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Critical Review

Mapping current trends in 3D printing and the impact on the recent landscape of drug development research

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ABSTRACT

Three Dimensional (3D) printing within the pharmaceutical industry is rapidly developing and current trends within drug development include the 3D printing of oral dosage forms, implants, hydrogels and topical drug delivery systems. 3D printed dosage forms can be used to treat a range of conditions varying from cardiovascular disease to recovery from orthopaedic surgery and the prevention of infection. Compared to traditional manufacturing methods, 3D printing allows the precise spatial control and deposition of material as layers. This results in a large degree of printing flexibility and means that a variety of complex designs can be printed accurately. By controlling factors such as the type of polymer, drug load and surface area a variety of controlled release dosage formulations can be produced and application in personalised medicine holds promise. Multiple release oral dosage forms can also be printed as well as those containing more than one Active Pharmaceutical Ingredient (API) which addresses polypharmacy and should aid medical treatment. This review studies recent trends in 3D printing and drug development, and current drawbacks are examined to evaluate the future potential to manufacture dosage forms.

INTRODUCTION

3D printing is an Additive Manufacturing process producing a 3D object which often exhibits complex structures which may be difficult or impossible to assemble in a single piece with conventional manufacturing techniques. A model is made using Computer Aided Design (CAD) and the object is printed by deposition of material in the X, Y and Z planes (Ventola, 2014; Nale and Kalbande, 2015; Feng et al., 2018). Materials used in this process include powders, plastics and metals (Ventola, 2014), and 3D printing requires processes such as printing-based inkjet systems, nozzle-based deposition systems and laser-based writing systems (Goole and Amighi, 2016). 3D printing was first established by Charles Hull in 1986 with the patency of Stereolithography SLA (Hull, 1986). Since then it has developed and is now used within many fields including the automotive industry, aerospace, the military (Gebler et al., 2014; Gross et al., 2014; Nale and Kalbande, 2015) houseware production and construction (Berman, 2012). Within healthcare 3D printing produces tissue, anatomical models and organs (Liaw and Guvendiren, 2017; Berman, 2012; Nale and Kalbande, 2015; Feng et al., 2018). The use of 3D printing within drug development has dramatically increased (Trenfield et al., 2018) over the past thirty years and now produces tablets, caplets, Orally Disintegrating Tablets (ODTS), implants, hydrogels, and topical delivery systems (Liaw and Guvendiren, 2017; Trenfield et al., 2018).

Currently 3D printing within drug development is centred on oral dosage forms. Orphan drug tablets can be manufactured as small batches on-demand and at low cost (Ciurczak, 2016; Trenfield et al., 2018; Awad et al., 2018a). Tester tablets are used by

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pharmaceutical companies to calibrate dissolution testers for immediate and continuous release dosage forms (Ciurczak, 2016). 3D printing enables these tablets to be produced in small batches as required (Ciurczak, 2016; Hsiao et al., 2018). This reduces waste and improves tablet reproducibility, thus increasing the reliability of conclusions drawn from dissolution testing (Ciurczak, 2016; Awad et al., 2018b). 3D printing can produce tablets that provide complex release profiles including delayed release and multiple-release dosage forms. Tablets containing more than one API can also be manufactured (Ventola, 2014; Maroni et al., 2017; Kadry et al., 2018; Goyanes et al., 2017a; Genina et al., 2017; Trenfield et al., 2018; Nale and Kalbande, 2015; Korte and Quodbach, 2018) which can decrease polypharmacy and increase medication efficacy. The production of medication by 3D printing may help to increase API solubility by producing amorphous forms. It may also be possible to limit the degradation of biologicals and prevent drug incompatibilities (Goole and Amighi, 2016) which should increase the bioavailability of the API and potentially lead to decreased dosing frequency, thus further improving patient compliance.

3D printed hydrogels can be used as scaffolds for the growth of cells in tissue engineering (Placone et al., 2017; Bertassoni et al., 2014), or implanted into the body to provide controlled API release (Gloria et al., 2016). Research in this area is improving although the focus on drug development is not yet at its peak.

Currently a large proportion of 3D printed implants also provide controlled API release, which is useful for the promotion of bone healing and the prevention of infection after orthopaedic surgery (Boetker et al., 2016). Implants have also been 3D printed that release hormones for contraceptive purposes (Kempin et al., 2017) therefore their application in medicine is increasing.

The 3D printing of topical dosage forms is still in its infancy but there are promises for future development. In particular microneedles are of interest, as microneedle moulds and microneedles themselves (Economidou et al., 2018; Luzuriaga et al., 2018) can be produced by 3D printing techniques.

MATERIALS AND METHODS

A major focus of 3D printing is the ability to produce personalised dosage forms on demand. This involves the tailoring of the medication dose to patient demographics (Trenfield et al., 2018; Ventola, 2014; Awad et al., 2018b, 2018a; Okwuosa et al., 2018) such as their genotype, age, weight, race, liver function, renal function and medical conditions (Ventola, 2014) This should improve medication efficacy and reduce adverse drug reactions, which should increase patient compliance and therefore improve future medical treatment.

Some research within the separate areas of oral dosage forms, hydrogels, implants and topical drug delivery has been completed. This has introduced 3D printing to drug development and manufacturing, however the information available is very specific to certain printers, APIs and processes. Consequently it is necessary to produce a systematic review using PRISMA guidelines (Moher et al., 2009) which groups all available research into set areas so that current trends can be established. It is hoped that quantitative analysis can also be completed so that a sound explanation of the current situation is obtained, areas that require improvement are highlighted and future research can be directed.

Currently only one licensed 3D printed product exists called Spritam, containing the drug levetiracetam. It is an ODT (Petty et al., 2002; Hsiao et al., 2018) and is produced by the Drop-on-Powder (DOP) technique which is a binder jetting process that prints liquid binder onto thin layers of powder (Shirazi et al., 2015). Although an ODT provides rapid drug release and is easy to take (Fitzgerald, 2015), the formulation production relies on solvent evaporation which produces highly porous structures. Consequently it is difficult to produce controlled release preparations in this manner and not all APIs are suitable for use (Goole and Amighi, 2016). Therefore it is necessary to understand the current limitations within the area of 3D printing and drug development. It would also be helpful to identify areas that require further development to aid future improvements and offer potential solutions in this area.

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Although not conducting a true systematic review, PRISMA guidelines (Moher et al., 2009) were followed in order to ensure a transparent non-biased approach to literature collection. Web of Science, Google Scholar, Scopus and Science Direct search engines were chosen as they have access to a wide range of peer reviewed articles which should cover all current research within the area of 3D printing and drug development, and should reduce the likelihood of error in interpreted information. The initial search was completed using the same search terms of '3D printing' and 'drug development or drug manufacturing' across all search engines so that the most relevant articles were found, and the search method was reliable. Where possible, the search was refined to select for the inclusion criteria of original research articles only and written in English. This enabled the selection of primary research in the form of articles, and ensured that current trends could be analysed.

An adapted version of the PRISMA flow diagram, as shown below (Figure 1), was used to document the process of sorting articles so that the search method was transparent and will be repeatable in future to allow comparison. After the initial searching, the article search was further refined manually by exclusion based on title. Titles which did not contain the words '3D printing' or other 3D printing processes such as Fused Deposition Modelling (FDM), Inkjet Printing (IP), Selective Laser Sintering (SLS), Stereolithography (SLA) and Drop-on-Demand (DOD) were excluded. Titles were also disregarded if they did not include anything to do with drug development or manufacturing, and if they stated that they were patents, citations or reviews so that only original research was analysed. Duplicates were then removed using the Mendeley referencing software to ensure accuracy. Full text articles were assessed for eligibility which involved studying the articles downloaded and looking for the emergence of current themes. Articles that were reviews, patents, citations or irrelevant, and had passed the initial screening because it was not clear from the title, were excluded. The article selection was narrowed down so that only those related to the review title were examined. For example, amongst the articles excluded were those concerning the 3D printing of tissues and 3D printing in general industry. In line with PRISMA guidelines, the quality of the articles was assessed so that only those deemed reputable were included. For example, acceptable articles were those that had been peer reviewed, clearly written and contained all of the relevant sections such as an introduction, methods, results, some form of analysis, discussion and conclusion, so that the research process could be followed. This enabled the collection of specific and accurate research that addressed the project objectives.

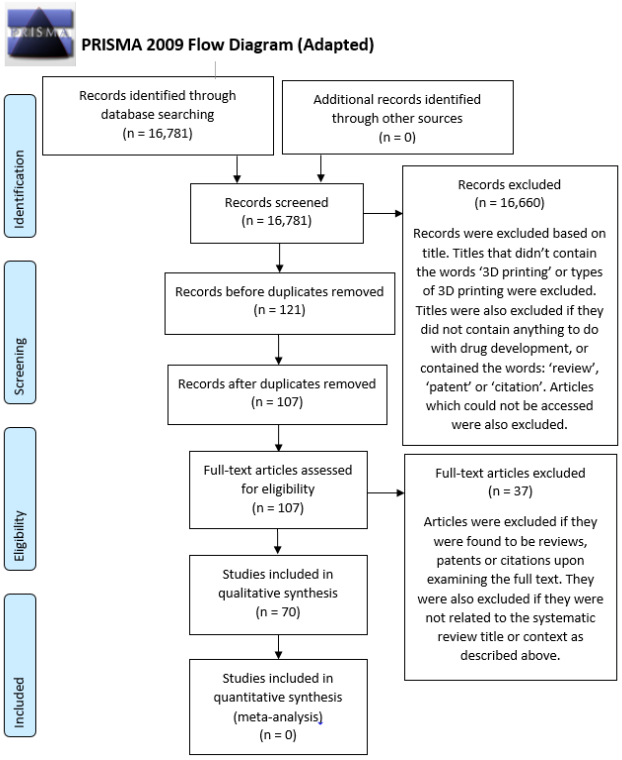

Figure 1 - The PRISMA flow diagram which has been adapted to suit the research collected, demonstrating the method of searching and reasons for article exclusion.

RESULTS AND DISCUSSION

Interest in 3D printing within drug development has increased dramatically over the last thirty years, as shown by Figure 2. The general trend indicates that the number of articles published annually is at an all-time high and as such research in this area is timely and of worth. This data was produced using the chosen search terms within Google Scholar only, without applying exclusion criteria so that a broad overview could be obtained.

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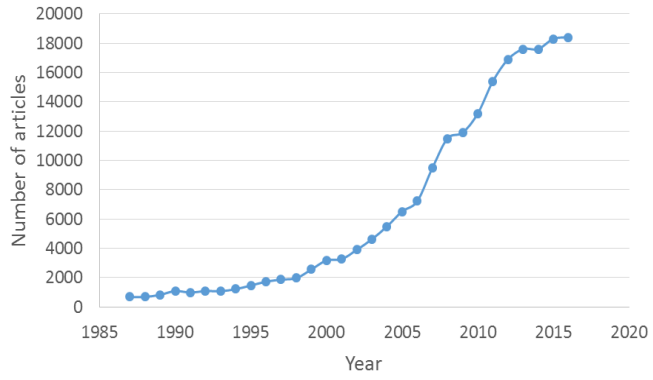

Figure 2 - Number of published articles containing information on 3D printing and drug development over the past thirty years

On analysis of the number of articles found using each search engine it is clear that Google Scholar had access to the most research.

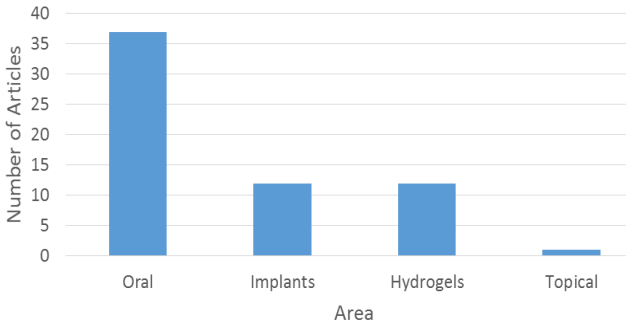

Figure 3: Distribution of dosage form focus detailed in articles examined

Initial identification of dosage form and administration route (Figure 3) demonstrated that the current main trends within 3D printing and drug development are oral dosage forms, hydrogels, implants and topical dosage forms. Most current research revolves around oral dosage forms. This is most likely as a result of the ease of manufacture, a large amount of published information and understanding and preferential selection as a dosage form as oral dosage forms are most widely accepted and used by patients as they are small, discreet and easy to take.

On further analysis for article quality it was determined that quality articles addressed key areas and report information on API release, API loading and statistical analysis. Articles within the key theme areas were not consistent in doing this, as shown in Figure 4. Whilst articles regarding oral dosage forms contained the most data on API loading and release, research on implants provided better statistical analysis.

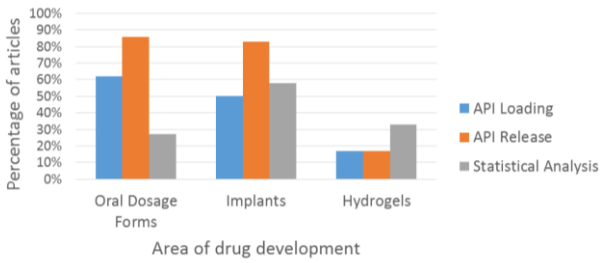

Figure 4: A graph to show the percentage of articles within the three areas of oral dosage forms (n=37), hydrogels (n=12) and implants (n=12) which include data on API loading, API release and statistical analysis. Quality articles were considered to contain all of this information thus showing the area to be well researched.

Statistical analysis improves the reliability of conclusions made in published articles and the abundance of papers applying statistical tools to provide an evidence base for their conclusions need to be increased to improve the quality of research in this area. Very few research articles were found concerning topical drug delivery, therefore this was excluded from the graph because it would not be representative of the entire area. Data for hydrogels was also limited as most current research revolves around the process of printing and tissue engineering, with limited potential for API release. Problems with 3D printing include API loading and release. For example Spritam is entirely dispersed in five seconds (Goole and Amighi, 2016), however oral dosage forms produced by SLA can take up to twenty hours for complete release (Martinez et al., 2017). These differences could be because 3D printing was not designed to build objects that are broken down.

A wide variety of APIs have been 3D printed, as shown in Table 1. Oral delivery systems tend to include APIs for medical conditions such as cardiovascular disease and diabetes whereas implants tend to be used to prevent infection so contain antibiotics, or used as hormonal contraceptives. Some articles do not focus on the therapeutic outcome, but examine the ability of certain 3D printers to produce set formulations. Therefore the API is chosen for its ease of printing and desirable characteristics such as good water solubility and high extrusion temperatures so that degradation is avoided.

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***Table 1**. A wide range of APIs were studied within the research articles reviewed. Paracetamol was used most commonly, in fifteen papers. Theophylline was the next most common, found in seven papers, whilst the majority of the APIs were found in one or two papers.*

API	No. of articles	API	No. of articles
4-ASA	2	Ibuprofen	2
5-ASA	2	Indomethacin	2
Aripiprazole	1	Isoniazid	2
Aspirin	1	Metformin	1
Atenolol	1	Methotrexate	2
Budesonide	2	Naproxen	2
Caffeine	2	Nifedipine	1
Captopril	2	Nitrofurantoin	4
Celecoxib	1	Oestrogen	1
Cidofovir	1	Paclitaxel	1
Curcumin	1	Pantoprazole	1
Deflazacort	1	Paracetamol	14
Dexamethasone	1	Pravastatin	1
Diclofenac	1	Prednisolone	2
Dipyridamole	4	Progesterone	1
Fenofibrate	1	Quinine	1
Fluorescein	1	Ramipril	2
Gentamicin	1	Rifampicin	2
Glipizide	1	Ropinirole	1
Guaifenesin	1	Silver	1
Haloperidol	2	T Cells	1
Hydrochlorothiazide	2	Theophylline	7

The main 3D printing techniques used in drug development are FDM, SLA, SLS, IP, and Injection Moulding (IM) (Tagami et al., 2017; Hsiao et al., 2018). 3D printing is useful because improvements can be made instantly by adjustment to the CAD file (Gupta et al., 2015). Commercial 3D printers have a higher resolution than traditional manufacturing methods and therefore allow greater customisation of infill percentages and geometries to tailor drug release rates (Weisman et al., 2015; Arafat et al., 2018b). Current research is aimed at personalised on-demand medication printing to reduce waste and mileage (Kurzrock and Stewart, 2016; Awad et al., 2018b). Importantly, the digital file of a vaccine for a global endemic could be sent around the world and administered in a short time (Kietzmann et al., 2015) thus saving lives.

SLA uses a laser to photopolymerise liquid resin forming a cross-linked polymer matrix, used mainly for tissue engineering and scaffolding. Release rate is controlled by the polymer. The number of photo-crosslinkable polymers is increasing, and include polyethylene glycol diacrylate (PEGDA) and polyhydroxyethylmethacrylate (pHEMA). SLA can print thermally labile APIs at a higher resolution and complexity than IP (Martinez et al., 2017; Wang et al., 2017; Economidou et al., 2018; Martinez et al., 2018), however a photo-initiator is often required such as riboflavin and triethanolamine. They are more biocompatible than others such as Irgacure (Martinez et al., 2017), however toxicity is still an issue (Martinez et al., 2017; Hsiao et al., 2018; Feng et al., 2018) thus limiting their use.

IP involves the deposition of droplets containing the API in solution. The dose depends on the drop size printed and control systems are being developed to predict the dissolution profile (Içten et al., 2015; Hirshfield et al., 2014). IP allows rapid polymerisation, co-deposition of multiple inks at high resolution and controlled distribution providing accurate dosing which is useful for potent drugs (Kyobula et al., 2017; Han et al., 2016; Pietrzak et al., 2015). However hollow structures cannot be printed, unlike FDM (Goyanes et al., 2014; Clark et al., 2017), leading to fewer printable geometries. Printing poorly water-soluble APIs is difficult. It is possible to mix them with polymers as a dispersion, solution or emulsion although this is difficult to scale up and high API to polymer ratios and temperatures cause solidification. These parameters alongside the viscosity of the polymer, pH, print speed and surface tension need to be tailored for optimal printing (Han et al., 2016; Wickstrm et al., 2017; Hirshfield et al., 2014; Hsu et al., 2013; Pietrzak et al., 2015; Clark et al., 2017).

SLS is a solvent free, one-step process. Temperature and laser scanning speed control the printed product. Objects produced are of a higher precision than FDM, however high energy lasers can degrade the API therefore SLS tends to be limited to tissue engineering or printing drug delivery devices where the API is loaded after printing. However, tablets were produced containing paracetamol (Fina et al., 2017, 2018b, 2018a), proving that printing oral dosage forms is possible and requires future development. Microspheres can also be printed which increases API solubility and reduces degradation (Wang et al., 2015).

FDM prints polymer filaments and is useful because it is cheap and versatile (Melocchi et al., 2016; Goyanes et al., 2016b, 2014; Skowyra et al., 2015; Goyanes et al.,

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2017a; Okwuosa et al., 2018). Intricate designs can be produced making FDM good for rapid prototyping where a representation of the item is created before it is mass produced, thus reducing development time and cost (Awad et al., 2018a; Melocchi et al., 2016; Glatzel et al., 2016; Feng et al., 2018; Okwuosa et al., 2018). Resolution is limited to a 0.4 mm tip (Melocchi et al., 2016; Goyanes et al., 2015c; Sadia et al., 2016) but granules, pellets, implants and transmucosal films can be printed (Goyanes et al., 2015c; Awad et al., 2018a).

Polymers can be loaded by swelling in a solution of the API. This reduces degradation and cost but produces low drug loads, often less than 3%, so is most appropriate for potent drugs (Goyanes et al., 2014; Tagami et al., 2017; Kempin et al., 2017; Goyanes et al., 2015b, 2016b). FDM is often combined with Hot Melt Extrusion (HME) which enables a higher drug loading (Smith et al., 2018; Yang et al., 2018; Melocchi et al., 2016; Goyanes et al., 2016b, 2015c, 2015a; Zhang et al., 2017a; Goyanes et al., 2015b; Khorasani et al., 2016) but is costly and may produce rough filaments that cause nozzle blockages, although this is compensated by the ease of storage and reduced waste (Skowyra et al., 2015; Zhang et al., 2017a; Nasereddin et al., 2018). Current research is also developing a method to screen the mechanical properties of hot-melt extruded filaments based on flexibility, to predetermine FDM suitability (Nasereddin et al., 2018). One major drawback is that extrusion temperatures can degrade drugs and excipients (Goyanes et al., 2014; Gupta et al., 2015; Genina et al., 2017; Okwuosa et al., 2018; Melocchi et al., 2018; Whyman et al., 2018; Kollamaram et al., 2018; Kempin et al., 2018; Goyanes et al., 2015a), as seen with 5-aminosalicylic acid (5-ASA) and curcumin. However this can be limited by increasing the print speed, choosing polymers with low extrusion temperatures (Kollamaram et al., 2018; Tagami et al., 2017; Boetker et al., 2016; Kempin et al., 2018; Goyanes et al., 2015a) and using carriers (Andersen et al., 2013). Higher temperatures cause reduced viscosity therefore better flow from the nozzle although a sufficient viscosity is needed to form a polymer strand for deposition (Kempin et al., 2017; Varan et al., 2017; Goyanes et al., 2015b; Li et al., 2018). A high breaking stress and long breaking distance is necessary for optimum printing (Zhang et al., 2017a; Goyanes et al., 2015a; Verstraete et al., 2018). Polyvinyl alcohol (PVA) and acrylonitrile butadiene have the best stiffness, toughness and melt velocity for printing. Drugs such as quinine often act as plasticisers and decrease the glass transition temperature which can promote degradation (Kempin et al., 2017; Varan et al., 2017; Goyanes et al., 2015b; Li et al., 2018) although printing can be done at room temperature which avoids stability problems (Khaled et al., 2015b, 2014).

Dual syringes can print complex materials accurately and affordably (Bootsma et al., 2017). The type and amount of plasticiser must be adjusted to enable the extrusion of higher drug loads and to improve filament quality (Melocchi et al., 2016; Goyanes et al., 2015c, 2015d, 2017a).

API release rate is dictated by a combination of API crystallinity, polymer crystallinity, API loading, extrusion temperature and solubility in release medium (Genina et al., 2016). It is important that drug dissolution reaches the FDA threshold (Jamróz et al., 2017), which it has done for most of the research available. Release is mostly dictated by an erosion-diffusion process. As the polymer disintegrates the API diffuses out therefore polymer choice is important (Tagami et al., 2017; Beck et al., 2017; Skowyra et al., 2015; Li et al., 2018; Sadia et al., 2018; Melocchi et al., 2015; Yang et al., 2018; Zhang et al., 2017a; Khaled et al., 2015b; Goyanes et al., 2015d, 2015a, 2015c, 2015b, 2016b, 2014, 2017a). APIs with a higher water solubility exhibit faster release (Goyanes et al., 2016b; Water et al., 2015; Genina et al., 2016) as disintegration depends on hydration, swelling and polymer break up. Barrier thickness and the physio-chemical properties of the polymer affect lag time. The use of water soluble polymers such as PVA improve dissolution enabling faster API release therefore tend to produce immediate release formulations (Melocchi et al., 2016; Verstraete et al., 2018; Jamróz et al., 2017; Skowyra et al., 2015; Okwuosa et al., 2016; Yang et al., 2018). For example immediate API release within 25 minutes can be obtained using hydroxypropyl cellulose (HPC) and Eudragit E to print tablets (Melocchi et al., 2016; Khaled et al., 2015a; Goyanes et al., 2015a, 2015b). Polymers that produce slow release are more limited, for example to PVA, polyamide (PA), ethylene vinyl acetate (EVA), polycaprolactone (PCL), methacrylic and cellulose polymers. Unfortunately they often have a low drug loading (below 30%) and require a plasticiser. High polymer concentration increases wettability and water uptake

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so increases swelling and gel barrier formation (Melocchi et al., 2016; Khaled et al., 2015b; Goyanes et al., 2015a, 2015b) thus delaying API release. Kempin et al., 2017 found that PCL provided the fastest rate of API release, when compared to Eudragit RS and EC as Eudragit is less prone to swelling (Kempin et al., 2017). An increase in the molecular weight of the polymer was also shown to prolong drug release. EVA copolymers vary in terms of vinyl acetate content, melting index and flexural modulus. Lower melt index causes greater swelling and makes printing more difficult; the flexural modulus is lower for EVA than PCL. If the melt index is too high droplets are not viscous enough to form. Melt index increases with vinyl acetate content and decreased polymer molecular weight (Genina et al., 2016). The device surface, size and cellular penetration is dictated by the polymer used, where reducing the size increases the surface area and bioavailability (Varan et al., 2017; Zhao et al., 2018).

A wide variety of polymers are used for 3D printing, as shown in Table 2. Selection of the polymer is a compromise between release properties, mechanical properties, degradation profile and processing (Water et al., 2015). Viscosity, shear thinning behaviour, elastic modulus and yield strength are important (Sommer et al., 2017). Polymer elasticity and brittleness dictate outflow from the nozzle and therefore the reproducibility of printing (Jamróz et al., 2017; Verstraete et al., 2018). Increasing polymer concentration increases viscosity which can make printing harder, however it has also been shown to increase elasticity. Sufficient viscosity is necessary to maintain structural integrity after printing (Ersumo et al., 2016; Abbadessa et al., 2017; Sayyar et al., 2017). Polylactic acid (PLA) and PCL are used for medical devices whereas PVA is used for oral dosage forms (Goyanes et al., 2016b). Insoluble polymers include ethylcellulose and Eudragit RL; soluble polymers include polyethylene oxide and Kollicoat; enteric soluble polymers include Eudragit L and hydroxypropylmethylcellulose acetate succinate (HPMCAS), and swellable/ erodible polymers include hydrophilic cellulose derivatives, PVA and Soluplus (Melocchi et al., 2016). Good mechanical properties, controlled API release, thermal stability and no cytotoxic effects have been shown for methyl methacrylate, butyl methacrylate, PLA, polyethylene glycol (PEG) and PEGDA photo-crosslinkable polymers for implant printing by SLA (Varan et al., 2017). Thermoplastic polyurethanes printed with FDM and IM enable a greater drug loading without HME processing (Verstraete et al., 2018). PLA and PCL are often used as they are viscous when molten, easily deposited and solidify when cool (Andersen et al., 2013). A high correlation between the target and achieved dose has been achieved especially when using Eudragit (Pietrzak et al., 2015).

Increasing the surface area to volume ratio increases the API release rate because water uptake and diffusion is promoted (Sadia et al., 2018; Kempin et al., 2017; Kyobula et al., 2017; Sommer et al., 2017; Tagami et al., 2018; Solanki et al., 2018; Pietrzak et al., 2015; Goyanes et al., 2015d; Skowyra et al., 2015). Therefore control of geometry (Genina et al., 2016; Varan et al., 2017) and porosity is important, with higher porosity often caused by low drug loads (Costa et al., 2015; Min et al., 2015; Ersumo et al., 2016; Sayyar et al., 2017), however this also leads to greater weight variation (Goyanes et al., 2016b; Fina et al., 2017; Verstraete et al., 2018). Channelling agents enhance permeability (Melocchi et al., 2016; Beck et al., 2017; Sadia et al., 2018), by increasing porosity which increases drug release (Melocchi et al., 2016; Beck et al., 2017; Solanki et al., 2018; Sadia et al., 2018; Arafat et al., 2018b). However API solubility and loading was shown to have a greater impact on API release than porosity for PVA printed caplets (Goyanes et al., 2016b; Pietrzak et al., 2015; Hsu et al., 2013). Also surface area was not shown to effect curcumin release from a PVA filament (Tagami et al., 2017) thus proving that all factors including API solubility and polymer type (Kyobula et al., 2017) must be considered when predicting API release.

In most cases a higher infill percentage causes slower API release (Beck et al., 2017; Kyobula et al., 2017; Zhang et al., 2017a; Li et al., 2018; Hsu et al., 2013; Tagami et al., 2017; Genina et al., 2016; Kempin et al., 2017; Water et al., 2015; Goyanes et al., 2015a, 2017a; Melocchi et al., 2015), which may be because the API is present in its crystalline state (Kyobula et al., 2017) or because structures are less porous with a lower surface area (Zhang et al., 2017a; Solanki et al., 2018). Although increasing the API load increases filament hardness which may limit printing. Therefore it is possible to control API release by controlling infill percentage. It is also important to select the best

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solvent to optimise drug loading, and use fillers to aid flow if necessary, such as tri-calcium phosphate (Goyanes et al., 2015a; Sadia et al., 2016).

Table 2. *A wide range of polymers were used within the 3D printing processes of FDM, IM, IP, DOD, SLA and SLS in the physical form of a filament, waxy solid, flakes, powder, neat, lyophilised, beads, liquid, viscous liquid, paste, crystals, solid, sheet, rod, resin, pellets or granules. The most common printing application is FDM and the most widely used polymers are HPMC and PCL.*

Polymer	Physical Form	Printing Application
Acrylonitrile butadiene styrene (ABS)	Filament	FDM, IM
Beeswax	Waxy Solid	IP
Chitosan	Flakes/ powder	FDM
Ethyl cellulose	Filament/ powder/neat	FDM
High impact polystyrene (HIPS)	Filament	FDM
Hydroxyethylcellulose (HEC)	Filament	FDM
Hydroxypropyl cellulose (HPC)	Powder/ filament	FDM, IM
Hydroxypropyl methyl cellulose (HPMC)	Powder/ filament	FDM, IM,DOD
Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	Powder/ filament	FDM, IM
Keratin	Lyophilised	SLA
Methacrylic acid (Methyl methacrylate copolymer)	Filament	FDM
Microcrystalline cellulose (MCC)	Powder/ filament	FDM
Poly (ethylene vinyl acetate)	Filament/ beads	FDM
Poly(acrylic acid) (PAA)	Powder	FDM
Poly(D,L-lactide-co-glycolide) (PLGA)	Liquid/ viscous liquid/paste/ filament	FDM, IP
Poly(ethylene glycol) dimethacrylate (PEGDMA)	Powder/resin /solution	SLA
Poly(ethylene oxide) (PEO)	Filament/ powder	FDM
Poly(ethylene-co-vinyl acetate)	Beads/ filament	FDM
Poly(L-lactide) (PLLA)	Filament/ powder	FDM
Poly(methacrylic acid-co-methyl methacrylate)		FDM
Poly(methyl methacrylate) (PMMA)	Neat/powder /crystalline/ resin	FDM
Poly(N-(2-hydroxypropyl) methacrylamide-mono/dilactate (pHPMAlac)	Powder	SLA
Poly(N-isopropylacrylamide) (PNIPAM)	Crystals/crystalline powder	IP
Poly3-hydroxybutyrate-co-3-hydroxyhexanoate (PHBHHx)	Powder	FDM
Polyamide (PA)	Powder	SLS, IM
Polycaprolactam	Powder	FDM, IM
Polycaprolactone (PCL)	Flakes/pellets /granules/ Filament	FDM, IP, SLA
Polycarbonate (PC)	Film/pellets	SLS, IM
Polyether ether ketone (PEEK)	Powder/ crystals/ filament	SLS,FDM
Polyethyene glycol diacrylate (PEGDA)	Solid	SLA
Polyethylene glycol (PEG)	Liquid	IP,SLA
Polyethylene glycol diacrylate (PEGDA)	Solid	SLA, IP
Polyethylenimine (PEI)	Viscous liquid	IP
Polylactic acid (PLA)	Filament	FDM, IM
Polyphenylsulfone (PPSF)	Sheet/rod/ filament	FDM
Polyvinyl alcohol (PVA)	Powder/ crystals/ filament	FDM, IM
Polyvinyl alcohol-polythylene glycol graft copoymer (Kollicoat IR)	Filament	FDM,SLS
Polyvinyl caprolactam-polyvinyl acetate-polyetylene glycol graft copolymer (Eudragit L, RL, RL-PO)	Filament	FDM
Polyvinylpyrrolidone (PVP)	Powder/crystals/filament	DOD,FDM
Sodium Alginate	Solid	IP
Sodium starch glycolate (SSG)	Powder	FDM
Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus)	Filament	FDM

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It is generally preferred that APIs are in their crystalline form because of lower energy states and thermodynamic favourability. However this makes the API less soluble, therefore lipid-based formulations such as emulsions are printed to increase the solubility of APIs with a low water solubility, as shown with celecoxib (Içten et al., 2017). Poorly soluble APIs such as nitrofurantoin and aripiprazole can be incorporated into a water soluble polymer to improve bioavailability (Sandler et al., 2014; Jamróz et al., 2017). Nanoparticles can be printed by IP, FDM and SLS which also improves the delivery of poorly water soluble APIs and unstable compounds thus potentially reintroducing previously discarded APIs. Greater control of API release is enabled (Wickstrm et al., 2017; Yuksel and Cullinan, 2016; Beck et al., 2017) however this is yet to be studied in humans.

As 3D printing was not originally designed for drug manufacture, toxic excipients and the limited number of polymers available is a challenge (Feng et al., 2018; Melocchi et al., 2016; Clark et al., 2017; Gupta et al., 2015; Kyobula et al., 2017; Sadia et al., 2016; Okwuosa et al., 2016). Polymer degradation can also occur as in the case of Eudragit RL, which lead to API degradation by lowering the melting point (Pietrzak et al., 2015; Sadia et al., 2016), proving that control of printing temperature is important. Printable edible inks are being researched, such as seaweed full of cellulose. However these inks often require additives to improve rheological properties for printing, therefore more need to be developed before the 3D printing of ingestible dosage forms is a success (Feng et al., 2018).

Research on human acceptability of 3D printed medicines has been completed (Goyanes et al., 2017b), however in vivo research regarding API release and pharmacokinetics has only been completed in rats for a tiny number of oral dosage forms (Genina et al., 2017; Goyanes et al., 2018; Arafat et al., 2018a) and two types of implants (Tappa et al., 2017; Min et al., 2015). The flexibility of 3D printing has also been demonstrated with the ability to titrate the dose of warfarin, a narrow therapeutic index drug, both in vitro and in vivo thus allowing accurate medication dosing (Arafat et al., 2018a). Even though in vitro results look promising, it is difficult to determine efficacy in man. Many more in vivo studies need to be undertaken before the utility of 3D printed formulations can be established. It is also argued that the 3D printing of medication has the potential to increase illegal and unregulated medication printing (Yampolskiy et al., 2016; Kietzmann et al., 2015) therefore strict regulations need to be considered before the 3D printing of medication can be commercialised.

Oral Dosage Forms

Tablets, caplets and ODTs can be 3D printed, as well as multiple tablet shapes which can't be produced using traditional methods (Awad et al., 2018a; Goyanes et al., 2015c; Khaled et al., 2015a). Tetrahedron shapes have a long stomach residence time and produce controlled release over ten hours (Goyanes et al., 2015c). Tablets printed as a torus shape were favoured in a randomised study by Goyanes et al., 2017b, proving the importance of being able to print varying shapes to improve patient compliance. Desktop 3D printers using room temperature extrusion can print tablets with immediate and slow release parts (Khaled et al., 2014; Awad et al., 2018a; Kempin et al., 2018), thus potentially making it possible to print medication at home. Controlling the internal structure also modifies release profiles (Goyanes et al., 2017a; Zhang et al., 2017a). For example a honeycomb architecture controls API release by tailoring the cell size, which influences the surface area (Tagami et al., 2017; Solanki et al., 2018) without needing to alter the formulation, thus saving money and time. Similarly 'gaplets' have been produced which contain a rigid multi-block design with fixed gaps and allow immediate API release (Arafat et al., 2018b).

Channelled tablets facilitate accelerated release and shorter channels cause faster dissolution therefore the number, width and length of channels can be tailored to the required release. However this approach is better suited to non-swelling systems as swelling can cause channel closure (Sadia et al., 2018).

Low flow rates used in FDM produce tablets with a lower density and infill percentage (Tagami et al., 2017), therefore showing faster API release than tablets printed by IM (Fina et al., 2017; Verstraete et al., 2018; Korte and Quodbach, 2018; Goyanes et al., 2016b). Low density tablets can enable gastro-retentive medication which increases the

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bioavailability for APIs absorbed in the stomach (Tagami et al., 2017; Li et al., 2018).

Tablets can be printed and then enteric coated to allow modified release. This can be done in one step using a dual nozzle FDM printer with separate polymers for the core, such as polyvinylpyrrolidone (PVP), and the coat, such as methacrylic acid copolymer (Korte and Quodbach, 2018; Whyman et al., 2018; Nasereddin et al., 2018). However nozzle clogging is an issue as material adheres to the inner wall due to a difference in nozzle temperatures (Whyman et al., 2018; Nasereddin et al., 2018; Goyanes et al., 2015b). Enteric coated tablets can show pH-dependent release in the small intestine caused by carboxylic acid groups. Shell thickness also dictates API release, with thicker and harder shells limiting release, regardless of the porosity (Zhang et al., 2017b; Okwuosa et al., 2018; Smith et al., 2018; Yang et al., 2018; Tagami et al., 2018; Goyanes et al., 2015b; Zhang et al., 2017a). Protection of the core from acidic medium is also enabled, but if the shell is not thick enough premature drug release occurs (Goyanes et al., 2015b).

Multinozzle 3D printing by FDM and IM produces multilayer devices containing APIs within separate internal structures (Maroni et al., 2017; Melocchi et al., 2015; Goyanes et al., 2015c). Pulsatile release is currently being researched for dietary supplements and other APIs (Melocchi et al., 2018). Two-pulse oral API delivery is enabled using pH-sensitive and time-dependent release dictated by the type of polymer, wall thickness, API loading and solubility (Maroni et al., 2017; Gupta et al., 2015; Melocchi et al., 2015, 2018; Yang et al., 2018; Khaled et al., 2015a). For example gel barrier formation delayed solvent penetration for two hours and rupture of the shell for another hour in one study. Multi-drug devices reduce polypharmacy and API interactions, (Maroni et al., 2017) as one tablet can treat an entire condition. For example a tablet with three slow release compartments containing pravastatin, atenolol and ramipril and immediate release compartments containing aspirin and hydrochlorothiazide, known as the Polycap, is used to treat cardiovascular disease (Khaled et al., 2015a). For diabetes with hypertension a caplet has been produced with two slow release compartments containing nifedipine and glipizide. An osmotic pump containing captopril is also incorporated to provide zero order release, thus enhancing plasma level control throughout the day (Khaled et al., 2015b). Dual-compartmental dosage units for Tuberculosis treatment reduced interactions and allowed maximum absorption by immediate rifampicin release from the unsealed compartment into the stomach and delayed isoniazid release from the sealed compartment into the small intestine. When compared to in vitro testing, API release was slower in rats, possibly due to their low fluid volume. However humans have a higher fluid volume and in general in vivo and in vitro release correlated. Sealing affected in vitro release but did not appear to slow release in vivo possibly because of mechanical stimulation causing de-capping or faster dissolution, therefore more in vivo studies are necessary (Genina et al., 2017).

Multiple-release caplets can be produced by embedding one caplet within a larger caplet (DuoCaplet). Drug release was manipulated by the site of API incorporation, and the lag time depended on external layer thickness. Longer lag times occurred with lower drug loads due to slower erosion-dissolution of the external layer. A problem was insufficient bilayer hardness and bonding leading to layer disruption (Goyanes et al., 2015d), and unsatisfactory reproducibility due to resolution (Genina et al., 2017) and material expansion (Maroni et al., 2017; Gupta et al., 2015; Melocchi et al., 2015). This can be overcome by adjustment of the gap between the two compartments, the amount of plasticiser added and extrusion speed (Maroni et al., 2017; Gupta et al., 2015). Drug load was also slightly less than optimal but due to loss of powder rather than degradation (Maroni et al., 2017). Acceptability of 'polypills' must be considered due to their size, as well as cost to the National Health Service. Doses of each API must be tailored for the individual and not supplied at a fixed amount. Also, regulatory approval has not been fully researched yet.

Quick Response (QR) codes containing the API can be inkjet-printed onto an ODT which can be read by a smartphone using a scanning app that will detail the API, dose, patient name, administration code, expiration date and manufacturer batch identification code. It is hoped that this could prevent people taking the wrong medicine and counterfeit medicines (Edinger et al., 2018; Wickstrm et al., 2017). However the practicality of this idea is debatable because the

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QR code integrity must be maintained upon storage and handling.

An interesting development is an easy to use and inexpensive portable 3D printing system which allows pathogen incubation and can print and test antibiotics to direct treatment (Glatzel et al., 2016). Therefore it is clear that the 3D printing of oral dosage forms is being widely researched and has the potential for success.

Topical Delivery Applications

Only a few original research articles related to topical drug delivery was found. A review article was also discovered which suggests that either the search terms did not target topical delivery systems, or the search engines do not store many of these articles. However it is clear that research into the 3D printing of topical delivery systems is limited, possibly because oral dosage forms are the current focus.

IP and SLA coat microneedle surfaces, for example with insulin and chemotherapy, print moulds that microneedles are cast in and print microneedles for controlled API release dictated by biodegradation. The first method for producing microneedles by Drop-on-solid (DOS) (also known as binder jetting) strategies was patented in 2012. Bio-compatible polymers used include PVA and PLA. Chitosan and collagen have potential use because chitosan is stable in a neutral environment, soluble in acidic environments and mucoadhesive, and collagen can be bio-printed as a hydrogel which can be used topically. Microneedles that administer vaccines are being explored, which would reduce pathogen transmission, patient discomfort and cost. A current problem is the limited number of biomaterials with a suitable viscosity at certain temperatures that are not photo-sensitive or degraded during printing and are suitable for bending (Economidou et al., 2018). However, biodegradable microneedle patches using PLA have been 3D printed by FDM. Resolution was significantly improved using a 'post fabrication chemical etching programme' which produced needle tip sizes in the range of 1 to 55 micrometres. The degradability of PLA can be used to control API release (Luzuriaga et al., 2018), thus showing the potential for success in this area.

One research article discovered compared FDM to SLA for the 3D printing of anti-acne devices, either as a patch or scaffold that has been tailored to the person's nose using 3D scanning. FDM used flexible polymers in the hope of producing comfortable devices. However NinjaFlex, a thermoplastic polyurethane polymer, produced a brittle filament that could not be printed. PCL and Flexible environmentally friendly (Flex Eco) PLA filaments were printed, although SLA was more successful because it enabled faster drug dissolution, higher resolution and greater drug loading due to the absence of heat (Goyanes et al., 2016a).

Similarly, 3D scanning and printing have been used to customise the shape and size of wound dressings for a specific patient. Silver and copper wound dressings showed the best antibacterial properties. The wound healing process can be enhanced by a fast release within 24 hours, followed by slow release over 72 hours (Muwaffak et al., 2017), thus potentially reducing the need for systemic antibiotics and therefore the threat of antibiotic resistance.

There is potential for 3D printing to produce devices specifically tailored to individuals which should increase treatment efficacy, particularly as one of the main problems with topical delivery is API penetration. However it appears that the 3D printing of topical delivery systems requires much more development.

Implants

3D printed implants provide modified API release (Costa et al., 2015; Boetker et al., 2016; Min et al., 2015; Varan et al., 2017), flexible dosing and precision medicine using multiple geometries. EVA is used for the modified release of indomethacin from an Intra-uterine Devices (IUD) and subcutaneous rods (Genina et al., 2016), PCL prints an IUD for indomethacin and contraceptive hormone release, and PLA prints disks for indomethacin (Kempin et al., 2017), nitrofurantoin (Boetker et al., 2016), gentamicin and methotrexate (Weisman et al., 2015) release as well as pessaries (Tappa et al., 2017).

Pharmaceutical and structural treatments are combined, for example Boetker et al., 2016 created implants made from PLA loaded with nitrofurantoin for bone regeneration and infection prevention (Deng

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et al., 2017), thus reducing transplant need (Nale and Kalbande, 2015). Polyether ether ketone (PEEK) scaffolds coated with silver nanoparticles are also used for this purpose, with a lower elastic modulus than titanium alloys that are closer to natural bone minimising implant rejection (Deng et al., 2017). Dexamethasone has also been successful in promoting bone formation because of its high stability and low cost, however it cannot be used at concentrations above 1000 nanomolar and for prolonged treatment due to bone loss and osteoporosis (Costa et al., 2015). Implants have also been designed to release isoniazid and rifampicin for the treatment of osteoarticular tuberculosis. Compared to oral formulations, liver and renal damage is eliminated as well as the need for frequent dosing. Studies in rabbits showed that both APIs remained above the Minimum Inhibitory Concentration (MIC) for more than eight weeks, however due to its porous structure the implant was degraded in three months (Min et al., 2015), thus use is limited to a certain timeframe.

Implants can be used for anti-infective purposes. For example nitrofurantoin was incorporated into PLA with the potential to produce catheters that prevent infection (Sandler et al., 2014). Also, paclitaxel and cidofovir were printed onto mucoadhesive films by IP for the local treatment of cervical cancer as a result of human papillomavirus infection. The poor solubility of paclitaxel is overcome by including it within cyclodextrin complexes and the release of cidofovir is controlled by encapsulation on PCL nanoparticles (Varan et al., 2017).

Lattices can be coated with functional groups enabling the attachment of T cells for immunotherapy and also facilitating stable lentiviral gene delivery. However this process needs to be simplified and scaled up (Delalat et al., 2017).

The 3D printing of oil-in-water emulsions into soft materials with multiphase architectures allows site-specific incorporation of hydrophilic and hydrophobic compounds. When stabilised by chitosan-modified silica nanoparticles the resultant ink has high yield stress, storage modulus and elastic recovery (Sommer et al., 2017).

Photo- and mechanochromic structures can be 3D printed, such as those containing spiropyran which changes colour on activation by mechanical force. Selective activation of different regions can be obtained by using two different responsive spiropyrans. These can be used as force sensors and scaffolds for small molecule release (Peterson et al., 2015).

Drug release must be considered when applying the implant to treatment. A burst phase tends to be experienced at first, followed by a more controlled release (Kempin et al., 2017; Sandler et al., 2014). However microparticles and nanoparticles are used to delay API release (Iwanaga et al., 2013; Varan et al., 2017). Drug loading is relative to implant use. For example Water et al., 2015 showed that even a low nitrofurantoin load of 10% was more effective at reducing bacterial growth than a placebo implant. Higher drug loading may be more effective, but care must be taken not to increase bacterial resistance and side effects. To control release of the API a balance between porosity, erosion rate and API loading is necessary (Sommer et al., 2017; Costa et al., 2015). This can be achieved by fine-tuning scaffold architecture using 3D printing and water soluble excipients such as hydroxypropyl methylcellulose (HPMC) can be incorporated to form pores. Increasing the concentration of HPMC increases pore formation and drug release rates, therefore API release can be controlled by manipulating HPMC concentration (Boetker et al., 2016).

Using biodegradable polymers such as PLA, EVA and PCL prevents problems with permanent implants such as surgery for removal, host immune responses, infection and toxicity (Boetker et al., 2016; Weisman et al., 2015). However, pure polylactic-co-glycolic acid (PLGA) and other biocompatible polymers cause a significant decrease in pH due to acidic degradation products, which could cause drug resistance. Mesoporous silica based materials are better for localised and controlled drug delivery without pH decreases (Min et al., 2015).

Increasing shear forces during extrusion, premixing of API and excipients or feeding excipients such as hydroxyapatite nanoparticles with osteoconductive properties as a suspension was shown to improve API dispersant size and homogeneity by fractioning large agglomerates (Water et al., 2015). Adding silicone to the polymer enabled more efficient extrusion and a consistent dispersion of the API. A vortex can also be

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used to suspend additives evenly on the surface (Weisman et al., 2015).

Magnetic resonance imaging and computerised tomography can print the appropriately shaped implant for the patient (Kempin et al., 2017) which can reduce problems such as pelvic inflammatory disease and uterine perforations in the case of IUDs. 3D printing also enables the API dose to be tailored to the individual for optimum efficacy (Tappa et al., 2017).

Problems with 3D printed implants include incomplete API release, which was encountered by Boetker et al., 2016 when insufficient HPMC was added (Water et al., 2015; Boetker et al., 2016) which proves the importance of water soluble polymers. Further problems include insufficient drug loading which can be caused by API loss during printing. This could be prevented by premixing the API and polymer (Boetker et al., 2016), however this is difficult when the API is supplied as a powder and the polymer is a filament in FDM. Consequently further development in FDM 3D printing is necessary to allow the direct feeding of different starting materials into the 3D printer.

Research in this area is developing, although improvements are necessary to balance optimal drug loading with the prevention of side effects, toxicity and the creation of bacterial resistance. Elution profiles also need to be fully understood. Future development could look at incorporating further immunosuppressors, antibiotics, anti-inflammatories and drugs that stimulate cellular proliferation into implants.

Hydrogels

Hydrogels can be used as implants, scaffolds to grow tissue or for drug testing. They can act as reservoirs and deliver specific APIs to a target site but it is also possible to design multilayer and injectable hydrogels. By varying the sequence of stacking it is possible to tailor hydrogel geometry, porosity and mechanical strength, where decreased scaffold stiffness occurs with increased porosity (Gloria et al., 2016). Hydrogel stiffness and permeability can also be manipulated by chemical modification of gel-forming polymers (Raman et al., 2016). Hydrogels allow nutrient diffusion to cells and characteristics such as spatial control and viscoelastic properties can be tailored to mimic different tissues (Han et al., 2016; Ersumo et al., 2016). Storage modulus, yield stress, and viscosity increase with polymer concentration, for example up to a methacrylated hyaluronic acid (HAMA) content of 0.75% w/w, but decrease above this. Crosslinkable polysaccharides such as hyaluronic acid improve mechanical properties and degradation profiles. More pronounced thermosensitivity, shear thinning and yield stress improve the printability of hydrogels (Abbadessa et al., 2017). Hydrocolloid polymers are used as they are safe and drug release is controlled by limiting diffusion rate through the polymer. Hydrogels made from hyaluronic acids, alginate and hydroxyethylcellulose (HEC) are biocompatible and show good printability, with PCL added for strength (Andersen et al., 2013).

Drug release is via diffusion through the swollen matrix, so increasing the water content enables faster swelling and release rates (Wang et al., 2017; Han et al., 2016; Boetker et al., 2016; Yang et al., 2018). Release rates are also controlled by surface area to volume ratio and the structure can be manipulated (Wang et al., 2017; Han et al., 2016; Boetker et al., 2016) to enable faster API release than hydrogels prepared using traditional methods (Wang et al., 2017). Humidity affects pore formation as smaller pores are formed and release rate increases when evaporation rate increases (Raman et al., 2016; Han et al., 2016). Crosslinkable components act as pore-forming agents, therefore increasing their concentration leads to faster water uptake and drug release. Higher viscosity hydrogels exhibit slower release rates and resin components can be altered to tailor release profiles (Martinez et al., 2017). Complex release profiles can also be planned by tuning hydrophobic and hydrophilic polymer concentrations (Abbadessa et al., 2017).

APIs are loaded by immersing the hydrogel in an aqueous solution so that it swells and the API enters by diffusion. Printing pre-swollen hydrogels enables entrapment of a known and high quantity of drug, encapsulation of poorly soluble drugs and ensures sufficient water for solubilisation and drug release (Martinez et al., 2017; Wang et al., 2017). A high water content is often required for appropriate printing viscosity and surface tension (Han et al., 2016). However, water contents above 20% can impede the

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reproducibility of printing as water dilutes the resin and reduces viscosity (Martinez et al., 2017; Bootsma et al., 2017).

Coupling SLA with a chemical conjugation technique enables spatial segregation and localisation of the API within different areas of the hydrogel, which increases the API release rate and prevents interactions (Raman et al., 2016). SLA also enables the fabrication of pre-swollen hydrogels such as ibuprofen-loaded hydrogels of cross-linked PEGDA. The degree of cross-linking is influenced by the ratio of diluent to resin and the concentration of cross-linking agents so that the hydrogels are capable of tuneable API release. (Martinez et al., 2017). Keratin is biodegradable, can self-assemble, has sufficient compressive moduli, provides adequate cell support and is made from the renewable resource of human hair. Sufficient uptake, swelling properties, and the ability to modify cross-linking density by modifying keratin content has made keratin suitable for the SLA printing of hydrogels used in tissue engineering and regenerative medicine (Placone et al., 2017; Bertassoni et al., 2014).

IP is often used for tissue bioprinting, requiring a limited number of materials including natural proteins, polysaccharides such as agar, fibrin, hyaluronic acid, gelatine, and collagen. Direct write printing allows greater control of macroscale structures and more straightforward bioprinting, however it is limited by viscosity and concentration (Bertassoni et al., 2014).

Shape memory hydrogels are printed using calcium cross-linked alginate. They form a reversible structure and have a high recovery; mechanical properties are restored in thirty minutes. The API is released during deformation so the hydrogel is useful for drug delivery in surgery. The use of alginate also promotes cell growth as it is a polysaccharide, and it does not degrade in vitro so is good for short term implantation (Wang et al., 2017). However drug leaching often occurs, so a shear thinning viscosity modifier such as HEC is often added to aid printing (Andersen et al., 2013).

Multilayer biodegradable conducting hydrogels can be produced for tissue engineering using graphene nanosheets in a chitosan host polymer which improves cell adhesion, proliferation and spreading (Sayyar et al., 2017).

Hydrogels can be printed containing small interfering ribonucleic acids (siRNAs) in a spatially controlled manner. Structures are seeded with mesenchymal stem cells so that selected siRNAs are delivered to cells and induce specific and localised gene silencing. Deposition of active molecules such as siRNAs, plasmid deoxyribonucleic acid (DNA) and viral vectors into hydrogels causes programmed differentiation of seeded stem cells. This can be used to create individualised tissues to fit patient data or used as a screening platform for different APIs (Andersen et al., 2013).

Current problems with hydrogels are insufficient mechanical strength and limited biocompatible materials (Andersen et al., 2013). A second polymer can be incorporated to form an interpenetrating cross-linked polymer network which improves mechanical strength and enables tuneable viscoelastic properties. For example acrylamide and hydroxyethyl acrylate (HEA) can form hydrogen bonds to create hydrogels with a higher elastic modulus (Bootsma et al., 2017). Research in this area is limited and could be improved with a better understanding of hydrogel behaviour, so that mechanical properties can be manipulated (Ersumo et al., 2016). It is hopeful that the use of hydrogels as API-eluting devices will develop in the future with a better understanding of excipient effect on hydrogel printing.

CONCLUSIONS

3D printing is a rapidly developing area of interest. It was concluded after analysis of 70 articles that the current main trends within 3D printing and drug development are the areas of oral dosage forms, implants, hydrogels and topical delivery systems. Oral dosage forms are currently the most widely researched area. Research in all areas is increasing, however substantial future development is required. 3D printing has the potential to offer on-demand medication production anywhere and improve medication efficacy by printing extremely valuable personalised dosage forms.

There have been successes, including the first 3D printed ODT, however current drawbacks include the limited availability of non-toxic excipients, polymers and printing processes that do not cause API degradation. Unfortunately there is currently very

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little in vivo testing of 3D printed formulations, therefore it is difficult to determine their efficacy in man.

Future evaluation should be aimed at a thorough analysis of one area established within the trends, for example by studying dissolution data for all of the current 3D printed oral dosage forms. The data collected is likely to be homogenous in such instance and therefore meta-analysis could be completed, providing a high standard of assessment. This data could be compared to dosage forms produced by traditional methods to conclude whether the 3D printing of medication is advantageous. Further developments require the completion of extensive in vivo studies and the production of more polymers and excipients that are biocompatible. However it is clear that 3D printing will improve the accessibility, efficacy and cost effectiveness of drug manufacture.

REFERENCES

Abbadessa, A., Landín, M., Oude Blenke, E., et al. (2017) Two-component thermosensitive hydrogels: Phase separation affecting rheological behavior. European Polymer Journal, 92 (December 2016): 13–26

Andersen, M.Ø., Le, D.Q.S., Chen, M., et al. (2013) Spatially controlled delivery of siRNAs to stem cells in implants generated by multi-component additive manufacturing. Advanced Functional Materials, 23 (45): 5599–5607

Arafat, B., Qinna, N., Cieszynska, M., et al. (2018a) Tailored on demand anti-coagulant dosing: An in vitro and in vivo evaluation of 3D printed purpose-designed oral dosage forms. European Journal of Pharmaceutics and Biopharmaceutics [online], 128 (March): 282–289. Available from: https://doi.org/10.1016/j.ejpb.2018.04.010

Arafat, B., Wojsz, M., Isreb, A., et al. (2018b) Tablet fragmentation without a disintegrant: A novel design approach for accelerating disintegration and drug release from 3D printed cellulosic tablets. European Journal of Pharmaceutical Sciences [online], 118 (March): 191–199. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0928098718301349

Awad, A., Trenfield, S.J., Gaisford, S., et al. (2018a) Accepted Manuscript Review 3D printed medicines: A new branch of digital healthcare. International Journal of Pharmaceutics [online], 548 (April): 586–596. Available from: https://doi.org/10.1016/j.ijpharm.2018.07.024

Awad, A., Trenfield, S.J., Goyanes, A., et al. (2018b) Title: Reshaping drug development using 3D printing. Drug Discovery Today [online], 23 (17): 1547–1555. Available from: https://doi.org/10.1016/j.drudis.2018.05.025//doi.org/10.1016/j.drudis.2018.05.025

Beck, R.C.R., Chaves, P.S., Goyanes, A., et al. (2017) 3D printed tablets loaded with polymeric nanocapsules: An innovative approach to produce customized drug delivery systems. International Journal of Pharmaceutics [online], 528 (1–2): 268–279. Available from: http://dx.doi.org/10.1016/j.ijpharm.2017.05.074

Berman, B. (2012) 3-D printing: The new industrial revolution. Business Horizons, 55 (2): 155–162

Bertassoni, L.E., Cardoso, J.C., Manoharan, V., et al. (2014) Direct-write bioprinting of cell-laden methacrylated gelatin hydrogels. Biofabrication, 6 (2)

Boetker, J., Water, J.J., Aho, J., et al. (2016) Modifying release characteristics from 3D printed drug-eluting products. European Journal of Pharmaceutical Sciences [online], 90: 47–52. Available from: http://dx.doi.org/10.1016/j.ejps.2016.03.013

Bootsma, K., Fitzgerald, M.M., Free, B., et al. (2017) 3D printing of an interpenetrating network hydrogel material with tunable viscoelastic properties. Journal of the Mechanical Behavior of Biomedical Materials [online], 70: 84–94. Available from: http://dx.doi.org/10.1016/j.jmbbm.2016.07.020

Ciurczak, E. (2016) 3-D Printing: Next Step or Parallel Technique to Continuous Manufacturing? CPhI Annua. [online]. CPhI. Available from: https://ubmemeaensoprod.s3.amazonaws.com/CPHI_EUROPE/cphi_annual_rep_2016_v31.pdf

Clark, E.A., Alexander, M.R., Irvine, D.J., et al. (2017) 3D printing of tablets using inkjet with UV photoinitiation. International Journal of Pharmaceutics [online], 529 (1–2): 523–530. Available from: http://dx.doi.org/10.1016/j.ijpharm.2017.06.085

Costa, P.F., Puga, A.M., Díaz-Gomez, L., et al. (2015) Additive manufacturing of scaffolds with dexamethasone controlled release for enhanced bone regeneration. International Journal of Pharmaceutics [online], 496 (2): 541–550. Available from: http://dx.doi.org/10.1016/j.ijpharm.2015.10.055

Delalat, B., Harding, F., Gundsambuu, B., et al. (2017) 3D printed lattices as an activation and expansion platform for T cell therapy. Biomaterials [online], 140: 58–68. Available from: http://dx.doi.org/10.1016/j.biomaterials.2017.05.009

Deng, L., Deng, Y. and Xie, K. (2017) AgNPs-decorated 3D printed PEEK implant for infection control and bone repair. Colloids and Surfaces B: Biointerfaces [online], 160: 483–492. Available from: http://dx.doi.org/10.1016/j.colsurfb.2017.09.061

Economidou, S.N., Lamprou, D.A. and Douroumis, D. (2018) 3D printing applications for transdermal drug delivery. International Journal of Pharmaceutics [online], (January): 0–1. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0378517318300437

Edinger, M., Bar-Shalom, D., Sandler, N., et al. (2018) QR encoded smart oral dosage forms by inkjet printing. International Journal of Pharmaceutics [online], 536 (1): 138–145. Available from: https://doi.org/10.1016/j.ijpharm.2017.11.052

https://doi.org/10.5920/bjpharm.2018.01

Ersumo, N., Witherel, C.E., Spiller, K.L., et al. (2016) Differences in time-dependent mechanical properties between extruded and molded hydrogels. Biofabrication [online], 8 (3): 035012. Available from: http://stacks.iop.org/1758-5090/8/i=3/a=035012?key=crossref.efc71d9f00035f417696ccc538001309

Feng, C., Zhang, M. and Bhandari, B. (2018) Materials Properties of Printable Edible Inks and Printing Parameters Optimization during 3D Printing: a review. Critical Reviews in Food Science and Nutrition [online], 0 (0): 1–8. Available from: https://www.tandfonline.com/doi/full/10.1080/10408398.2018.1481823

Fina, F., Goyanes, A., Gaisford, S., et al. (2017) Selective laser sintering (SLS) 3D printing of medicines. International Journal of Pharmaceutics [online], 529 (1–2): 285–293. Available from: http://dx.doi.org/10.1016/j.ijpharm.2017.06.082

Fina, F., Goyanes, A., Madla, C.M., et al. (2018a) 3D printing of drug-loaded gyroid lattices using selective laser sintering. International Journal of Pharmaceutics, 547 (1–2): 44–52

Fina, F., Madla, C.M., Goyanes, A., et al. (2018b) Fabricating 3D printed orally disintegrating printlets using selective laser sintering. International Journal of Pharmaceutics [online], 541 (1–2): 101–107. Available from: https://doi.org/10.1016/j.ijpharm.2018.02.015

Fitzgerald, S. (2015) FDA Approves First 3D-Printed Epilepsy Drug. Neurology Today [online], 15 (18): 26–27. Available from: http://journals.lww.com/neurotodayonline/fulltext/2015/09170/FDA_Approves_First_3D_Printed_Epilepsy_Drug.11.aspx

Gebler, M., Schoot Uiterkamp, A.J.M. and Visser, C. (2014) A global sustainability perspective on 3D printing technologies. Energy Policy [online], 74 (C): 158–167. Available from: http://dx.doi.org/10.1016/j.enpol.2014.08.033

Genina, N., Boetker, J.P., Colombo, S., et al. (2017) Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: From drug product design to in vivo testing. Journal of Controlled Release [online], 268 (August): 40–48. Available from: https://doi.org/10.1016/j.jconrel.2017.10.003

Genina, N., Holländer, J., Jukarainen, H., et al. (2016) Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices. European Journal of Pharmaceutical Sciences [online], 90: 53–63. Available from: http://dx.doi.org/10.1016/j.ejps.2015.11.005

Glatzel, S., Hezwani, M., Kitson, P.J., et al. (2016) A Portable 3D Printer System for the Diagnosis and Treatment of Multidrug-Resistant Bacteria. Chem, 1 (3): 494–504

Gloria, A., Russo, T., Rodrigues, D.F.L., et al. (2016) From 3D Hierarchical Scaffolds for Tissue Engineering to Advanced Hydrogel-Based and Complex Devices for in situ Cell or Drug Release. Procedia CIRP [online], 49: 72–75. Available from: http://dx.doi.org/10.1016/j.procir.2015.07.036

Goole, J. and Amighi, K. (2016) 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. International Journal of Pharmaceutics, 499 (1–2): 376–394

Goyanes, A., Buanz, A.B.M., Basit, A.W., et al. (2014) Fused-filament 3D printing (3DP) for fabrication of tablets. International Journal of Pharmaceutics, 476 (1): 88–92

Goyanes, A., Buanz, A.B.M., Hatton, G.B., et al. (2015a) 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. European Journal of Pharmaceutics and Biopharmaceutics [online], 89: 157–162. Available from: http://dx.doi.org/10.1016/j.ejpb.2014.12.003

Goyanes, A., Chang, H., Sedough, D., et al. (2015b) Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing. International Journal of Pharmaceutics [online], 496 (2): 414–420. Available from: http://dx.doi.org/10.1016/j.ijpharm.2015.10.039

Goyanes, A., Det-Amornrat, U., Wang, J., et al. (2016a) 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems. Journal of Controlled Release [online], 234: 41–48. Available from: http://dx.doi.org/10.1016/j.jconrel.2016.05.034

Goyanes, A., Fernández-Ferreiro, A., Majeed, A., et al. (2018) PET/CT imaging of 3D printed devices in the gastrointestinal tract of rodents. International Journal of Pharmaceutics [online], 536 (1): 158–164. Available from: https://doi.org/10.1016/j.ijpharm.2017.11.055

Goyanes, A., Fina, F., Martorana, A., et al. (2017a) Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing. International Journal of Pharmaceutics [online], 527 (1–2): 21–30. Available from: http://dx.doi.org/10.1016/j.ijpharm.2017.05.021

Goyanes, A., Kobayashi, M., Martínez-Pacheco, R., et al. (2016b) Fused-filament 3D printing of drug products: Microstructure analysis and drug release characteristics of PVA-based caplets. International Journal of Pharmaceutics [online], 514 (1): 290–295. Available from: http://dx.doi.org/10.1016/j.ijpharm.2016.06.021

Goyanes, A., Robles Martinez, P., Buanz, A., et al. (2015c) Effect of geometry on drug release from 3D printed tablets. International Journal of Pharmaceutics [online], 494 (2): 657–663. Available from: http://dx.doi.org/10.1016/j.ijpharm.2015.04.069

Goyanes, A., Scarpa, M., Kamlow, M., et al. (2017b) Patient acceptability of 3D printed medicines. International Journal of Pharmaceutics [online], 530 (1–2): 71–78. Available from: http://dx.doi.org/10.1016/j.ijpharm.2017.07.064

Goyanes, A., Wang, J., Buanz, A., et al. (2015d) 3D Printing of Medicines: Engineering Novel Oral Devices with Unique Design and Drug Release Characteristics. Molecular Pharmaceutics, 12 (11): 4077–4084

Gross, B.C., Erkal, J.L., Lockwood, S.Y., et al. (2014) Evaluation of 3D printing and its potential impact on biotechnology and the chemical sciences. Analytical Chemistry, 86 (7): 3240–3253

https://doi.org/10.5920/bjpharm.2018.01

Gupta, M.K., Meng, F., Johnson, B.N., et al. (2015) 3D Printed Programmable Release Capsules. Nano Letters, 15 (8): 5321–5329

Han, B., Yun, G.Y., Boley, J.W., et al. (2016) Dropwise gelation-dehydration kinetics during drop-on-demand printing of hydrogel-based materials. International Journal of Heat and Mass Transfer [online], 97: 15–25. Available from: http://dx.doi.org/10.1016/j.ijheatmasstransfer.2016.01.030

Hirshfield, L., Giridhar, A., Taylor, L.S., et al. (2014) Dropwise additive manufacturing of pharmaceutical products for solvent-based dosage forms. Journal of Pharmaceutical Sciences [online], 103 (2): 496–506. Available from: http://dx.doi.org/10.1002/jps.23803

Hsiao, W.K., Lorber, B., Reitsamer, H., et al. (2018) 3D printing of oral drugs: a new reality or hype? Expert Opinion on Drug Delivery [online], 15 (1): 1–4. Available from: https://doi.org/10.1080/17425247.2017.1371698

Hsu, H. yun, Toth, S., Simpson, G.J., et al. (2013) Effect of substrates on naproxen-polyvinylpyrrolidone solid dispersions formed via the drop printing technique. Journal of Pharmaceutical Sciences [online], 102 (2): 638–648. Available from: http://dx.doi.org/10.1002/jps.23397

Hull, C.W. (1986) Apparatus for production of three-dimensional objects by stereolithography. US Patent 4,575,330 [online], pp. 1–16. Available from: http://www.google.com/patents/US4575330

Içten, E., Nagy, Z.K. and Reklaitis, G. V. (2015) Process control of a dropwise additive manufacturing system for pharmaceuticals using polynomial chaos expansion based surrogate model. Computers and Chemical Engineering, 83: 221–231

Içten, E., Purohit, H.S., Wallace, C., et al. (2017) Dropwise additive manufacturing of pharmaceutical products for amorphous and self emulsifying drug delivery systems. International Journal of Pharmaceutics [online], 524 (1–2): 424–432. Available from: http://dx.doi.org/10.1016/j.ijpharm.2017.04.003

Iwanaga, S., Saito, N., Sanae, H., et al. (2013) Facile fabrication of uniform size-controlled microparticles and potentiality for tandem drug delivery system of micro/nanoparticles. Colloids and Surfaces B: Biointerfaces [online], 109: 301–306. Available from: http://dx.doi.org/10.1016/j.colsurfb.2013.04.007

Jamróz, W., Kurek, M., Łyszczarz, E., et al. (2017) 3D printed orodispersible films with Aripiprazole. International Journal of Pharmaceutics, 533 (2): 413–420

Kadry, H., Al-Hilal, T.A., Keshavarz, A., et al. (2018) Multi-purposable filaments of HPMC for 3D printing of medications with tailored drug release and timed-absorption. International Journal of Pharmaceutics [online], 544 (1): 285–296. Available from: https://doi.org/10.1016/j.ijpharm.2018.04.010

Kempin, W., Domsta, V., Grathoff, G., et al. (2018) Immediate Release 3D-Printed Tablets Produced Via Fused Deposition Modeling of a Thermo-Sensitive Drug. Pharmaceutical Research, 35 (6)

Kempin, W., Franz, C., Koster, L.C., et al. (2017) Assessment of different polymers and drug loads for fused deposition modeling of drug loaded implants. European Journal of Pharmaceutics and Biopharmaceutics [online], 115: 84–93. Available from: http://dx.doi.org/10.1016/j.ejpb.2017.02.014

Khaled, S.A., Burley, J.C., Alexander, M.R., et al. (2014) Desktop 3D printing of controlled release pharmaceutical bilayer tablets. International Journal of Pharmaceutics [online], 461 (1–2): 105–111. Available from: http://dx.doi.org/10.1016/j.ijpharm.2013.11.021

Khaled, S.A., Burley, J.C., Alexander, M.R., et al. (2015a) 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. Journal of Controlled Release, 217: 308–314

Khaled, S.A., Burley, J.C., Alexander, M.R., et al. (2015b) 3D printing of tablets containing multiple drugs with defined release profiles. International Journal of Pharmaceutics, 494 (2): 643–650

Khorasani, M., Edinger, M., Raijada, D., et al. (2016) Near-infrared chemical imaging (NIR-CI) of 3D printed pharmaceuticals. International Journal of Pharmaceutics [online], 515 (1–2): 324–330. Available from: http://dx.doi.org/10.1016/j.ijpharm.2016.09.075

Kietzmann, J., Pitt, L. and Berthon, P. (2015) Disruptions, decisions, and destinations: Enter the age of 3-D printing and additive manufacturing. Business Horizons [online], 58 (2): 209–215. Available from: http://dx.doi.org/10.1016/j.bushor.2014.11.005

Kollamaram, G., Croker, D.M., Walker, G.M., et al. (2018) Low temperature fused deposition modeling (FDM) 3D printing of thermolabile drugs. International Journal of Pharmaceutics [online], 545 (1–2): 144–152. Available from: https://doi.org/10.1016/j.ijpharm.2018.04.055

Korte, C. and Quodbach, J. (2018) 3D-Printed Network Structures as Controlled-Release Drug Delivery Systems: Dose Adjustment, API Release Analysis and Prediction. AAPS PharmSciTech [online], (5). Available from: http://link.springer.com/10.1208/s12249-018-1017-0

Kurzrock, R. and Stewart, D.J. (2016) Click chemistry, 3D-printing, and omics: the future of drug development. Oncotarget [online], 7 (3): 2155–2158. Available from: http://www.oncotarget.com/fulltext/6787

Kyobula, M., Adedeji, A., Alexander, M.R., et al. (2017) 3D inkjet printing of tablets exploiting bespoke complex geometries for controlled and tuneable drug release. Journal of Controlled Release [online], 261 (March): 207–215. Available from: http://dx.doi.org/10.1016/j.jconrel.2017.06.025

Li, Q., Guan, X., Cui, M., et al. (2018) Preparation and investigation of novel gastro-floating tablets with 3D extrusion-based printing. International Journal of Pharmaceutics [online], 535 (1–2): 325–332. Available from: https://doi.org/10.1016/j.ijpharm.2017.10.037

Liaw, C.-Y. and Guvendiren, M. (2017) Current and emerging applications of 3D printing in medicine. Biofabrication [online], 9 (2): 024102. Available from: http://stacks.iop.org/1758-5090/9/i=2/a=024102?key=crossref.dbe0d751c4f233af94cfbf7cc9f80cd6

Luzuriaga, M.A., Berry, D.R., Reagan, J.C., et al. (2018) Biodegradable 3D printed polymer microneedles for

https://doi.org/10.5920/bjpharm.2018.01

transdermal drug delivery. Lab on a Chip, 18 (8): 1223–1230

Maroni, A., Melocchi, A., Parietti, F., et al. (2017) 3D printed multi-compartment capsular devices for two-pulse oral drug delivery. Journal of Controlled Release [online], 268 (August): 10–18. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0168365917308957

Martinez, P.R., Goyanes, A., Basit, A.W., et al. (2017) Fabrication of drug-loaded hydrogels with stereolithographic 3D printing. International Journal of Pharmaceutics [online], 532 (1): 313–317. Available from: http://dx.doi.org/10.1016/j.ijpharm.2017.09.003

Martinez, P.R., Goyanes, A., Basit, A.W., et al. (2018) Influence of Geometry on the Drug Release Profiles of Stereolithographic (SLA) 3D-Printed Tablets. AAPS PharmSciTech [online], pp. 1–7. Available from: http://link.springer.com/10.1208/s12249-018-1075-3

Melocchi, A., Parietti, F., Loreti, G., et al. (2015) 3D printing by fused deposition modeling (FDM) of a swellable/erodible capsular device for oral pulsatile release of drugs. Journal of Drug Delivery Science and Technology [online], 30: 360–367. Available from: http://dx.doi.org/10.1016/j.jddst.2015.07.016

Melocchi, A., Parietti, F., Maccagnan, S., et al. (2018) Industrial Development of a 3D-Printed Nutraceutical Delivery Platform in the Form of a Multicompartment HPC Capsule. AAPS PharmSciTech [online]. Available from: http://link.springer.com/10.1208/s12249-018-1029-9

Melocchi, A., Parietti, F., Maroni, A., et al. (2016) Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling. International Journal of Pharmaceutics [online], 509 (1–2): 255–263. Available from: http://dx.doi.org/10.1016/j.ijpharm.2016.05.036

Min, Z., Kun, L., Yufang, Z., et al. (2015) 3D-printed hierarchical scaffold for localized isoniazid/rifampin drug delivery and osteoarticular tuberculosis therapy. Acta Biomaterialia [online], 16 (1): 145–155. Available from: http://dx.doi.org/10.1016/j.actbio.2015.01.034

Moher, D., Liberati, A., Tetzlaff, J., et al. (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj [online], 339 (jul21 1): b2535–b2535. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.b2535

Muwaffak, Z., Goyanes, A., Clark, V., et al. (2017) Patient-specific 3D scanned and 3D printed antimicrobial polycaprolactone wound dressings. International Journal of Pharmaceutics [online], 527 (1–2): 161–170. Available from: http://dx.doi.org/10.1016/j.ijpharm.2017.04.077

Nale, S.B. and Kalbande, P.A.G. (2015) A Review on 3D Printing Technology. 2018 Advances in Science and Engineering Technology International Conferences (ASET), 2 (9): 33–36

Nasereddin, J.M., Wellner, N., Alhijjaj, M., et al. (2018) Development of a Simple Mechanical Screening Method for Predicting the Feedability of a Pharmaceutical FDM 3D Printing Filament. Pharmaceutical Research, 35 (8)

Okwuosa, T.C., Soares, C., Gollwitzer, V., et al. (2018) On demand manufacturing of patient-specific liquid capsules via co-ordinated 3D printing and liquid dispensing. European Journal of Pharmaceutical Sciences [online], 118 (December 2017): 134–143. Available from: https://doi.org/10.1016/j.ejps.2018.03.010

Okwuosa, T.C., Stefaniak, D., Arafat, B., et al. (2016) A Lower Temperature FDM 3D Printing for the Manufacture of Patient-Specific Immediate Release Tablets. Pharmaceutical Research [online], 33 (11): 2704–2712. Available from: http://dx.doi.org/10.1007/s11095-016-1995-0

Peterson, G.I., Larsen, M.B., Ganter, M.A., et al. (2015) 3D-printed mechanochromic materials. ACS Applied Materials and Interfaces, 7 (1): 577–583

Petty, J.D., Huckins, J.N. and David, A. (2002) (12) Patent Application Publication (10) Pub . No .: US 2002/0187020 A1., 1 (19)

Pietrzak, K., Isreb, A. and Alhnan, M.A. (2015) A flexible-dose dispenser for immediate and extended release 3D printed tablets. European Journal of Pharmaceutics and Biopharmaceutics [online], 96: 380–387. Available from: http://dx.doi.org/10.1016/j.ejpb.2015.07.027

Placone, J.K., Navarro, J., Laslo, G.W., et al. (2017) Development and Characterization of a 3D Printed, Keratin-Based Hydrogel. Annals of Biomedical Engineering, 45 (1): 237–248

Raman, R., Clay, N.E., Sen, S., et al. (2016) 3D printing enables separation of orthogonal functions within a hydrogel particle. Biomedical Microdevices [online], 18 (3): 1–7. Available from: http://dx.doi.org/10.1007/s10544-016-0068-9

Sadia, M., Arafat, B., Ahmed, W., et al. (2018) Channelled tablets: An innovative approach to accelerating drug release from 3D printed tablets. Journal of Controlled Release [online], 269 (November 2017): 355–363. Available from: https://doi.org/10.1016/j.jconrel.2017.11.022

Sadia, M., Sośnicka, A., Arafat, B., et al. (2016) Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. International Journal of Pharmaceutics, 513 (1–2): 659–668

Sandler, N., Salmela, I., Fallarero, A., et al. (2014) Towards fabrication of 3D printed medical devices to prevent biofilm formation. International Journal of Pharmaceutics [online], 459 (1–2): 62–64. Available from: http://dx.doi.org/10.1016/j.ijpharm.2013.11.001

Sayyar, S., Gambhir, S., Chung, J., et al. (2017) 3D printable conducting hydrogels containing chemically converted graphene. Nanoscale [online], 9 (5): 2038–2050. Available from: http://xlink.rsc.org/?DOI=C6NR07516A

Shirazi, S.F.S., Gharehkhani, S., Mehrali, M., et al. (2015) A review on powder-based additive manufacturing for tissue engineering: Selective laser sintering and inkjet 3D printing. Science and Technology of Advanced Materials, 16 (3)

Skowyra, J., Pietrzak, K. and Alhnan, M.A. (2015) Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling

https://doi.org/10.5920/bjpharm.2018.01

(FDM) 3D printing. European Journal of Pharmaceutical Sciences [online], 68: 11–17. Available from: http://dx.doi.org/10.1016/j.ejps.2014.11.009

Smith, D.M., Kapoor, Y., Klinzing, G.R., et al. (2018) Pharmaceutical 3D printing: Design and qualification of a single step print and fill capsule. International Journal of Pharmaceutics, 544 (1): 21–30

Solanki, N.G., Tahsin, M., Shah, A. V., et al. (2018) Formulation of 3D Printed Tablet for Rapid Drug Release by Fused Deposition Modeling: Screening Polymers for Drug Release, Drug-Polymer Miscibility and Printability. Journal of Pharmaceutical Sciences [online], 107 (1): 390–401. Available from: https://doi.org/10.1016/j.xphs.2017.10.021

Sommer, M.R., Alison, L., Minas, C., et al. (2017) 3D printing of concentrated emulsions into multiphase biocompatible soft materials. Soft Matter [online], 13 (9): 1794–1803. Available from: http://xlink.rsc.org/?DOI=C6SM02682F

Tagami, T., Fukushige, K., Ogawa, E., et al. (2017) 3D Printing Factors Important for the Fabrication of Polyvinylalcohol Filament-Based Tablets. Biological & Pharmaceutical Bulletin [online], 40 (3): 357–364. Available from: https://www.jstage.jst.go.jp/article/bpb/40/3/40_b16-00878/_article

Tagami, T., Nagata, N., Hayashi, N., et al. (2018) Defined drug release from 3D-printed composite tablets consisting of drug-loaded polyvinylalcohol and a water-soluble or water-insoluble polymer filler. International Journal of Pharmaceutics [online], 543 (1–2): 361–367. Available from: https://doi.org/10.1016/j.ijpharm.2018.03.057

Tappa, K., Jammalamadaka, U., Ballard, D.H., et al. (2017) Medication eluting devices for the field of OBGYN (MEDOBGYN): 3D printed biodegradable hormone eluting constructs, a proof of concept study. PLoS ONE, 12 (8): 1–17

Trenfield, S.J., Awad, A., Goyanes, A., et al. (2018) 3D Printing Pharmaceuticals: Drug Development to Frontline Care. Trends in Pharmacological Sciences, 39 (5): 440–451

Varan, C., Wickström, H., Sandler, N., et al. (2017) Inkjet printing of antiviral PCL nanoparticles and anticancer cyclodextrin inclusion complexes on bioadhesive film for cervical administration. International Journal of Pharmaceutics, 531 (2): 701–713

Ventola, C.L. (2014) Medical Applications for 3D Printing: Current and Projected Uses. P & T : a peer-reviewed journal for formulary management [online], 39 (10): 704–711. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25336867%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4189697%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4189697&tool=pmcentrez&rendertype=abstract

Verstraete, G., Samaro, A., Grymonpré, W., et al. (2018) 3D printing of high drug loaded dosage forms using thermoplastic polyurethanes. International Journal of Pharmaceutics [online], 536 (1): 318–325. Available from: https://doi.org/10.1016/j.ijpharm.2017.12.002

Wang, G., Wang, P., Zhen, Z., et al. (2015) Preparation of PA12 microspheres with tunable morphology and size for use in SLS processing. Materials and Design [online], 87: 656–662. Available from: http://dx.doi.org/10.1016/j.matdes.2015.08.083

Wang, Y., Miao, Y., Zhang, J., et al. (2017) Three-dimensional printing of shape memory hydrogels with internal structure for drug delivery. Materials Science and Engineering C [online], 84 (November 2017): 44–51. Available from: https://doi.org/10.1016/j.msec.2017.11.025

Water, J.J., Bohr, A., Boetker, J., et al. (2015) Three-dimensional printing of drug-eluting implants: Preparation of an antimicrobial polylactide feedstock material. Journal of Pharmaceutical Sciences [online], 104 (3): 1099–1107. Available from: http://dx.doi.org/10.1002/jps.24305

Weisman, J.A., Nicholson, J.C., Tappa, K., et al. (2015) Antibiotic and chemotherapeutic enhanced three-dimensional printer filaments and constructs for biomedical applications. International Journal of Nanomedicine, 10: 357–370

Whyman, S., Arif, K.M. and Potgieter, J. (2018) Design and development of an extrusion system for 3D printing biopolymer pellets. International Journal of Advanced Manufacturing Technology, 96 (9–12): 3417–3428

Wickstrm, H., Hilgert, E., Nyman, J.O., et al. (2017) Inkjet printing of drug-loaded mesoporous silica nanoparticles—a platform for drug development. Molecules, 22 (11): 1–20

Yampolskiy, M., Skjellum, A., Kretzschmar, M., et al. (2016) Using 3D printers as weapons. International Journal of Critical Infrastructure Protection [online], 14: 58–71. Available from: http://dx.doi.org/10.1016/j.ijcip.2015.12.004

Yang, Y., Wang, H., Li, H., et al. (2018) 3D printed tablets with internal scaffold structure using ethyl cellulose to achieve sustained ibuprofen release. European Journal of Pharmaceutical Sciences [online], 115 (January): 11–18. Available from: https://doi.org/10.1016/j.ejps.2018.01.005

Yuksel, A. and Cullinan, M. (2016) Modeling of nanoparticle agglomeration and powder bed formation in microscale selective laser sintering systems. Additive Manufacturing [online], 12: 204–215. Available from: http://dx.doi.org/10.1016/j.addma.2016.07.002

Zhang, J., Feng, X., Patil, H., et al. (2017a) Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets. International Journal of Pharmaceutics [online], 519 (1–2): 186–197. Available from: http://dx.doi.org/10.1016/j.ijpharm.2016.12.049

Zhang, J., Yang, W., Vo, A.Q., et al. (2017b) Hydroxypropyl methylcellulose-based controlled release dosage by melt extrusion and 3D printing: Structure and drug release correlation. Carbohydrate Polymers [online], 177 (June): 49–57. Available from: https://doi.org/10.1016/j.carbpol.2017.08.058

Zhao, J., Xu, X., Wang, M., et al. (2018) A new model of a 3D-printed shell with convex drug release profile. Dissolution Technologies, 25 (1): 24–28