation type. Drug concentration detected by the portable NIR was compared to that obtained by high performance liquid chromatography, where a paired *t*-test showed there was no significant difference between the two methods. PLS has also been used to predicted the crystallinity of lopinavir in SLS-printed products, providing valuable insight into the potential solubility of a drug [246].

Hyperspectral imaging, also referred to as chemical imaging, is another vibrational spectroscopy-based technique with applications in pharmaceutical 3DP QC [247]. The advantage of this technique is that it combines both spectral and spatial information, whereby materials invisible to the naked eye are made evident. Images mapping product drug concentration or distribution are produced by generating a spectrum for each pixel from a basic original image. This results in a 3D array for each sample, where the x- and y-coordinates represent the spatial coordinates, and the z-coordinate reflects wavenumbers [248]. Thus, hyperspectral images are multivariate in nature, and can be overwhelming to interpret in their raw form. Fortunately, ML can be used to analyse this type of data, including cutting edge deep learning [249, 250].

Hyperspectral imaging has been used to reveal the distribution of drugs in polymeric matrices, also elucidating the state of the drug (e.g. molecularly dispersed) [251]. PCA can be utilised to eliminate noise in the data and identify patterns of spectral data, facilitating rapid interpretation of hyperspectral images [252]. As an example, PCA has been used to colour-code the concentration of drug on images of tablets, with the colour shade signifying PCA score: reflecting drug concentration [253]. To date,

hyperspectral imaging paired with PCA has been used to visualise the concentration of theophylline in IJP-printed products [254] (***Figure 15*** **(C)**), clindamycin palmitate hydrochloride in SLS tablets [255], and indomethacin in FDM printed products [251]. Such research demonstrates the use of ML in providing pharmaceutical insight at a microstructural level, aiding understanding of the performance of a printed product. The benefits of this approach will be further realised as more complex formulations are subject to ML QC, such as multi-drug polyprints.

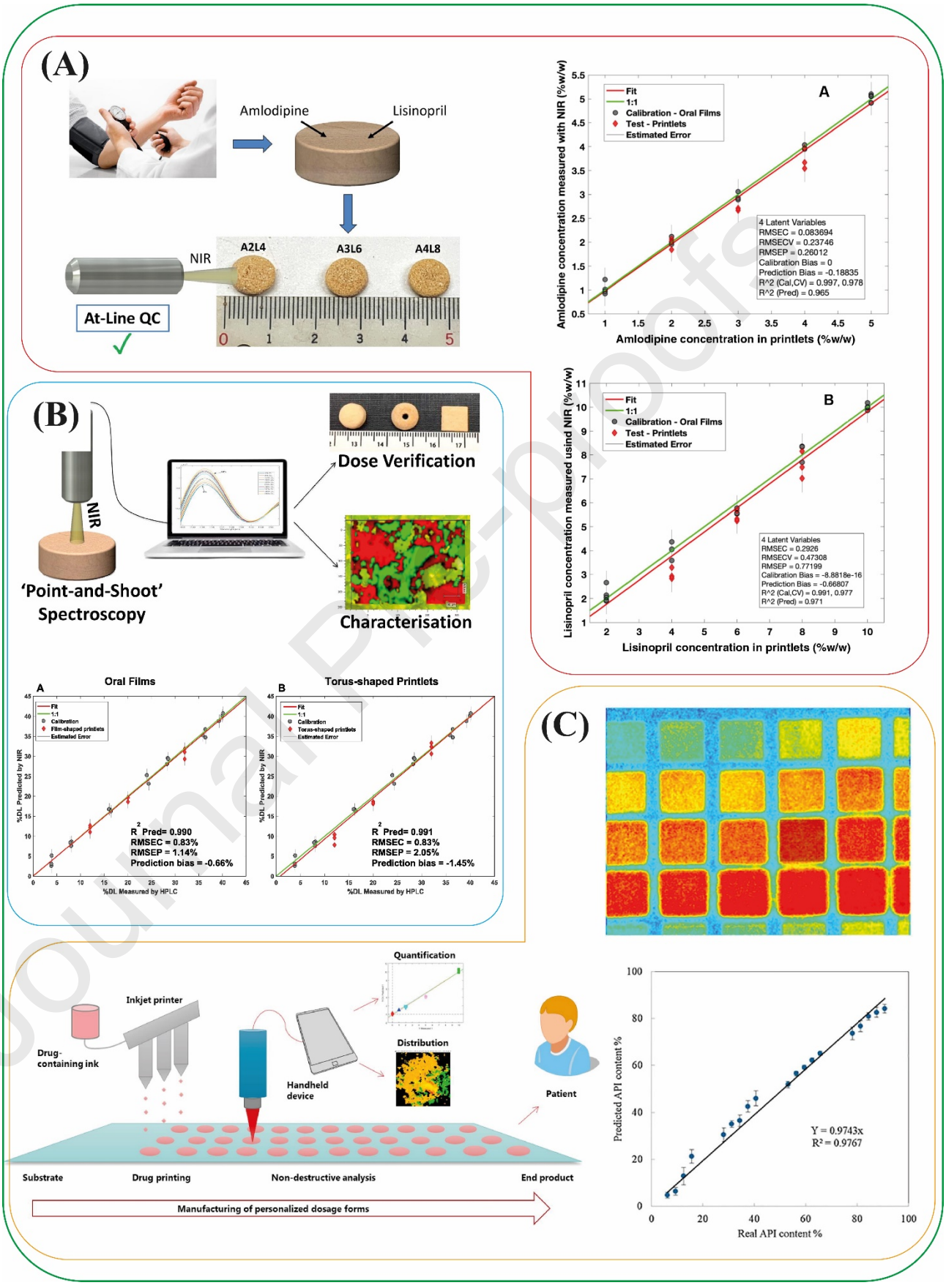


Figure 15. Applications of ML post-print. **(A)** PLS, a supervised learner, was combined with NIR spectroscopy for non-destructive verification of a Printlet™ with two drugs [244]. **(B)** Example of PLS-NIR spectroscopy used for dose verification in Printlets™ with varying geometries [245]. **(C)** NIR-chemical imaging combined with PCA, an unsupervised learner, used for qualitatively visualising the distribution of drug and excipient [254].

6 Machine Learning vs. Non-ML Techniques

Numerous industrial sectors have come to rely on traditional optimisation techniques (such as DoE, mechanistic modelling, pharmacokinetics (PK) modelling, and FEA), so are ML techniques really favourable for adoption in pharmaceutical 3DP? In short, ML is the future of process optimisation, and will likely combine with elements of traditional tools or supersede them entirely [206, 256, 257]. Whereas traditional techniques are often limited by their scope of use (e.g., PK modelling focuses on *in vivo* drug behaviour), ML can cover the breadth of existing non-AI tools combined. For example, one goal of ML is to develop end-to-end application, where the end product can be predicted from the start; in the context of 3DP pharmaceuticals, the goal would be to predict PK behaviour, for example, using the composition of the formulation. This is because ML algorithms do not need to be pre-coded with 'rules' on a system, instead they are coded to learn rules autonomously. As such, ML techniques can be trained to learn patterns within any dataset and thus solve problems across all subjects. This is useful for pharmaceutical 3DP, as the field inherently contains numerous disciplines: chemistry, mechanical engineering, pharmacokinetics, and pharmaceutics, to name a few. ML can be applied to consider how all of these factors interplay in the pharmaceutical 3DP pipeline.

Whilst DoE can also be applied to a breadth of fields, its low data capacity limits its utility in pharmaceutical 3DP. ML algorithms can seamlessly handle datasets with thousands of entries; this would entirely overwhelm DoE and would demand an infeasible number of manual experiments. Due to the large number of options within the pharmaceutical 3DP process, DoE models would be too narrow to model complex processes with many interacting factors. Another drawback of DoE compared to ML is that it often requires operators to perform experiments that they know will be unsuccessful, yet DoE demands the unsuccessful results to build its model. For example, researchers may know in advance that combinations of variables in a factorial design will not result in an optimal process outcome, however they must waste time and resources performing the permutation anyway to satisfy the model's

statistical methods. In comparison, ML does not set rigid boundaries on how input data should be organised within a parameter search space. This is clearly an advantage where researchers have large volumes of data that was not collected with DoE in mind; with ML, it can still be used and interpreted [154]. On the other hand, without specialist human input some ML models (such as reinforcement techniques) may suggest parameters that are not feasible in a specific setting (e.g., very slow printing speeds in an emergency medical unit). Thus, it is prudent that specialists still check ML decisions, especially when outputs will directly affect patient care.

ML can be combined with DoE, FEA, and mechanistic models to form hybrid models, which are yet to be thoroughly explored in 3DP [257-260]. For example, the optimisation cycle in FEA can become both costly and time-intensive, and ML has been used to address this issue [261, 262]. A further drawback to FEA is that specialised knowledge is required. Take for example FEA applied to tableting, where domain expertise in particle physics is needed to understand the deformation particles are subjected to [263]. Whereas ML does not require in-depth knowledge, provided a sufficient amount of data is available. Moreover, ML provides the opportunity for continuous processes, which has the potential to achieve intelligent 3DP automation [264, 265]. Nevertheless, there is an opportunity for existing DoE, FEA and mechanistic modellers to exploit ML to further enrich their research.

Just as 3DP can be integrated with other technologies (e.g., medical imaging) so can ML, resulting in a closed-loop system suitable for IoT. Here, *in situ* sensors will indeed play a crucial part in maintaining autonomy, in addition to computer vision techniques. An enabling aspect of ML is the ability to process different data formats, such as images, videos, and other data formats, which the non-AI techniques discussed herein are unable to do. Regarding the implementation of ML, open-source programming languages like Python, R, and Java can be used to construct ML models. **Table *2*** provides a summary of the unique benefits and drawbacks for all the discussed techniques.

Table 2. Summary of the advantages and drawbacks of each optimisation technique. All techniques do provide benefits, however comparing the advantages with respect to one another helps to highlight ML's strengths.

Technique	Benefits	Limitations
DoE	• In common use by pharmaceutical industry	• Commercial software is expensive • Restricted to small datasets

	• Not subject specific	• Restricted data formats • Additional experiments needed
FEA	• Physical phenomenon extrapolates well to new designs	• Computationally demanding • Additional experiments needed • Restricted data formats
Mechanistic Modelling	• 'White box' effect • No commercial software required • PK modelling is widely used in the pharmaceutical industry • PK modelling can reduce the number of animal experiments	• Expertise in physical phenomenon needed • Complex experiments needed • Restricted data formats
ML	• Can process both linear and non-linear relationships • Can process high-dimensional datasets • Processes various data formats • No commercial software required • Instantaneous predictions • Continuous learning • Facilitates *in situ* predictions • Models can be developed for end-to-end applications • Compatible with 'Internet of Things'	• 'Black box' effect • Requires deep mathematical knowledge to model and interpret results • Pre-processing data can be time-consuming with unstructured data • Processing videos can be computationally demanding • Still subject to bias if input data is not managed correctly

One salient drawback of ML that should be considered is the 'black box' effect. As ML models deal with more and more complex datasets, their decision processes typically follow suite. Complex decision processes within algorithms can become difficult for humans to interpret and importantly, sense check. Transparency in ML techniques' methods are paramount in clinical settings, where

clinicians and patients need to trust algorithm outputs [266]. This therefore applies to pharmaceutical 3DP, where ML algorithms could be autonomously controlling the personalised production of medicines [267]. A number of steps can be taken to avoid the 'black box' effect [268]. Firstly, developers should verify the quality of the data being fed to ML algorithms. The axiom 'garbage in equals garbage out' still rings true in the age of AI. The quality of an algorithm's output is defined substantially by the quality of the data fed to it. ML does not yet offer a bypass for meticulous data collection. When implementing ML in pharmaceutical 3DP, it should be assured that data is accurate and fully descriptive of a wide variety of 3DP techniques and patient populations. There has recently been a drive to ensure that AI data is fully inclusive across genders, ethnicities, socioeconomic statuses, and cultures; without recognition of diversity AI is not suitable for mainstream use [269, 270]. ML algorithms can be adapted to be more transparent. For example, models can output relationships they have found between data features and produce graphics that outline decision processes [271, 272]. Ultimately, transparency is key if AI is to be successful combined with 3DP in healthcare settings. Policy makers must be sure that technology is enhancing patient care, rather than mystifying it. AI systems within 3DP must also ensure data security, especially when dealing with sensitive patient data. Such data will require secure Cloud storage and protection from hacking. Decisions made by algorithms will require stringent record keeping for audit and regulatory purposes. Blockchain, a digital tamper-proof ledger, will be ideally suited to this purpose, allowing end-to-end traceability of AI activity throughout the pharmaceutical 3DP pipeline [273].

7 Internet of Things for Pharmaceutical 3D Printing

IoT technology will be transformative for many processes within medicine and manufacturing, offering significant utility in the 3DP of medicines [274]. At present, the pharmaceutical 3DP pipeline contains multiple separate processes that require human interaction: formulation design, formulation compounding, 3DP, potential post-processing, and finally QC and medicine release. As demonstrated in this review, ML can facilitate each stage of the pipeline. Additionally, an interconnected network of devices and robots could remove the need for human hands to carry out tasks and move materials between development stages. Moreover, an intelligent and interconnected network of devices and robots could even obviate the need for human brainpower: realising the vision of fully autonomous production of personalised 3DP medicines. This is the future of Industry 4.0. When IoT and AI are combined, they result in a cyber-physical system [275]. As pharmaceutical 3DP itself is already a digitalised process, it is perfectly aligned for incorporation into a cyber-physical system. Though once the upfront cost of sensors, robots, and other hardware would prohibit complete digitalisation of the

pharmaceutical 3DP pipeline, these elements are consistently becoming cheaper and more accessible [237]. Essentially, ML would provide actionable insight from data, to which 3DP will execute. Whilst building a pharmaceutical 3DP cyber-physical system may still present relatively large upfront costs, the resultant obviation of human labour will dramatically reduce expenditure in the medium to long term. Moreover, machines and AI algorithms can work 24/7 at full capacity without increasing error or the need for rest; hence facilitating high throughput production of patient-centred medicines at all hours of the day, every day of the year. **Figure 16** is an illustration depicting stages of the 3DP workflow that can be interconnected with IoT and AI.

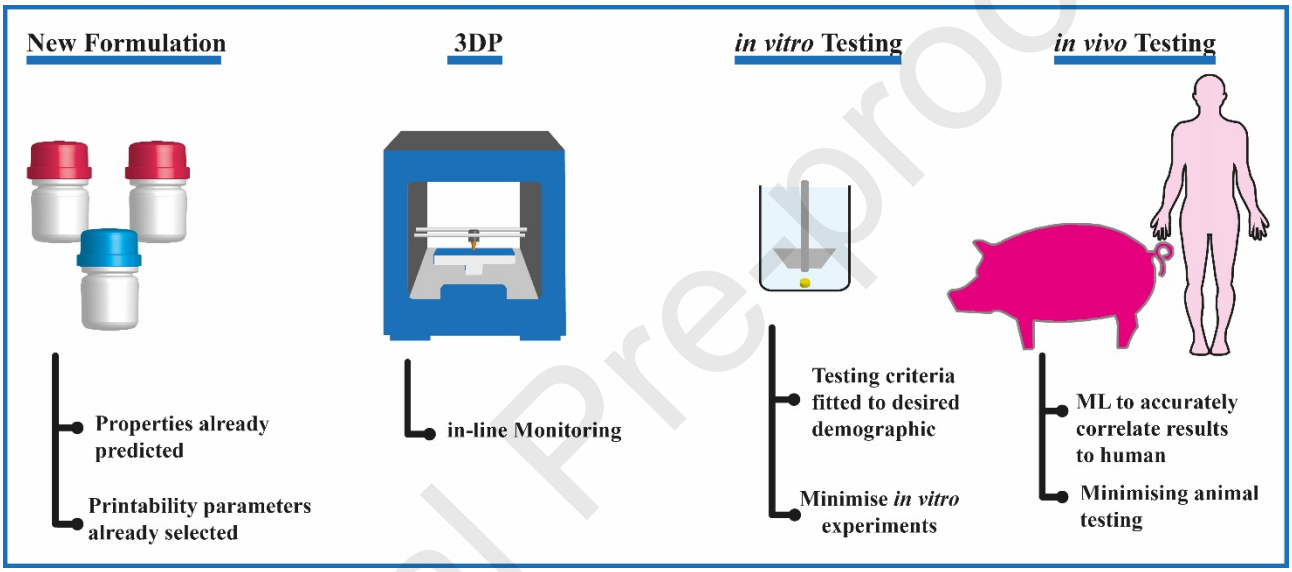


Figure 16. Stages of pharmaceutical 3DP that can be interconnected with IoT and AI, facilitating a fully autonomous pipeline.

8 Pharmaceutical 3D Printing's Intelligent Trajectory

It is only a matter of time until AI plays an integral role in the development and manufacture of medicines. Compared to other industries, such as the entertainment and financial sectors, the pharmaceutical industry sits well behind the adoption of AI curve. At this time, it would be wise for the pharmaceutical industry to combine its current cutting-edge techniques with AI-guided 3DP, because 3DP is already digital and aligned with personalised medicine. This move would drive the pharmaceutical industry forward to fully harness modern technological capabilities. Adopting AI-guided 3DP now will accelerate the translation of 3DP medicines into healthcare settings, upgrading patient care to a personalised model sooner. The majority of ML studies in 3DP medicines has been applied to oral-

formulations, and further research needs to explore the feasibility of ML in fabricating other delivery devices [276]. A concerted effort is being made to address the current challenges of combining AI with pharmaceutical 3DP; such as lack of AI skillset, algorithm decision-making transparency, and production of ML techniques that provide high performances even with small datasets [8, 277]. These issues are universally felt across both academia and industry, irrespective of the research field, thus driving a collective impetus. There are also challenges specific to pharmaceutical 3DP that can be resolved. For instance, consideration should be given to producing a unified database relevant to pharmaceutical 3DP that will facilitate data mining. As progress continues, it will become increasingly tiresome to data-mine directly from individual published articles or produce data in house. A structured database will readily allow the extraction of ML-friendly relevant data for use by all, which could be achieved through a strategic and unified approach to data collection. These efforts will ultimately aid policymakers in assessing AI's contribution to pharmaceutical 3DP, expediting clinical translation.

9 Conclusion

In this review we have highlighted how AI can be combined with pharmaceutical 3DP pipeline. It is paramount that medicine moves away from its longstanding 'one size fits all' paradigm of pharmaceutical provision and embraces administration of personalised medicines. Pharmaceutical 3DP can provide the supply of personalised medicines in the clinic, but currently requires the presence and expertise of experienced 3DP practitioners. Multiple methods of traditional process optimisation techniques, such as FEA, mechanistic modelling, and DoE, exist; however none are equipped to fully optimise the multiple stages of pharmaceutical 3DP. In comparison, ML can provide intelligent optimisation of each stage of 3DP medicines' production. This will eventually remove the need for constant expert input into 3DP medicine development, thus removing barriers to clinical adoption of the technology. Moreover, each stage of the pharmaceutical 3DP pipeline can be built into an intelligent IoT, in which smart hardware can handle every stage of development: from formulation design to final product release. Such an outcome would remove the need for human labour in the pharmaceutical 3DP entirely: granting patients 24/7 supply of bespoke, personalised medicines.

10 Acknowledgements

The authors thank the Engineering and Physical Sciences Research Council (EPSRC), UK for its financial support (EP/S009000/1, EP/S023054/1, and EP/L01646X).

References

[1] Z. Halim, R. Kalsoom, S. Bashir, G. Abbas, Artificial intelligence techniques for driving safety and vehicle crash prediction, Artificial Intelligence Review, 46 (2016) 351-387.

[2] R.J. Meuth, P. Robinette, D.C. Wunsch, Computational intelligence meets the NetFlix prize, 2008 IEEE International Joint Conference on Neural Networks (IEEE World Congress on Computational Intelligence), 2008, pp. 686-691.

[3] A. Bahrammirzaee, A comparative survey of artificial intelligence applications in finance: artificial neural networks, expert system and hybrid intelligent systems, Neural Computing and Applications, 19 (2010) 1165-1195.

[4] M. May, Eight ways machine learning is assisting medicine, Nat Med, 27 (2021) 2-3.

[5] A.W. Senior, R. Evans, J. Jumper, J. Kirkpatrick, L. Sifre, T. Green, C. Qin, A. Zidek, A.W.R. Nelson, A. Bridgland, H. Penedones, S. Petersen, K. Simonyan, S. Crossan, P. Kohli, D.T. Jones, D. Silver, K. Kavukcuoglu, D. Hassabis, Improved protein structure prediction using potentials from deep learning, Nature, 577 (2020) 706-710.

[6] M. Hilbert, P. López, The World's Technological Capacity to Store, Communicate, and Compute Information, Science, 332 (2011) 60.

[7] A. Esteva, A. Robicquet, B. Ramsundar, V. Kuleshov, M. DePristo, K. Chou, C. Cui, G. Corrado, S. Thrun, J. Dean, A guide to deep learning in healthcare, Nature Medicine, 25 (2019) 24-29.

[8] M. Elbadawi, S. Gaisford, A.W. Basit, Advanced machine-learning techniques in drug discovery, Drug Discov Today, (2020).

[9] U.R. Acharya, S.L. Oh, Y. Hagiwara, J.H. Tan, H. Adeli, Deep convolutional neural network for the automated detection and diagnosis of seizure using EEG signals, Computers in Biology and Medicine, 100 (2018) 270-278.

[10] A. Statnikov, C.F. Aliferis, I. Tsamardinos, D. Hardin, S. Levy, A comprehensive evaluation of multicategory classification methods for microarray gene expression cancer diagnosis, Bioinformatics, 21 (2005) 631-643.

[11] S. Kato, E. Takeuchi, Y. Ishiguro, Y. Ninomiya, K. Takeda, T. Hamada, An Open Approach to Autonomous Vehicles, IEEE Micro, 35 (2015) 60-68.

[12] M. Alaa, A.A. Zaidan, B.B. Zaidan, M. Talal, M.L.M. Kiah, A review of smart home applications based on Internet of Things, Journal of Network and Computer Applications, 97 (2017) 48-65.

[13] P. Shah, F. Kendall, S. Khozin, R. Goosen, J. Hu, J. Laramie, M. Ringel, N. Schork, Artificial intelligence and machine learning in clinical development: a translational perspective, npj Digital Medicine, 2 (2019) 69.

[14] FDA, FDA Permits Marketing of Artificial Intelligence-based Device to Detect Certain Diabetes-related Eye Problems., 2018.

[15] FDA, FDA Permits Marketing of Clinical Decision Support Software for Alerting Providers of a Potential Stroke in Patients, 2018.

[16] P. Pérez, J.M. Suñé-Negre, M. Miñarro, M. Roig, R. Fuster, E. García-Montoya, C. Hernández, R. Ruhí, J.R. Ticó, A new expert systems (SeDeM Diagram) for control batch powder formulation and preformulation drug products, European Journal of Pharmaceutics and Biopharmaceutics, 64 (2006) 351-359.

[17] F.R. Ahmed, M.H. Shoaib, R.I. Yousuf, T. Ali, K.E. Geckeler, F. Siddiqui, K. Ahmed, F. Qazi, Clay nanotubes as a novel multifunctional excipient for the development of directly compressible diclofenac potassium tablets in a SeDeM driven QbD environment, European Journal of Pharmaceutical Sciences, 133 (2019) 214-227.

[18] H. Leuenberger, M.N. Leuenberger, Impact of the digital revolution on the future of pharmaceutical formulation science, European Journal of Pharmaceutical Sciences, 87 (2016) 100-111.

[19] S.J. Trenfield, A. Awad, C.M. Madla, G.B. Hatton, J. Firth, A. Goyanes, S. Gaisford, A.W. Basit, Shaping the future: recent advances of 3D printing in drug delivery and healthcare, Expert Opinion on Drug Delivery, 16 (2019) 1081-1094.

[20] A.M. Vargason, A.C. Anselmo, S. Mitragotri, The evolution of commercial drug delivery technologies, Nature Biomedical Engineering, (2021).

[21] A.J. Capel, R.P. Rimington, M.P. Lewis, S.D.R. Christie, 3D printing for chemical, pharmaceutical and biological applications, Nature Reviews Chemistry, 2 (2018) 422-436.

[22] A. Awad, S.J. Trenfield, A. Goyanes, S. Gaisford, A.W. Basit, Reshaping drug development using 3D printing, Drug Discov Today, 23 (2018) 1547-1555.

[23] R. Durga Prasad Reddy, V. Sharma, Additive manufacturing in drug delivery applications: A review, Int J Pharm, 589 (2020) 119820.

[24] J. Norman, R.D. Madurawe, C.M. Moore, M.A. Khan, A. Khairuzzaman, A new chapter in pharmaceutical manufacturing: 3D-printed drug products, Adv Drug Deliv Rev, 108 (2017) 39-50.

[25] S.H. Lim, H. Kathuria, J.J.Y. Tan, L. Kang, 3D printed drug delivery and testing systems - a passing fad or the future?, Adv Drug Deliv Rev, 132 (2018) 139-168.

[26] C.I. Gioumouxouzis, C. Karavasili, D.G. Fatouros, Recent advances in pharmaceutical dosage forms and devices using additive manufacturing technologies, Drug Discov Today, 24 (2019) 636-643.

[27] M.A. Alhnan, T.C. Okwuosa, M. Sadia, K.W. Wan, W. Ahmed, B. Arafat, Emergence of 3D Printed Dosage Forms: Opportunities and Challenges, Pharm Res, 33 (2016) 1817-1832.

[28] Y. Zheng, F. Deng, B. Wang, Y. Wu, Q. Luo, X. Zuo, X. Liu, L. Cao, M. Li, H. Lu, S. Cheng, X. Li, Melt Extrusion Deposition (MEDTM) 3D Printing Technology- A Paradigm Shift in Design and Development of Modified Release Drug Products, International Journal of Pharmaceutics, (2021) 120639.

[29] A. Melocchi, M. Uboldi, M. Cerea, A. Foppoli, A. Maroni, S. Moutaharrik, L. Palugan, L. Zema, A. Gazzaniga, A Graphical Review on the Escalation of Fused Deposition Modeling (FDM) 3D Printing in the Pharmaceutical Field, Journal of Pharmaceutical Sciences, 109 (2020) 2943-2957.

[30] A. Awad, F. Fina, A. Goyanes, S. Gaisford, A.W. Basit, 3D printing: Principles and pharmaceutical applications of selective laser sintering, Int J Pharm, 586 (2020) 119594.

[31] X. Xu, A. Awad, P. Robles-Martinez, S. Gaisford, A. Goyanes, A.W. Basit, Vat photopolymerization 3D printing for advanced drug delivery and medical device applications, J Control Release, (2020).

[32] A. Awad, A. Yao, S.J. Trenfield, A. Goyanes, S. Gaisford, A.W. Basit, 3D printed tablets (Printlets) with braille and moon patterns for visually impaired patients, Pharmaceutics, 12 (2020).

[33] P. Robles-Martinez, X. Xu, S.J. Trenfield, A. Awad, A. Goyanes, R. Telford, A.W. Basit, S. Gaisford, 3D printing of a multi-layered polypill containing six drugs using a novel stereolithographic method, Pharmaceutics, 11 (2019).

[34] J.J. Ong, A. Awad, A. Martorana, S. Gaisford, E. Stoyanov, A.W. Basit, A. Goyanes, 3D printed opioid medicines with alcohol-resistant and abuse-deterrent properties, Int J Pharm, 579 (2020) 119169.

[35] M. Vivero-Lopez, X. Xu, A. Muras, A. Otero, A. Concheiro, S. Gaisford, A.W. Basit, C. Alvarez-Lorenzo, A. Goyanes, Anti-biofilm multi drug-loaded 3D printed hearing aids, Materials Science and Engineering C, 119 (2021).

[36] M. Falahati, P. Ahmadvand, S. Safaee, Y.-C. Chang, Z. Lyu, R. Chen, L. Li, Y. Lin, Smart polymers and nanocomposites for 3D and 4D printing, Materials Today, (2020).

[37] R. Govender, S. Abrahmsén-Alami, A. Larsson, S. Folestad, Therapy for the individual: Towards patient integration into the manufacturing and provision of pharmaceuticals, European Journal of Pharmaceutics and Biopharmaceutics, 149 (2020) 58-76.

[38] A. Goyanes, C.M. Madla, A. Umerji, G. Duran Piñeiro, J.M. Giraldez Montero, M.J. Lamas Diaz, M. Gonzalez Barcia, F. Taherali, P. Sánchez-Pintos, M.L. Couce, S. Gaisford, A.W. Basit, Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: First single-centre, prospective, crossover study in patients, International Journal of Pharmaceutics, 567 (2019).

[39] A. Zemmar, A.M. Lozano, B.J. Nelson, The rise of robots in surgical environments during COVID-19, Nature Machine Intelligence, 2 (2020) 566-572.

[40] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, The Lancet, 395 (2020) 507-513.

[41] J. Lee, H. Davari, J. Singh, V. Pandhare, Industrial Artificial Intelligence for industry 4.0-based manufacturing systems, Manufacturing Letters, 18 (2018) 20-23.

[42] J. Qin, Y. Liu, R. Grosvenor, Multi-source data analytics for AM energy consumption prediction, Advanced Engineering Informatics, 38 (2018) 840-850.

[43] L. Kong, X. Peng, Y. Chen, P. Wang, M. Xu, Multi-sensor measurement and data fusion technology for manufacturing process monitoring: a literature review, International Journal of Extreme Manufacturing, 2 (2020) 022001.

[44] A. Awad, S.J. Trenfield, S. Gaisford, A.W. Basit, 3D printed medicines: A new branch of digital healthcare, Int J Pharm, 548 (2018) 586-596.

[45] A. Goyanes, A.B. Buanz, G.B. Hatton, S. Gaisford, A.W. Basit, 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets, Eur J Pharm Biopharm, 89 (2015) 157-162.

[46] J. Skowyra, K. Pietrzak, M.A. Alhnan, Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing, Eur J Pharm Sci, 68 (2015) 11-17.

[47] A. Goyanes, F. Fina, A. Martorana, D. Sedough, S. Gaisford, A.W. Basit, Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing, Int J Pharm, 527 (2017) 21-30.

[48] A. Maroni, A. Melocchi, F. Parietti, A. Foppoli, L. Zema, A. Gazzaniga, 3D printed multi-compartment capsular devices for two-pulse oral drug delivery, J Control Release, 268 (2017) 10-18.

[49] J.A. Weisman, J.C. Nicholson, K. Tappa, U. Jammalamadaka, C.G. Wilson, D.K. Mills, Antibiotic and chemotherapeutic enhanced three-dimensional printer filaments and constructs for biomedical applications, Int J Nanomedicine, 10 (2015) 357-370.

[50] A. Goyanes, U. Det-Amornrat, J. Wang, A.W. Basit, S. Gaisford, 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems, J Control Release, 234 (2016) 41-48.

[51] W. Jamroz, M. Kurek, E. Lyszczarz, J. Szafraniec, J. Knapik-Kowalczuk, K. Syrek, M. Paluch, R. Jachowicz, 3D printed orodispersible films with Aripiprazole, Int J Pharm, 533 (2017) 413-420.

[52] G.K. Eleftheriadis, C. Ritzoulis, N. Bouropoulos, D. Tzetzis, D.A. Andreadis, J. Boetker, J. Rantanen, D.G. Fatouros, Unidirectional drug release from 3D printed mucoadhesive buccal films using FDM technology: In vitro and ex vivo evaluation, European Journal of Pharmaceutics and Biopharmaceutics, 144 (2019) 180-192.

[53] K. Liang, S. Carmone, D. Brambilla, J.-C. Leroux, 3D printing of a wearable personalized oral delivery device: A first-in-human study, Science Advances, 4 (2018) eaat2544.

[54] M.A. Luzuriaga, D.R. Berry, J.C. Reagan, R.A. Smaldone, J.J. Gassensmith, Biodegradable 3D printed polymer microneedles for transdermal drug delivery, Lab Chip, 18 (2018) 1223-1230.

[55] J. Fu, X. Yu, Y. Jin, 3D printing of vaginal rings with personalized shapes for controlled release of progesterone, Int J Pharm, 539 (2018) 75-82.

[56] H. Chim, D.W. Hutmacher, A.M. Chou, A.L. Oliveira, R.L. Reis, T.C. Lim, J.T. Schantz, A comparative analysis of scaffold material modifications for load-bearing applications in bone tissue engineering, Int J Oral Maxillofac Surg, 35 (2006) 928-934.

[57] S.A. Stewart, J. Dominguez-Robles, V.J. McIlorum, E. Mancuso, D.A. Lamprou, R.F. Donnelly, E. Larraneta, Development of a Biodegradable Subcutaneous Implant for Prolonged Drug Delivery Using 3D Printing, Pharmaceutics, 12 (2020).

[58] N. Genina, J. Hollander, H. Jukarainen, E. Makila, J. Salonen, N. Sandler, Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices, Eur J Pharm Sci, 90 (2016) 53-63.

[59] J. Zhang, X. Feng, H. Patil, R.V. Tiwari, M.A. Repka, Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets, Int J Pharm, 519 (2017) 186-197.

[60] M. Alhijjaj, J. Nasereddin, P. Belton, S. Qi, Impact of Processing Parameters on the Quality of Pharmaceutical Solid Dosage Forms Produced by Fused Deposition Modeling (FDM), Pharmaceutics, 11 (2019).

[61] Y.J.N. Tan, W.P. Yong, H.R. Low, J.S. Kochhar, J. Khanolkar, T.S.E. Lim, Y. Sun, J.Z.E. Wong, S. Soh, Customizable drug tablets with constant release profiles via 3D printing technology, International Journal of Pharmaceutics, 598 (2021) 120370.

[62] M. Sadia, B. Arafat, W. Ahmed, R.T. Forbes, M.A. Alhnan, Channelled tablets: An innovative approach to accelerating drug release from 3D printed tablets, J Control Release, 269 (2018) 355-363.

[63] N. Genina, J.P. Boetker, S. Colombo, N. Harmankaya, J. Rantanen, A. Bohr, Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: From drug product design to in vivo testing, J Control Release, 268 (2017) 40-48.

[64] A. Goyanes, P. Robles Martinez, A. Buanz, A.W. Basit, S. Gaisford, Effect of geometry on drug release from 3D printed tablets, International Journal of Pharmaceutics, 494 (2015) 657-663.

[65] B.C. Pereira, A. Isreb, M. Isreb, R.T. Forbes, E.F. Oga, M.A. Alhnan, Additive Manufacturing of a Point-of-Care "Polypill:" Fabrication of Concept Capsules of Complex Geometry with Bespoke Release against Cardiovascular Disease, Adv Healthc Mater, (2020) e2000236.

[66] A. Goyanes, J. Wang, A. Buanz, R. Martínez-Pacheco, R. Telford, S. Gaisford, A.W. Basit, 3D Printing of Medicines: Engineering Novel Oral Devices with Unique Design and Drug Release Characteristics, Molecular Pharmaceutics, 12 (2015) 4077-4084.

[67] C.P.P. Pere, S.N. Economidou, G. Lall, C. Ziraud, J.S. Boateng, B.D. Alexander, D.A. Lamprou, D. Douroumis, 3D printed microneedles for insulin skin delivery, International Journal of Pharmaceutics, 544 (2018) 425-432.

[68] N. Yang, H. Chen, H. Han, Y. Shen, S. Gu, Y. He, S. Guo, 3D printing and coating to fabricate a hollow bullet-shaped implant with porous surface for controlled cytoxan release, International Journal of Pharmaceutics, 552 (2018) 91-98.

[69] A. Melocchi, N. Inverardi, M. Uboldi, F. Baldi, A. Maroni, S. Pandini, F. Briatico-Vangosa, L. Zema, A. Gazzaniga, Retentive device for intravesical drug delivery based on water-induced shape memory response of poly(vinyl alcohol): design concept and 4D printing feasibility, International Journal of Pharmaceutics, 559 (2019) 299-311.

[70] G. Kollamaram, D.M. Croker, G.M. Walker, A. Goyanes, A.W. Basit, S. Gaisford, Low temperature fused deposition modeling (FDM) 3D printing of thermolabile drugs, International Journal of Pharmaceutics, 545 (2018) 144-152.

[71] I.J. Solomon, P. Sevvel, J. Gunasekaran, A review on the various processing parameters in FDM, Materials Today: Proceedings, 37 (2021) 509-514.

[72] A. Goyanes, N. Allahham, S.J. Trenfield, E. Stoyanov, S. Gaisford, A.W. Basit, Direct powder extrusion 3D printing: Fabrication of drug products using a novel single-step process, International Journal of Pharmaceutics, 567 (2019) 118471.

[73] M. Fanous, S. Gold, S. Muller, S. Hirsch, J. Ogorka, G. Imanidis, Simplification of fused deposition modeling 3D-printing paradigm: Feasibility of 1-step direct powder printing for immediate release dosage form production, International Journal of Pharmaceutics, 578 (2020) 119124.

[74] R. Thakkar, R. Thakkar, A. Pillai, E.A. Ashour, M.A. Repka, Systematic screening of pharmaceutical polymers for hot melt extrusion processing: a comprehensive review, International Journal of Pharmaceutics, 576 (2020) 118989.

[75] D.K. Tan, M. Maniruzzaman, A. Nokhodchi, Advanced pharmaceutical applications of hot-melt extrusion coupled with fused deposition modelling (FDM) 3D printing for personalised drug delivery, Pharmaceutics, 10 (2018) 203.

[76] I. Seoane-Viaño, P. Januskaite, C. Alvarez-Lorenzo, A.W. Basit, A. Goyanes, Semi-solid extrusion 3D printing in drug delivery and biomedicine: Personalised solutions for healthcare challenges, Journal of Controlled Release, 332 (2021) 367-389.

[77] K. Vithani, A. Goyanes, V. Jannin, A.W. Basit, S. Gaisford, B.J. Boyd, An Overview of 3D Printing Technologies for Soft Materials and Potential Opportunities for Lipid-based Drug Delivery Systems, Pharmaceutical Research, 36 (2018) 4.

[78] I. Seoane-Viaño, N. Gómez-Lado, H. Lázare-Iglesias, X. García-Otero, J.R. Antúnez-López, Á. Ruibal, J.J. Varela-Correa, P. Aguiar, A.W. Basit, F.J. Otero-Espinar, M. González-Barcia, A. Goyanes, A. Luzardo-Álvarez, A. Fernández-Ferreiro, 3D Printed Tacrolimus Rectal Formulations Ameliorate Colitis in an Experimental Animal Model of Inflammatory Bowel Disease, Biomedicines, 8 (2020) 563.

[79] I. Seoane-Viaño, J.J. Ong, A. Luzardo-Álvarez, M. González-Barcia, A.W. Basit, F.J. Otero-Espinar, A. Goyanes, 3D printed tacrolimus suppositories for the treatment of ulcerative colitis, Asian Journal of Pharmaceutical Sciences, (2020).

[80] P. Januskaite, X. Xu, S.R. Ranmal, S. Gaisford, A.W. Basit, C. Tuleu, A. Goyanes, I Spy with My Little Eye: A Paediatric Visual Preferences Survey of 3D Printed Tablets, Pharmaceutics, 12 (2020) 1100.

[81] J. Conceição, X. Farto-Vaamonde, A. Goyanes, O. Adeoye, A. Concheiro, H. Cabral-Marques, J.M. Sousa Lobo, C. Alvarez-Lorenzo, Hydroxypropyl-β-cyclodextrin-based fast dissolving carbamazepine printlets prepared by semisolid extrusion 3D printing, Carbohydrate Polymers, 221 (2019) 55-62.

[82] A. Liaskoni, R.D. Wildman, C.J. Roberts, 3D printed polymeric drug-eluting implants, International Journal of Pharmaceutics, 597 (2021) 120330.

[83] M. Elbadawi, D. Nikjoo, T. Gustafsson, S. Gaisford, A.W. Basit, Pressure-assisted microsyringe 3D printing of oral films based on pullulan and hydroxypropyl methylcellulose, International Journal of Pharmaceutics, 595 (2021) 120197.

[84] G. Chen, Y. Xu, P. Chi Lip Kwok, L. Kang, Pharmaceutical Applications of 3D Printing, Additive Manufacturing, 34 (2020) 101209.

[85] O. Diegel, A. Nordin, D. Motte, A Practical Guide to Design for Additive Manufacturing, Springer, Singapore, 2020.

[86] P. Robles Martinez, A.W. Basit, S. Gaisford, The history, developments and opportunities of stereolithography, AAPS Advances in the Pharmaceutical Sciences Series, 2018, pp. 55-79.

[87] J. Stampfl, S. Baudis, C. Heller, R. Liska, A. Neumeister, R. Kling, A. Ostendorf, M. Spitzbart, Photopolymers with tunable mechanical properties processed by laser-based high-resolution stereolithography, Journal of Micromechanics and Microengineering, 18 (2008) 125014.

[88] X. Xu, P. Robles-Martinez, C.M. Madla, F. Joubert, A. Goyanes, A.W. Basit, S. Gaisford, Stereolithography (SLA) 3D printing of an antihypertensive polyprintlet: Case study of an unexpected photopolymer-drug reaction, Additive Manufacturing, 33 (2020).

[89] P.R. Martinez, A. Goyanes, A.W. Basit, S. Gaisford, Fabrication of drug-loaded hydrogels with stereolithographic 3D printing, International Journal of Pharmaceutics, 532 (2017) 313-317.

[90] J. Wang, A. Goyanes, S. Gaisford, A.W. Basit, Stereolithographic (SLA) 3D printing of oral modified-release dosage forms, International Journal of Pharmaceutics, 503 (2016) 207-212.

[91] H. Kadry, S. Wadnap, C. Xu, F. Ahsan, Digital light processing (DLP)3D-printing technology and photoreactive polymers in fabrication of modified-release tablets, European Journal of Pharmaceutical Sciences, 135 (2019) 60-67.

[92] M. Krkobabić, D. Medarević, S. Cvijić, B. Grujić, S. Ibrić, Hydrophilic excipients in digital light processing (DLP) printing of sustained release tablets: Impact on internal structure and drug dissolution rate, International Journal of Pharmaceutics, 572 (2019).

[93] Z. Li, C. Wang, W. Qiu, R. Liu, Antimicrobial Thiol–ene–acrylate Photosensitive Resins for DLP 3D Printing, Photochemistry and Photobiology, 95 (2019) 1219-1229.

[94] C.J. Bloomquist, M.B. Mecham, M.D. Paradzinsky, R. Janusziewicz, S.B. Warner, J.C. Luft, S.J. Mecham, A.Z. Wang, J.M. DeSimone, Controlling release from 3D printed medical devices using CLIP and drug-loaded liquid resins, Journal of Controlled Release, 278 (2018) 9-23.

[95] C.L. Caudill, J.L. Perry, S. Tian, J.C. Luft, J.M. DeSimone, Spatially controlled coating of continuous liquid Interface production microneedles for transdermal protein delivery, Journal of Controlled Release, 284 (2018) 122-132.

[96] P.J. Bartolo, Stereolithography Materials, Processes and Applications, Springer2011.

[97] S.E. Evans, T. Harrington, M.C. Rodriguez Rivero, E. Rognin, T. Tuladhar, R. Daly, 2D and 3D inkjet printing of biopharmaceuticals – A review of trends and future perspectives in research and manufacturing, International Journal of Pharmaceutics, 599 (2021) 120443.

[98] H.K. Cader, G.A. Rance, M.R. Alexander, A.D. Gonçalves, C.J. Roberts, C.J. Tuck, R.D. Wildman, Water-based 3D inkjet printing of an oral pharmaceutical dosage form, International Journal of Pharmaceutics, 564 (2019) 359-368.

[99] M. Edinger, D. Bar-Shalom, N. Sandler, J. Rantanen, N. Genina, QR encoded smart oral dosage forms by inkjet printing, International Journal of Pharmaceutics, 536 (2018) 138-145.

[100] S.J. Trenfield, H. Xian Tan, A. Awad, A. Buanz, S. Gaisford, A.W. Basit, A. Goyanes, Track-and-trace: Novel anti-counterfeit measures for 3D printed personalized drug products using smart material inks, International Journal of Pharmaceutics, 567 (2019) 118443.

[101] W. World Health Organization, Substandard and falsified medical products, 2018.

[102] E.A. Clark, M.R. Alexander, D.J. Irvine, C.J. Roberts, M.J. Wallace, S. Sharpe, J. Yoo, R.J.M. Hague, C.J. Tuck, R.D. Wildman, 3D printing of tablets using inkjet with UV photoinitiation, International Journal of Pharmaceutics, 529 (2017) 523-530.

[103] E.A. Clark, M.R. Alexander, D.J. Irvine, C.J. Roberts, M.J. Wallace, J. Yoo, R.D. Wildman, Making tablets for delivery of poorly soluble drugs using photoinitiated 3D inkjet printing, International Journal of Pharmaceutics, 578 (2020) 118805.

[104] G.F. Acosta-Vélez, T.Z. Zhu, C.S. Linsley, B.M. Wu, Photocurable poly(ethylene glycol) as a bioink for the inkjet 3D pharming of hydrophobic drugs, International Journal of Pharmaceutics, 546 (2018) 145-153.

[105] R. Daly, T.S. Harrington, G.D. Martin, I.M. Hutchings, Inkjet printing for pharmaceutics – A review of research and manufacturing, International Journal of Pharmaceutics, 494 (2015) 554-567.

[106] A. Awad, A. Goyanes, S. Gaisford, A.W. Basit, Advances in powder bed fusion 3D printing in drug delivery and healthcare, Advanced Drug Delivery Reviews, in press (2021).

[107] F. Fina, A. Goyanes, C.M. Madla, A. Awad, S.J. Trenfield, J.M. Kuek, P. Patel, S. Gaisford, A.W. Basit, 3D printing of drug-loaded gyroid lattices using selective laser sintering, International Journal of Pharmaceutics, 547 (2018) 44-52.

[108] F. Fina, C.M. Madla, A. Goyanes, J. Zhang, S. Gaisford, A.W. Basit, Fabricating 3D printed orally disintegrating printlets using selective laser sintering, International Journal of Pharmaceutics, 541 (2018) 101-107.

[109] N. Allahham, F. Fina, C. Marcuta, L. Kraschew, W. Mohr, S. Gaisford, A.W. Basit, A. Goyanes, Selective Laser Sintering 3D Printing of Orally Disintegrating Printlets Containing Ondansetron, Pharmaceutics, 12 (2020) 110.

[110] A. Awad, F. Fina, A. Goyanes, S. Gaisford, A.W. Basit, 3D printing: Principles and pharmaceutical applications of selective laser sintering, International Journal of Pharmaceutics, 586 (2020) 119594.

[111] S.J. Trenfield, C.M. Madla, A.W. Basit, S. Gaisford, Binder Jet Printing in Pharmaceutical Manufacturing, 3D Printing of Pharmaceuticals, Springer, Cham2018, pp. 41-54.

[112] X. Wang, L. Xu, G. Zheng, J. Jiang, D. Sun, W. Li, Formation of suspending beads-on-a-string structure in electrohydrodynamic printing process, Materials & Design, 204 (2021) 109692.

[113] J. Plog, Y. Jiang, Y. Pan, A.L. Yarin, Electrostatically-assisted direct ink writing for additive manufacturing, Additive Manufacturing, 39 (2021) 101644.

[114] I. Liashenko, J. Rosell-Llompart, A. Cabot, Ultrafast 3D printing with submicrometer features using electrostatic jet deflection, Nature Communications, 11 (2020) 753.

[115] C. Wei, J. Dong, Direct fabrication of high-resolution three-dimensional polymeric scaffolds using electrohydrodynamic hot jet plotting, Journal of Micromechanics and Microengineering, 23 (2013) 025017.

[116] S. Wu, Z. Ahmad, J.-S. Li, M.-W. Chang, Fabrication of flexible composite drug films via foldable linkages using electrohydrodynamic printing, Materials Science and Engineering: C, 108 (2020) 110393.

[117] J.-C. Wang, H. Zheng, M.-W. Chang, Z. Ahmad, J.-S. Li, Preparation of active 3D film patches via aligned fiber electrohydrodynamic (EHD) printing, Scientific Reports, 7 (2017) 43924.

[118] S. Wu, J.-S. Li, J. Mai, M.-W. Chang, Three-Dimensional Electrohydrodynamic Printing and Spinning of Flexible Composite Structures for Oral Multidrug Forms, ACS Applied Materials & Interfaces, 10 (2018) 24876-24885.

[119] B. Wang, X. Chen, Z. Ahmad, J. Huang, M.-W. Chang, 3D electrohydrodynamic printing of highly aligned dual-core graphene composite matrices, Carbon, 153 (2019) 285-297.

[120] B. Wang, S. Wu, Z. Ahmad, J.-s. Li, M.-W. Chang, Co-printing of vertical axis aligned micron-scaled filaments via simultaneous dual needle electrohydrodynamic printing, European Polymer Journal, 104 (2018) 81-89.

[121] D. Gao, J.G. Zhou, Designs and applications of electrohydrodynamic 3D printing, Int J Bioprint, 5 (2018) 172-172.

[122] M. Mao, J. He, X. Li, B. Zhang, Q. Lei, Y. Liu, D. Li, The emerging frontiers and applications of high-resolution 3D printing, Micromachines, 8 (2017) 113.

[123] J.R. Wagner, E.M. Mount, H.F. Giles, 25 - Design of Experiments, in: J.R. Wagner, E.M. Mount, H.F. Giles (Eds.) Extrusion (Second Edition), William Andrew Publishing, Oxford, 2014, pp. 291-308.

[124] M. Wikberg, G. Alderborn, Compression characteristics of granulated materials II. Evaluation of granule fragmentation during compression by tablet permeability and porosity measurements, International Journal of Pharmaceutics, 62 (1990) 229-241.

[125] D. Moldenhauer, D.C.Y. Nguyen, L. Jescheck, F. Hack, D. Fischer, A. Schneeberger, 3D screen printing – An innovative technology for large-scale manufacturing of pharmaceutical dosage forms, International Journal of Pharmaceutics, 592 (2021).

[126] P. Goos, B. Jones, Optimal Design of Experiments, 1 ed., John Wiley & Sons, Ltd., West Sussex, United Kingdom, 2011.

[127] J. Zhang, R. Thakkar, Y. Zhang, M. Maniruzzaman, Structure-function correlation and personalized 3D printed tablets using a quality by design (QbD) approach, International Journal of Pharmaceutics, 590 (2020) 119945.

[128] E. Carlier, S. Marquette, C. Peerboom, L. Denis, S. Benali, J.M. Raquez, K. Amighi, J. Goole, Investigation of the parameters used in fused deposition modeling of poly(lactic acid) to optimize 3D printing sessions, International Journal of Pharmaceutics, 565 (2019) 367-377.

[129] A.Q. Vo, J. Zhang, D. Nyavanandi, S. Bandari, M.A. Repka, Hot melt extrusion paired fused deposition modeling 3D printing to develop hydroxypropyl cellulose based floating tablets of cinnarizine, Carbohydrate Polymers, 246 (2020) 116519.

[130] E. Tsintavi, D.M. Rekkas, R. Bettini, Partial tablet coating by 3D printing, International Journal of Pharmaceutics, 581 (2020) 119298.

[131] S.F. Barakh Ali, E.M. Mohamed, T. Ozkan, M.A. Kuttolamadom, M.A. Khan, A. Asadi, Z. Rahman, Understanding the effects of formulation and process variables on the printlets quality manufactured by selective laser sintering 3D printing, International Journal of Pharmaceutics, 570 (2019) 118651.

[132] D. Roush, D. Asthagiri, D.K. Babi, S. Benner, C. Bilodeau, G. Carta, P. Ernst, M. Fedesco, S. Fitzgibbon, M. Flamm, J. Griesbach, T. Grosskopf, E.B. Hansen, T. Hahn, S. Hunt, F. Insaidoo, A. Lenhoff, J. Lin, H. Marke, B. Marques, E. Papadakis, F. Schlegel, A. Staby, M. Stenvang, L. Sun, P.M. Tessier, R. Todd, E. von Lieres, J. Welsh, R. Willson, G. Wang, T. Wucherpfennig, O. Zavalov, Toward in silico CMC: An industrial collaborative approach to model-based process development, Biotechnology and Bioengineering, 117 (2020) 3986-4000.

[133] M.J. Jafari, M. Pouyakian, A. khanteymoori, S.M. Hanifi, Development of a framework for dynamic risk assessment of environmental impacts in chemicals warehouse using CFD-BN, International Journal of Environmental Science and Technology, (2021).

[134] M. Nurhaniza, M.K.A. Ariffin, A. Ali, F. Mustapha, A.W. Noraini, Finite element analysis of composites materials for aerospace applications, IOP Conference Series: Materials Science and Engineering, 11 (2010) 012010.

[135] M. Aghaamoo, Z. Zhang, X. Chen, J. Xu, Deformability-based circulating tumor cell separation with conical-shaped microfilters: Concept, optimization, and design criteria, Biomicrofluidics, 9 (2015) 034106.

[136] I. Xenikakis, M. Tzimtzimis, K. Tsongas, D. Andreadis, E. Demiri, D. Tzetzis, D.G. Fatouros, Fabrication and finite element analysis of stereolithographic 3D printed microneedles for transdermal delivery of model dyes across human skin in vitro, European Journal of Pharmaceutical Sciences, 137 (2019) 104976.

[137] H.S. Ramanath, C.K. Chua, K.F. Leong, K.D. Shah, Melt flow behaviour of poly-ε-caprolactone in fused deposition modelling, Journal of Materials Science: Materials in Medicine, 19 (2008) 2541-2550.

[138] Y. Yang, J. Fang, L. Shen, W. Shan, Simulation and evaluation of rupturable coated capsules by finite element method, International Journal of Pharmaceutics, 519 (2017) 220-229.

[139] H.-J. Lee, I.-H. Kwon, H.-G. Lee, Y.-B. Kwon, H.-M. Woo, S.-M. Cho, Y.-W. Choi, J. Chon, K. Kim, D.-W. Kim, C.-W. Park, Spiral mouthpiece design in a dry powder inhaler to improve aerosolization, International Journal of Pharmaceutics, 553 (2018) 149-156.

[140] H.L. Wei, T. Mukherjee, W. Zhang, J.S. Zuback, G.L. Knapp, A. De, T. DebRoy, Mechanistic models for additive manufacturing of metallic components, Progress in Materials Science, 116 (2021) 100703.

[141] T. DebRoy, T. Mukherjee, H.L. Wei, J.W. Elmer, J.O. Milewski, Metallurgy, mechanistic models and machine learning in metal printing, Nature Reviews Materials, (2020).

[142] S. Eyerman, K. Hoste, L. Eeckhout, Mechanistic-empirical processor performance modeling for constructing CPI stacks on real hardware, (IEEE ISPASS) IEEE International Symposium on Performance Analysis of Systems and Software, 2011, pp. 216-226.

[143] F. Wang, G. Wang, F. Ning, Z. Zhang, Fiber–matrix impregnation behavior during additive manufacturing of continuous carbon fiber reinforced polylactic acid composites, Additive Manufacturing, (2020) 101661.

[144] F. Wang, Z. Zhang, F. Ning, G. Wang, C. Dong, A mechanistic model for tensile property of continuous carbon fiber reinforced plastic composites built by fused filament fabrication, Additive Manufacturing, 32 (2020) 101102.

[145] T. Hafkamp, G. van Baars, B. de Jager, P. Etman, Real-time feedback controlled conversion in vat photopolymerization of ceramics: A proof of principle, Additive Manufacturing, 30 (2019) 100775.

[146] A.S.J. Suiker, Mechanical performance of wall structures in 3D printing processes: Theory, design tools and experiments, International Journal of Mechanical Sciences, 137 (2018) 145-170.

[147] M. Elbadawi, J. Rivera-Armenta, B. Cruz, Polymeric Additive Manufacturing: The Necessity and Utility of Rheology, Polymer Rheology, 10 (2018).

[148] A. Zidan, A. Alayoubi, S. Asfari, J. Coburn, B. Ghammraoui, S. Aqueel, C.N. Cruz, M. Ashraf, Development of mechanistic models to identify critical formulation and process variables of pastes for 3D printing of modified release tablets, Int J Pharm, 555 (2019) 109-123.

[149] A. Zidan, A. Alayoubi, J. Coburn, S. Asfari, B. Ghammraoui, C.N. Cruz, M. Ashraf, Extrudability analysis of drug loaded pastes for 3D printing of modified release tablets, Int J Pharm, 554 (2019) 292-301.

[150] T. Davenport, R. Kalakota, The potential for artificial intelligence in healthcare, Future Healthc J, 6 (2019) 94-98.

[151] R. Mazumder, T. Hastie, R. Tibshirani, Spectral regularization algorithms for learning large incomplete matrices, Journal of Machine Learning Research, 11 (2010) 2287-2322.

[152] J.B. Heaton, N.G. Polson, J.H. Witte, Deep learning for finance: deep portfolios, Applied Stochastic Models in Business and Industry, 33 (2017) 3-12.

[153] E.J. Topol, High-performance medicine: the convergence of human and artificial intelligence, Nat Med, 25 (2019) 44-56.

[154] L.E. McCoubrey, M. Elbadawi, M. Orlu, S. Gaisford, A.W. Basit, Harnessing machine learning for development of microbiome therapeutics, Gut Microbes, 13 (2021) 1-20.

[155] T. Economist, Not So Big, The Economist, 435 (2020) S5-S6.

[156] M. Elbadawi, B. Muniz Castro, F.K.H. Gavins, J.J. Ong, S. Gaisford, G. Perez, A.W. Basit, P. Cabalar, A. Goyanes, M3DISEEN: A novel machine learning approach for predicting the 3D printability of medicines, Int J Pharm, 590 (2020) 119837.

[157] À. Bravo, J. Piñero, N. Queralt-Rosinach, M. Rautschka, L.I. Furlong, Extraction of relations between genes and diseases from text and large-scale data analysis: implications for translational research, BMC Bioinformatics, 16 (2015) 55.

[158] L. Sun, C. Hsiung, C.G. Pederson, P. Zou, V. Smith, M. von Gunten, N.A. O'Brien, Pharmaceutical Raw Material Identification Using Miniature Near-Infrared (MicroNIR) Spectroscopy and Supervised Pattern Recognition Using Support Vector Machine, Applied Spectroscopy, 70 (2016) 816-825.

[159] G. James, D. Witten, T. Hastie, R. Tibshirani, Linear Regression, An Introduction to Statistical Learning: with Applications in R, Springer New York, New York, NY, 2013, pp. 59-126.

[160] G. James, D. Witten, T. Hastie, R. Tibshirani, Tree-Based Methods, An Introduction to Statistical Learning: with Applications in R, Springer New York, New York, NY, 2013, pp. 303-335.

[161] R. Rodríguez-Pérez, M. Vogt, J. Bajorath, Support Vector Machine Classification and Regression Prioritize Different Structural Features for Binary Compound Activity and Potency Value Prediction, ACS Omega, 2 (2017) 6371-6379.

[162] J. Zou, Y. Han, S.-S. So, Overview of Artificial Neural Networks, in: D.J. Livingstone (Ed.) Artificial Neural Networks: Methods and Applications, Humana Press, Totowa, NJ, 2009, pp. 14-22.

[163] Y.h. Taguchi, Identification of candidate drugs using tensor-decomposition-based unsupervised feature extraction in integrated analysis of gene expression between diseases and DrugMatrix datasets, Scientific Reports, 7 (2017) 13733.

[164] H. Bisgin, Z. Liu, H. Fang, X. Xu, W. Tong, Mining FDA drug labels using an unsupervised learning technique - topic modeling, BMC Bioinformatics, 12 (2011).

[165] D. Wulsin, B. Litt, An unsupervised method for identifying regions that initiate seizures on intracranial EEG, Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS, 2011, pp. 3091-3094.

[166] S. Ko, J. Choi, J. Ahn, GVES: machine learning model for identification of prognostic genes with a small dataset, Sci Rep, 11 (2021) 439.

[167] R. Xu, D. Wunsch Ii, Survey of clustering algorithms, IEEE Transactions on Neural Networks, 16 (2005) 645-678.

[168] Y.-H. Wang, Y. Li, S.-L. Yang, L. Yang, Classification of Substrates and Inhibitors of P-Glycoprotein Using Unsupervised Machine Learning Approach, Journal of Chemical Information and Modeling, 45 (2005) 750-757.

[169] D.M. Camacho, K.M. Collins, R.K. Powers, J.C. Costello, J.J. Collins, Next-Generation Machine Learning for Biological Networks, Cell, 173 (2018) 1581-1592.

[170] M. Chen, S. Mao, Y. Liu, Big Data: A Survey, Mobile Networks and Applications, 19 (2014) 171-209.

[171] Y. Wang, Y. Yang, Y. Liu, A.A. Bharath, A Recursive Ensemble Learning Approach With Noisy Labels or Unlabeled Data, IEEE Access, 7 (2019) 36459-36470.

[172] E.O. Neftci, B.B. Averbeck, Reinforcement learning in artificial and biological systems, Nature Machine Intelligence, 1 (2019) 133-143.

[173] D. Silver, J. Schrittwieser, K. Simonyan, I. Antonoglou, A. Huang, A. Guez, T. Hubert, L. Baker, M. Lai, A. Bolton, Y. Chen, T. Lillicrap, F. Hui, L. Sifre, G. van den Driessche, T. Graepel, D. Hassabis, Mastering the game of Go without human knowledge, Nature, 550 (2017) 354-359.

[174] I.J. Sledge, J.C. Príncipe, Balancing exploration and exploitation in reinforcement learning using a value of information criterion, 2017 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP), 2017, pp. 2816-2820.

[175] M. Abadi, P. Barham, J. Chen, Z. Chen, A. Davis, J. Dean, M. Devin, S. Ghemawat, G. Irving, M. Isard, M. Kudlur, J. Levenberg, R. Monga, S. Moore, D.G. Murray, B. Steiner, P. Tucker, V. Vasudevan, P. Warden, M. Wicke, Y. Yu, X. Zheng, TensorFlow: A system for large-scale machine learning, Proceedings of the 12th USENIX Symposium on Operating Systems Design and Implementation, OSDI 2016, 2016, pp. 265-283.

[176] J. Jiménez-Luna, F. Grisoni, G. Schneider, Drug discovery with explainable artificial intelligence, Nature Machine Intelligence, 2 (2020) 573-584.

[177] W. Nash, T. Drummond, N. Birbilis, A review of deep learning in the study of materials degradation, npj Materials Degradation, 2 (2018) 37.

[178] M. Wainberg, D. Merico, A. Delong, B.J. Frey, Deep learning in biomedicine, Nature Biotechnology, 36 (2018) 829-838.

[179] N. Sarah Arden, A.C. Fisher, K. Tyner, L.X. Yu, S.L. Lee, M. Kopcha, Industry 4.0 for Pharmaceutical Manufacturing: Preparing for the Smart Factories of the Future, International Journal of Pharmaceutics, (2021) 120554.

[180] A.E. Gongora, B. Xu, W. Perry, C. Okoye, P. Riley, K.G. Reyes, E.F. Morgan, K.A. Brown, A Bayesian experimental autonomous researcher for mechanical design, Science Advances, 6 (2020) eaaz1708.

[181] K. Ruberu, M. Senadeera, S. Rana, S. Gupta, J. Chung, Z. Yue, S. Venkatesh, G. Wallace, Coupling machine learning with 3D bioprinting to fast track optimisation of extrusion printing, Applied Materials Today, 22 (2021) 100914.

[182] I. Karakurt, A. Aydoğdu, S. Çıkrıkcı, J. Orozco, L. Lin, Stereolithography (SLA) 3D printing of ascorbic acid loaded hydrogels: A controlled release study, International Journal of Pharmaceutics, 584 (2020).

[183] Y. Mai, D.A.I. Ashiru-Oredope, Z. Yao, L. Dou, C.M. Madla, F. Taherali, S. Murdan, A.W. Basit, Boosting drug bioavailability in men but not women through the action of an excipient, International Journal of Pharmaceutics, 587 (2020) 119678.

[184] C. Stillhart, K. Vucicevic, P. Augustijns, A.W. Basit, H. Batchelor, T.R. Flanagan, I. Gesquiere, R. Greupink, D. Keszthelyi, M. Koskinen, C.M. Madla, C. Matthys, G. Miljus, M.G. Mooij, N. Parrott, A.L. Ungell, S.N. de Wildt, M. Orlu, S. Klein, A. Mullertz, Impact of gastrointestinal physiology on drug absorption in special populations--An UNGAP review, Eur J Pharm Sci, 147 (2020) 105280.

[185] G.B. Hatton, C.M. Madla, S.C. Rabbie, A.W. Basit, All disease begins in the gut: Influence of gastrointestinal disorders and surgery on oral drug performance, Int J Pharm, 548 (2018) 408-422.

[186] G.B. Hatton, C.M. Madla, S.C. Rabbie, A.W. Basit, Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discovery Today, 24 (2019) 417-427.

[187] F.J. Varum, G.B. Hatton, A.W. Basit, Food, physiology and drug delivery, Int J Pharm, 457 (2013) 446-460.

[188] L. Dou, F.K.H. Gavins, Y. Mai, C.M. Madla, F. Taherali, M. Orlu, S. Murdan, A.W. Basit, Effect of food and an animal's sex on p-glycoprotein expression and luminal fluids in the gastrointestinal tract of wistar rats, Pharmaceutics, 12 (2020).

[189] H.A. Merchant, F. Liu, M. Orlu Gul, A.W. Basit, Age-mediated changes in the gastrointestinal tract, International Journal of Pharmaceutics, 512 (2016) 382-395.

[190] T. Vallet, H. Michelon, M. Orlu, Y. Jani, P. Leglise, S. Laribe-Caget, M. Piccoli, A.L. Fur, F. Liu, F. Ruiz, V. Boudy, Acceptability in the older population: The importance of an appropriate tablet size, Pharmaceutics, 12 (2020) 1-11.

[191] Z. Vinarov, B. Abrahamsson, P. Artursson, H. Batchelor, P. Berben, A. Bernkop-Schnürch, J. Butler, J. Ceulemans, N. Davies, D. Dupont, G.E. Flaten, N. Fotaki, B.T. Griffin, V. Jannin, J. Keemink, F. Kesisoglou, M. Koziolek, M. Kuentz, A. Mackie, A.J. Meléndez-Martínez, M. McAllister, A. Müllertz, C.M. O'Driscoll, N. Parrott, J. Paszkowska, P. Pavek, C.J.H. Porter, C. Reppas, C. Stillhart, K. Sugano, E. Toader, K. Valentová, M. Vertzoni, S.N. De Wildt, C.G. Wilson, P. Augustijns, Current challenges and future perspectives in oral absorption research: An opinion of the UNGAP network, Advanced Drug Delivery Reviews, 171 (2021) 289-331.

[192] Y. Mai, L. Dou, Z. Yao, C.M. Madla, F.K.H. Gavins, F. Taherali, H. Yin, M. Orlu, S. Murdan, A.W. Basit, Quantification of P-Glycoprotein in the Gastrointestinal Tract of Humans and Rodents: Methodology, Gut Region, Sex, and Species Matter, Molecular Pharmaceutics, (2021).

[193] T. von Erlach, S. Saxton, Y. Shi, D. Minahan, D. Reker, F. Javid, Y.-A.L. Lee, C. Schoellhammer, T. Esfandiary, C. Cleveland, L. Booth, J. Lin, H. Levy, S. Blackburn, A. Hayward, R. Langer, G. Traverso, Robotically handled whole-tissue culture system for the screening of oral drug formulations, Nature Biomedical Engineering, 4 (2020) 544-559.

[194] Z. Vinarov, M. Abdallah, J.A.G. Agundez, K. Allegaert, A.W. Basit, M. Braeckmans, J. Ceulemans, M. Corsetti, B.T. Griffin, M. Grimm, D. Keszthelyi, M. Koziolek, C.M. Madla, C. Matthys, L.E. McCoubrey, A. Mitra, C. Reppas, J. Stappaerts, N. Steenackers, N.L. Trevaskis, T. Vanuytsel, M. Vertzoni, W. Weitschies, C. Wilson, P. Augustijns, Impact of gastrointestinal tract variability on oral drug absorption and pharmacokinetics: An UNGAP review, European Journal of Pharmaceutical Sciences, 162 (2021) 105812.

[195] G.B. Hatton, V. Yadav, A.W. Basit, H.A. Merchant, Animal Farm: Considerations in Animal Gastrointestinal Physiology and Relevance to Drug Delivery in Humans, Journal of Pharmaceutical Sciences, 104 (2015) 2747-2776.

[196] H.M. Fadda, T. Sousa, A.S. Carlsson, B. Abrahamsson, J.G. Williams, D. Kumar, A.W. Basit, Drug Solubility in Luminal Fluids from Different Regions of the Small and Large Intestine of Humans, Molecular Pharmaceutics, 7 (2010) 1527-1532.

[197] M. Vertzoni, P. Augustijns, M. Grimm, M. Koziolek, G. Lemmens, N. Parrott, C. Pentafragka, C. Reppas, J. Rubbens, J. Van Den Abeele, T. Vanuytsel, W. Weitschies, C.G. Wilson, Impact of regional differences along the gastrointestinal tract of healthy adults on oral drug absorption: An UNGAP review, European Journal of Pharmaceutical Sciences, 134 (2019) 153-175.

[198] M. Koziolek, S. Alcaro, P. Augustijns, A.W. Basit, M. Grimm, B. Hens, C.L. Hoad, P. Jedamzik, C.M. Madla, M. Maliepaard, L. Marciani, A. Maruca, N. Parrott, P. Pávek, C.J.H. Porter, C. Reppas, D. van Riet-Nales, J. Rubbens, M. Statelova, N.L. Trevaskis, K. Valentová, M. Vertzoni, D.V. Čepo, M. Corsetti, The mechanisms of pharmacokinetic food-drug interactions – A perspective from the UNGAP group, European Journal of Pharmaceutical Sciences, 134 (2019) 31-59.

[199] C.M. Christine M. Madla, F.K.H. Gavins, H.A. Merchant, M. Orlu, S. Murdan, A.W. Basit, Let's Talk About Sex: Differences in Drug Therapy in Males and Females, Advanced Drug Delivery Reviews, in press (2021).

[200] B. Bhhatarai, W.P. Walters, C.E.C.A. Hop, G. Lanza, S. Ekins, Opportunities and challenges using artificial intelligence in ADME/Tox, Nature Materials, 18 (2019) 418-422.

[201] S.A. Damiati, Digital Pharmaceutical Sciences, AAPS PharmSciTech, 21 (2020) 206.

[202] K.K. Mak, M.R. Pichika, Artificial intelligence in drug development: present status and future prospects, Drug Discov Today, 24 (2019) 773-780.

[203] R. Han, H. Xiong, Z. Ye, Y. Yang, T. Huang, Q. Jing, J. Lu, H. Pan, F. Ren, D. Ouyang, Predicting physical stability of solid dispersions by machine learning techniques, Journal of Controlled Release, 311-312 (2019) 16-25.

[204] C. Huang, E.A. Clayton, L.V. Matyunina, L.D.E. McDonald, B.B. Benigno, F. Vannberg, J.F. McDonald, Machine learning predicts individual cancer patient responses to therapeutic drugs with high accuracy, Scientific Reports, 8 (2018).

[205] A.C. King, M. Woods, W. Liu, Z. Lu, D. Gill, M.R.H. Krebs, High-throughput measurement, correlation analysis, and machine-learning predictions for pH and thermal stabilities of Pfizer-generated antibodies, Protein Science, 20 (2011) 1546-1557.

[206] Y. Li, M.R. Abbaspour, P.V. Grootendorst, A.M. Rauth, X.Y. Wu, Optimization of controlled release nanoparticle formulation of verapamil hydrochloride using artificial neural networks with genetic algorithm and response surface methodology, European Journal of Pharmaceutics and Biopharmaceutics, 94 (2015) 170-179.

[207] Y. Yang, Z. Ye, Y. Su, Q. Zhao, X. Li, D. Ouyang, Deep learning for in vitro prediction of pharmaceutical formulations, Acta Pharmaceutica Sinica B, 9 (2019) 177-185.

[208] H.M. Zawbaa, J. Szlęk, C. Grosan, R. Jachowicz, A. Mendyk, Computational Intelligence Modeling of the Macromolecules Release from PLGA Microspheres—Focus on Feature Selection, PLoS One, 11 (2016) e0157610.

[209] M. Madzarevic, D. Medarevic, A. Vulovic, T. Sustersic, J. Djuris, N. Filipovic, S. Ibric, Optimization and Prediction of Ibuprofen Release from 3D DLP Printlets Using Artificial Neural Networks, Pharmaceutics, 11 (2019).

[210] M. Elbadawi, T. Gustaffson, S. Gaisford, A.W. Basit, 3D printing tablets: Predicting printability and drug dissolution from rheological data, International Journal of Pharmaceutics, 590 (2020) 119868.

[211] Y. Baranwal, A.D. Román-Ospino, G. Keyvan, J.M. Ha, E.P. Hong, F.J. Muzzio, R. Ramachandran, Prediction of dissolution profiles by non-destructive NIR spectroscopy in bilayer tablets, International Journal of Pharmaceutics, 565 (2019) 419-436.

[212] E. Hernandez, P. Pawar, G. Keyvan, Y. Wang, N. Velez, G. Callegari, A. Cuitino, B. Michniak-Kohn, F.J. Muzzio, R.J. Romañach, Prediction of dissolution profiles by non-destructive near infrared spectroscopy in tablets subjected to different levels of strain, Journal of Pharmaceutical and Biomedical Analysis, 117 (2016) 568-576.

[213] D.L. Galata, A. Farkas, Z. Könyves, L.A. Mészáros, E. Szabó, I. Csontos, A. Pálos, G. Marosi, Z.K. Nagy, B. Nagy, Fast, Spectroscopy-Based Prediction of In Vitro Dissolution Profile of Extended Release Tablets Using Artificial Neural Networks, Pharmaceutics, 11 (2019) 400.

[214] M.P. Freitas, A. Sabadin, L.M. Silva, F.M. Giannotti, D.A. do Couto, E. Tonhi, R.S. Medeiros, G.L. Coco, V.F.T. Russo, J.A. Martins, Prediction of drug dissolution profiles from tablets using NIR diffuse reflectance spectroscopy: A rapid and nondestructive method, Journal of Pharmaceutical and Biomedical Analysis, 39 (2005) 17-21.

[215] Y. Zhao, W. Li, Z. Shi, J.K. Drennen, C.A. Anderson, Prediction of Dissolution Profiles From Process Parameters, Formulation, and Spectroscopic Measurements, Journal of Pharmaceutical Sciences, 108 (2019) 2119-2127.

[216] J. Petrović, S. Ibrić, G. Betz, Z. Đurić, Optimization of matrix tablets controlled drug release using Elman dynamic neural networks and decision trees, International Journal of Pharmaceutics, 428 (2012) 57-67.

[217] A.O. Abioye, A. Kola-Mustapha, G.T. Chi, S. Ilya, Quantification of in situ granulation-induced changes in pre-compression, solubility, dose distribution and intrinsic in vitro release characteristics of ibuprofen–cationic dextran conjugate crystanules, International Journal of Pharmaceutics, 471 (2014) 453-477.

[218] G. Stanojević, D. Medarević, I. Adamov, N. Pešić, J. Kovačević, S. Ibrić, Tailoring Atomoxetine Release Rate from DLP 3D-Printed Tablets Using Artificial Neural Networks: Influence of Tablet Thickness and Drug Loading, Molecules (Basel, Switzerland), 26 (2020).

[219] D. Reker, Y. Shi, A.R. Kirtane, K. Hess, G.J. Zhong, E. Crane, C.-H. Lin, R. Langer, G. Traverso, Machine Learning Uncovers Food- and Excipient-Drug Interactions, Cell Reports, 30 (2020) 3710-3716.e3714.

[220] D. Reker, Y. Rybakova, A.R. Kirtane, R. Cao, J.W. Yang, N. Navamajiti, A. Gardner, R.M. Zhang, T. Esfandiary, J. L'Heureux, T. von Erlach, E.M. Smekalova, D. Leboeuf, K. Hess, A. Lopes, J. Rogner, J. Collins, S.M. Tamang, K. Ishida, P. Chamberlain, D. Yun, A. Lytton-Jean, C.K. Soule, J.H. Cheah, A.M. Hayward, R. Langer, G. Traverso, Computationally guided high-throughput design of self-assembling drug nanoparticles, Nature Nanotechnology, (2021).

[221] P. Costa, J.M. Sousa Lobo, Modeling and comparison of dissolution profiles, European Journal of Pharmaceutical Sciences, 13 (2001) 123-133.

[222] M. Madzarevic, D. Medarevic, A. Vulovic, T. Sustersic, J. Djuris, N. Filipovic, S. Ibric, Optimization and prediction of ibuprofen release from 3D DLP printlets using artificial neural networks, Pharmaceutics, 11 (2019) 544.

[223] P.J. Kondiah, P.P. Kondiah, Y.E. Choonara, T. Marimuthu, V. Pillay, A 3D Bioprinted Pseudo-Bone Drug Delivery Scaffold for Bone Tissue Engineering, Pharmaceutics, 12 (2020) 166.

[224] M. Luo, F. Nie, X. Chang, Y. Yang, A.G. Hauptmann, Q. Zheng, Avoiding Optimal Mean ℓ2,1-Norm Maximization-Based Robust PCA for Reconstruction, Neural Computation, 29 (2017) 1124-1150.

[225] M. Khodayar, O. Kaynak, M.E. Khodayar, Rough Deep Neural Architecture for Short-Term Wind Speed Forecasting, IEEE Transactions on Industrial Informatics, 13 (2017) 2770-2779.

[226] J.M. Nasereddin, N. Wellner, M. Alhijjaj, P. Belton, S. Qi, Development of a Simple Mechanical Screening Method for Predicting the Feedability of a Pharmaceutical FDM 3D Printing Filament, Pharmaceutical Research, 35 (2018) 151.

[227] C. Ding, X. He, K-means clustering via principal component analysis, Proceedings of the twenty-first international conference on Machine learning, Association for Computing Machinery, Banff, Alberta, Canada, 2004, pp. 29.

[228] M. Alhijjaj, J. Nasereddin, P. Belton, S. Qi, Impact of Processing Parameters on the Quality of Pharmaceutical Solid Dosage Forms Produced by Fused Deposition Modeling (FDM), Pharmaceutics, 11 (2019) 633.

[229] Y. Yang, Y. Zhou, X. Lin, Q. Yang, G. Yang, Printability of external and internal structures based on digital light processing 3D printing technique, Pharmaceutics, 12 (2020).

[230] G.P. Andrews, O. Abu-Diak, F. Kusmanto, P. Hornsby, Z. Hui, D.S. Jones, Physicochemical characterization and drug-release properties of celecoxib hot-melt extruded glass solutions, Journal of Pharmacy and Pharmacology, 62 (2010) 1580-1590.

[231] E.R. Davies, Computer vision: principles, algorithms, applications, learning, Academic Press2017.

[232] L. Scime, J. Beuth, Anomaly detection and classification in a laser powder bed additive manufacturing process using a trained computer vision algorithm, Additive Manufacturing, 19 (2018) 114-126.

[233] Z. Jin, Z. Zhang, G.X. Gu, Autonomous in-situ correction of fused deposition modeling printers using computer vision and deep learning, Manufacturing Letters, 22 (2019) 11-15.

[234] Z. Zhu, H.S. Park, M.C. McAlpine, 3D printed deformable sensors, Science Advances, 6 (2020) eaba5575.

[235] Y. Seto, K. Mori, S. Aikou, Robotic surgery for esophageal cancer: Merits and demerits, Annals of Gastroenterological Surgery, 1 (2017) 193-198.

[236] M. Elbadawi, J.J. Ong, T. Pollard, S. Gaisford, A.W. Basit, Additive Manufacturable Materials for Electrochemical Biosensor Electrode, Advanced Functional Materials, (2020).

[237] T.D. Pollard, J.J. Ong, A. Goyanes, M. Orlu, S. Gaisford, M. Elbadawi, A.W. Basit, Electrochemical biosensors: a nexus for precision medicine, Drug Discov Today, (2020).

[238] A. Biancolillo, F. Marini, Chemometric Methods for Spectroscopy-Based Pharmaceutical Analysis, Frontiers in Chemistry, 6 (2018).

[239] A. Melocchi, F. Briatico-Vangosa, M. Uboldi, F. Parietti, M. Turchi, D. von Zeppelin, A. Maroni, L. Zema, A. Gazzaniga, A. Zidan, Quality considerations on the pharmaceutical applications of fused deposition modeling 3D printing, International Journal of Pharmaceutics, 592 (2021) 119901.

[240] C.C. Corredor, D. Bu, G. McGeorge, Chapter 9 - Applications of MVDA and PAT for Drug Product Development and Manufacturing, in: A.P. Ferreira, J.C. Menezes, M. Tobyn (Eds.) Multivariate Analysis in the Pharmaceutical Industry, Academic Press2018, pp. 211-234.

[241] T.F. O'Connor, L.X. Yu, S.L. Lee, Emerging technology: A key enabler for modernizing pharmaceutical manufacturing and advancing product quality, International Journal of Pharmaceutics, 509 (2016) 492-498.

[242] P.S. Sampaio, A. Soares, A. Castanho, A.S. Almeida, J. Oliveira, C. Brites, Optimization of rice amylose determination by NIR-spectroscopy using PLS chemometrics algorithms, Food Chemistry, 242 (2018) 196-204.

[243] G. James, D. Witten, T. Hastie, R. Tibshirani, Linear Model Selection and Regularization, An Introduction to Statistical Learning: with Applications in R, Springer New York, New York, NY, 2013, pp. 203-264.

[244] S.J. Trenfield, H.X. Tan, A. Goyanes, D. Wilsdon, M. Rowland, S. Gaisford, A.W. Basit, Non-destructive dose verification of two drugs within 3D printed polyprintlets, International Journal of Pharmaceutics, 577 (2020) 119066.

[245] S.J. Trenfield, A. Goyanes, R. Telford, D. Wilsdon, M. Rowland, S. Gaisford, A.W. Basit, 3D printed drug products: Non-destructive dose verification using a rapid point-and-shoot approach, International Journal of Pharmaceutics, 549 (2018) 283-292.

[246] R. Hamed, E.M. Mohamed, Z. Rahman, M.A. Khan, 3D-printing of lopinavir printlets by selective laser sintering and quantification of crystalline fraction by XRPD-chemometric models, International Journal of Pharmaceutics, 592 (2021) 120059.

[247] P.Y. Sacré, C. De Bleye, P.F. Chavez, L. Netchacovitch, P. Hubert, E. Ziemons, Data processing of vibrational chemical imaging for pharmaceutical applications, Journal of Pharmaceutical and Biomedical Analysis, 101 (2014) 123-140.

[248] C.L.M. Morais, P.L. Martin-Hirsch, F.L. Martin, A three-dimensional principal component analysis approach for exploratory analysis of hyperspectral data: identification of ovarian cancer samples based on Raman microspectroscopy imaging of blood plasma, Analyst, 144 (2019) 2312-2319.

[249] W. Zhao, S. Du, Spectral–Spatial Feature Extraction for Hyperspectral Image Classification: A Dimension Reduction and Deep Learning Approach, IEEE Transactions on Geoscience and Remote Sensing, 54 (2016) 4544-4554.

[250] K. Golhani, S.K. Balasundram, G. Vadamalai, B. Pradhan, A review of neural networks in plant disease detection using hyperspectral data, Information Processing in Agriculture, 5 (2018) 354-371.

[251] N. Scoutaris, S.A. Ross, D. Douroumis, 3D Printed “Starmix” Drug Loaded Dosage Forms for Paediatric Applications, Pharmaceutical Research, 35 (2018) 34.

[252] M. Akbari Lakeh, A. Tu, D.C. Muddiman, H. Abdollahi, Discriminating normal regions within cancerous hen ovarian tissue using multivariate hyperspectral image analysis, Rapid Communications in Mass Spectrometry, 33 (2019) 381-391.

[253] M. Edinger, D. Bar-Shalom, J. Rantanen, N. Genina, Visualization and Non-Destructive Quantification of Inkjet-Printed Pharmaceuticals on Different Substrates Using Raman Spectroscopy and Raman Chemical Imaging, Pharmaceutical Research, 34 (2017) 1023-1036.

[254] H. Vakili, R. Kolakovic, N. Genina, M. Marmion, H. Salo, P. Ihalainen, J. Peltonen, N. Sandler, Hyperspectral imaging in quality control of inkjet printed personalised dosage forms, International Journal of Pharmaceutics, 483 (2015) 244-249.

[255] E.M. Mohamed, S.F. Barakh Ali, Z. Rahman, S. Dharani, T. Ozkan, M.A. Kuttolamadom, M.A. Khan, Formulation Optimization of Selective Laser Sintering 3D-Printed Tablets of Clindamycin Palmitate Hydrochloride by Response Surface Methodology, AAPS PharmSciTech, 21 (2020) 232.

[256] J. Freiesleben, J. Keim, M. Grutsch, Machine learning and Design of Experiments: Alternative approaches or complementary methodologies for quality improvement?, Quality and Reliability Engineering International, 36 (2020) 1837-1848.

[257] Y. Kosugi, N. Hosea, Prediction of Oral Pharmacokinetics Using a Combination of In Silico Descriptors and In Vitro ADME Properties, Molecular Pharmaceutics, (2021).

[258] B. Cao, L.A. Adutwum, A.O. Oliynyk, E.J. Luber, B.C. Olsen, A. Mar, J.M. Buriak, How To Optimize Materials and Devices via Design of Experiments and Machine Learning: Demonstration Using Organic Photovoltaics, ACS Nano, 12 (2018) 7434-7444.

[259] Y. Wang, J.M. Lamim Ribeiro, P. Tiwary, Machine learning approaches for analyzing and enhancing molecular dynamics simulations, Current Opinion in Structural Biology, 61 (2020) 139-145.

[260] N. Gaw, A. Hawkins-Daarud, L.S. Hu, H. Yoon, L. Wang, Y. Xu, P.R. Jackson, K.W. Singleton, L.C. Baxter, J. Eschbacher, A. Gonzales, A. Nespodzany, K. Smith, P. Nakaji, J.R. Mitchell, T. Wu, K.R. Swanson, J. Li, Integration of machine learning and mechanistic models accurately predicts variation in cell density of glioblastoma using multiparametric MRI, Scientific Reports, 9 (2019) 10063.

[261] I. Baturynska, O. Semeniuta, K. Martinsen, Optimization of Process Parameters for Powder Bed Fusion Additive Manufacturing by Combination of Machine Learning and Finite Element Method: A Conceptual Framework, Procedia CIRP, 67 (2018) 227-232.

[262] G.X. Gu, C.-T. Chen, D.J. Richmond, M.J. Buehler, Bioinspired hierarchical composite design using machine learning: simulation, additive manufacturing, and experiment, Materials Horizons, 5 (2018) 939-945.

[263] R.W. Lewis, D.T. Gethin, X.S. Yang, R.C. Rowe, A combined finite-discrete element method for simulating pharmaceutical powder tableting, International Journal for Numerical Methods in Engineering, 62 (2005) 853-869.

[264] H. Ko, P. Witherell, N.Y. Ndiaye, Y. Lu, Machine Learning based Continuous Knowledge Engineering for Additive Manufacturing, 2019 IEEE 15th International Conference on Automation Science and Engineering (CASE), 2019, pp. 648-654.

[265] A. Gioiello, A. Piccinno, A.M. Lozza, B. Cerra, The Medicinal Chemistry in the Era of Machines and Automation: Recent Advances in Continuous Flow Technology, Journal of Medicinal Chemistry, 63 (2020) 6624-6647.

[266] C.K. Lee, M. Samad, I. Hofer, M. Cannesson, P. Baldi, Development and validation of an interpretable neural network for prediction of postoperative in-hospital mortality, NPJ Digit Med, 4 (2021) 8.

[267] T. Wuest, D. Weimer, C. Irgens, K.-D. Thoben, Machine learning in manufacturing: advantages, challenges, and applications, Production & Manufacturing Research, 4 (2016) 23-45.

[268] C.B. Azodi, J. Tang, S.-H. Shiu, Opening the Black Box: Interpretable Machine Learning for Geneticists, Trends in Genetics, 36 (2020) 442-455.

[269] S. Leavy, Gender bias in artificial intelligence: the need for diversity and gender theory in machine learning, Proceedings of the 1st International Workshop on Gender Equality in Software Engineering, Association for Computing Machinery, Gothenburg, Sweden, 2018, pp. 14–16.

[270] A. Noseworthy Peter, I. Attia Zachi, C. Brewer LaPrincess, N. Hayes Sharonne, X. Yao, S. Kapa, A. Friedman Paul, F. Lopez-Jimenez, Assessing and Mitigating Bias in Medical Artificial Intelligence, Circulation: Arrhythmia and Electrophysiology, 13 (2020) e007988.

[271] M. Moradi, M. Samwald, Post-hoc explanation of black-box classifiers using confident itemsets, Expert Systems with Applications, 165 (2021).

[272] R. Piltaver, M. Luštrek, S. Džeroski, M. Gjoreski, M. Gams, Learning comprehensible and accurate hybrid trees, Expert Systems with Applications, 164 (2021).

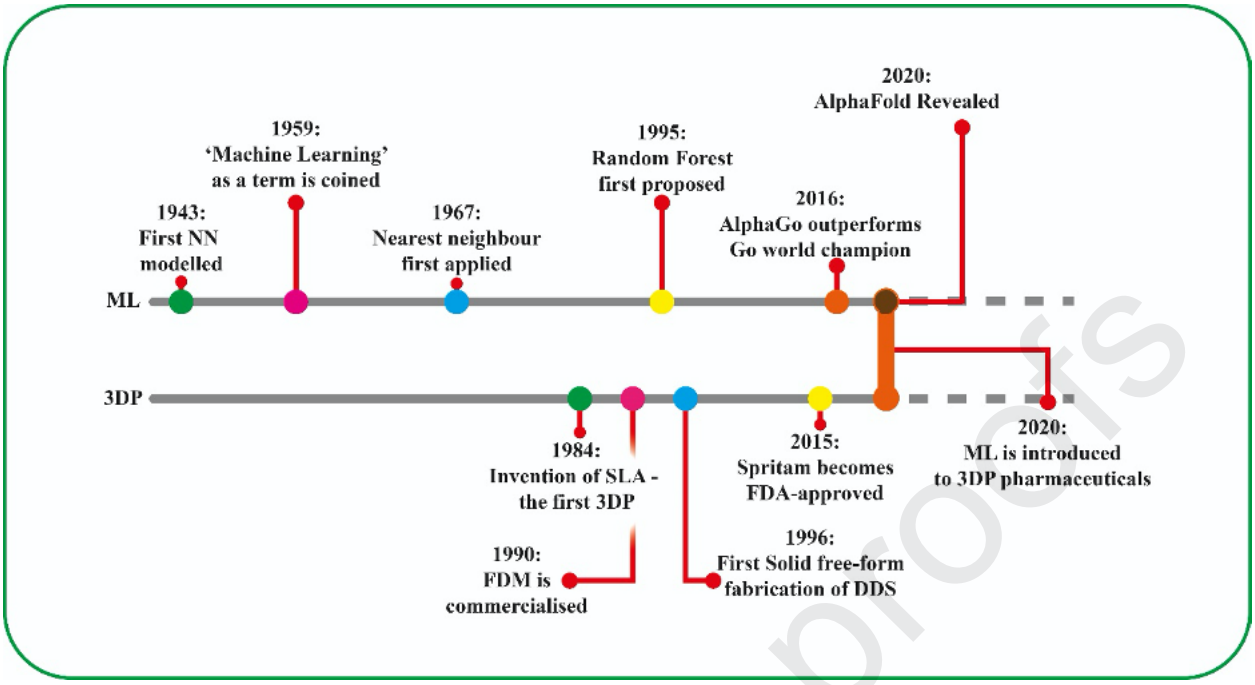
[273] F. Leal, A.E. Chis, S. Caton, H. González–Vélez, J.M. García–Gómez, M. Durá, A. Sánchez–García, C. Sáez, A. Karageorgos, V.C. Gerogiannis, A. Xenakis, E. Lallas, T. Ntounas, E. Vasileiou, G. Mountzouris, B. Otti, P. Pucci, R. Papini, D. Cerrai, M. Mier, Smart Pharmaceutical Manufacturing: Ensuring End-to-End Traceability and Data Integrity in Medicine Production, Big Data Research, 24 (2021).

[274] N.A. Fountas, N.M. Vaxevanidis, Optimization of fused deposition modeling process using a virus-evolutionary genetic algorithm, Computers in Industry, 125 (2021) 103371.

[275] T.A. Dixon, T.C. Williams, I.S. Pretorius, Sensing the future of bio-informational engineering, Nature Communications, 12 (2021) 388.

[276] M. Elbadawi, L.E. McCoubrey, F.K.H. Gavins, J.J. Ong, A. Goyanes, S. Gaisford, A.W. Basit, Disrupting 3D Printing of Medicines with Machine Learning, Trends in Pharmacological Sciences, in press.

[277] H. Narayanan, F. Dingfelder, A. Butté, N. Lorenzen, M. Sokolov, P. Arosio, Machine Learning for Biologics: Opportunities for Protein Engineering, Developability, and Formulation, Trends in Pharmacological Sciences, 42 (2021) 151-165.



1