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3D printed implantable drug delivery devices for women's health: Formulation challenges and regulatory perspective

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ABSTRACT

Modern pharmaceutical interventions are shifting from traditional "one-size-fits-all" approaches toward tailored therapies. Following the regulatory approval of Spritam®, the first marketed drug manufactured using three-dimensional printing (3DP) technologies, there is a precedence set for the use of 3DP in the manufacture of pharmaceutical products. The involvement of 3DP technologies in pharmaceutical research has demonstrated its capabilities in enabling the customisation of characteristics such as drug dosing, release characteristics and product designs on an individualised basis. Nonetheless, research into 3DP implantable drug delivery devices lags behind that for oral devices, cell-based therapies and tissue engineering applications.

The recent efforts and initiatives to address the disparity in women's health is overdue but should provide a drive for more research into this area, especially using new and emerging technologies as 3DP. Therefore, the focus of this review has been placed on the unique opportunity of formulating personalised implantable drug delivery systems using 3DP for women's health applications, particularly passive implants. An evaluation of the current landscape and key formulation challenges for achieving this is provided supplemented with critical insight into the current global regulatory status and its outlook.

Contents

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1. Introduction

Three-dimensional printing (3DP), also known as additive manufacturing, is an umbrella term including several manufacturing technologies where a solid structure is built by binding or depositing materials in successive layers [1]. As modern healthcare is adopting a paradigm shift from traditional "one-size-fits-all" approaches towards patient-centric care, optimal dosing and release characteristics of drug delivery must be established on an individual basis to achieve efficacious and safe therapeutic outcomes [2]. Whilst pharmacogenomics provides a driving force for designing tailored drug dose regimens and treatments based on personal clinical variables, current large batch production processes adopted by pharmaceutical manufacturers are unable to deal with individualised particularities, therefore various therapeutic gaps prevail [3,4]. Personalised dosing requires high flexibility of production processes, and the multiple steps of conventional large scale production of oral dosage forms such tablets (including milling, mixing, granulation, drying, pressing, etc) makes it difficult to cater for personalised dosing [5]. For example, it would not be possible to use conventional tablet manufacturing processes to produce duoCaplet, in which different drugs were incorporated in various configurations in a single oral product [6,7].

In recent years 3DP has demonstrated its potential in becoming a significantly disruptive technology, particularly in fabricating personalised drug delivery systems (Fig. 1) [8]. This has been demonstrated in Spritam®, a novel formulation of levetiracetam, which was the first 3DP drug to gain approval from the U.S. Food and Drug Administration (FDA) in 2015 and has set the innovation benchmark for utilising 3DP technologies in pharmaceutical development. Using a powder bed fusion technology (ZipDose®), rapidly dissolving orodispersible tablets with minimal water requirements were developed [4]. High doses of active pharmaceutical ingredients (APIs) in orodispersable tablets often present technological issues in manufacturing and quality control processes, whereas 3DP techniques enable tablets with doses of up to 1000 mg to be produced. The highly soluble form produced is beneficial amongst patients with swallowing difficulties or children, thereby promoting adherence and compliance [1,9].

Various 3DP technologies exist, which are classified into seven categories by the American Society of Testing and Materials (ASTM) based on the additive processes involved (Fig. 2) [10,11]. The initial stages of object preparation for printing are undifferentiated, which involves the design of the object using computer-aided design (CAD) software or imaging techniques, followed by the export of the developed models to stereolithography (STL) file formats. This represents the surface geometry of the desired object, which is tessellated into sets of oriented triangulated facets, providing coordinate data of each vertex position. The STL file is imported to the 'slicer' software, where the digital 3D model converts into printing instructions through many flat horizontal layers, calculating the time and the material amount required by the printer i.e., geometric code or G-code file [9,12]. Pharmaceutical research has been abundant in utilising 3DP technologies such as Fused Deposition Modelling (FDM), Selective Laser Sintering (SLS), Stereolithography (SLA) and Binder Jetting [5,11,13], which are summarised in Fig. 2 while a more extensive discussion is provided in various reviews [14,15].

Fused deposition modelling (FDM) is a frequently used, low-cost 3DP technology, where the desired object is formed by layering thermoplastic filaments [16] (Fig. 3a). Hot-melt extrusion (HME) is often coupled with FDM to produce homogenous dispersions of drug-loaded polymeric filaments [17]. On the other hand, vat photpolymerisation produces 3D objects by the curing of photo-sensitive materials (Fig. 3c) while selective laser sintering (SLS) utilises powdered material for 3DP objects. A laser is used to sinter the desired object shape onto the powder bed surface, which binds the powder particles together (Fig. 3b) [18–21]. Binder Jetting technologies precisely deposit liquid binder material across a thin and even layer of powder (Fig. 3d). Like SLS, the residual powder remains surrounding the object for support [20,22]. An ultraviolet laser or a digital light projection technique is used to cure a thin liquid resin layer into the desired pattern, where gelation occurs in the exposed polymer layer. The 3D object is further

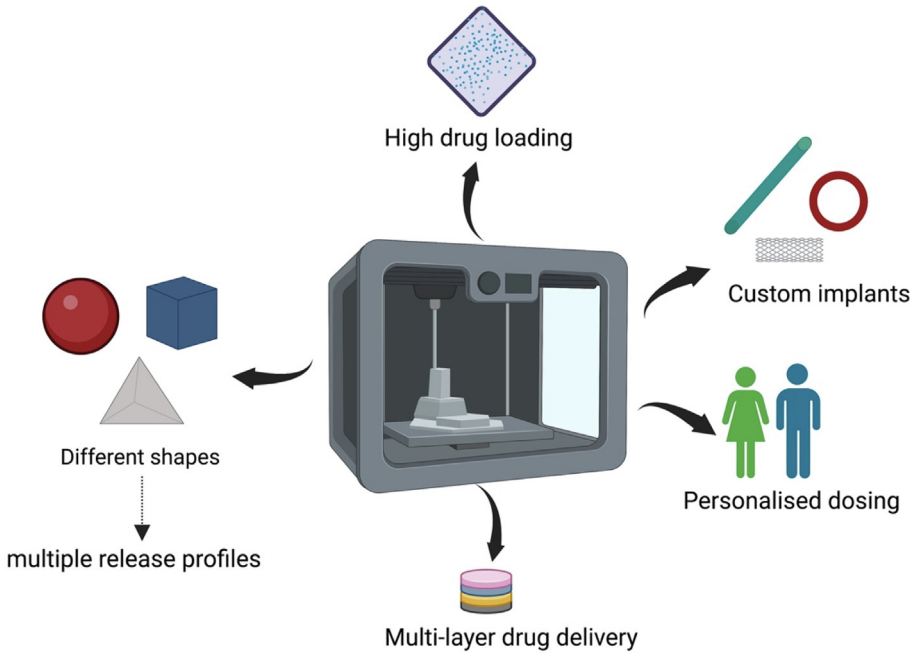

Fig. 1. An overview of the customisable characteristics offered by 3D printing technologies in drug delivery products. Based on information from Mathew et al., 2020[2] Created with BioRender.com.

Material Extrusion	• Fused deposition modelling (FDM) • Melt extrusion deposition (MED™)
Powder Bed Fusion	• Selective laser sintering (SLS), • Selective laser melting (SLM) • Direct metal laser sintering (DMLS) • Electron beam melting (EBM)
Material Jetting	• Inkjet printing • MultiJet modelling (MJM) • Drop on Demand (DOD)
Binder Jetting	• Powder bed inkjet printing • ZipDose®
Directed Energy Deposition	• Electron beam additive manufacturing (EBAM) • Laser metal deposition (LMD) • Direct metal tooling (DMT)
Vat Photopolymerisation	• Stereolithography (SLA) • Digital light processing (DLP) • Continuous layer interface production (CLIP)
Sheet Lamination	• Laminated object manufacturing (LOM) • Ultrasonic additive manufacturing (UAM) • Selective deposition lamination (SDL)

Fig. 2. ASTM Classification of the main 3DP technologies (based on information from Trenfield et al., 2019 and Bailey et al., 2016[10,30].

cured by post-printing processing to enhance the mechanical integrity and appearance of the finalised product [5,23].

Advancements in 3DP technologies and material science have contributed to the ultimate ambition of drug delivery, which is the local delivery of drugs to specific disease sites with minimal systemic effects [24]. Implantable drug delivery devices (dosage forms containing APIs within a sustained release delivery matrix) offer targeted treatments, where a protected and sustained interaction between the drug and diseased tissue occurs [25,26]. With 3DP offering the potential to personalise drug delivery implants, this allows for tailored dosage forms with sustained-release profiles to be produced for each patient [2,21].

Over the past few years alone, various review publications have discussed the need for 3DP technologies to produce patient-specific drug delivery systems. However, a few of these reviews have placed particular focus on implantable drug delivery devices exclusively [14,24] and almost none focused on applications to women's health. The application to women's health is unique in the sense that drugs are used for treatment of disease of the female reproductive organs, as well as for addressing other women's health conditions such as contraception, menopause and infertility. The disparity in women's health in general is global; according to UN Women, every day 830 women die from preventable causes related to pregnancy and childbirth globally [27]. What is more, World Health Organisation's data show the inequality in accessing essential services such as family planning (Fig. 4) [28].

Recent efforts aiming to address this legacy, such as the UK's first women's health strategy for England published in July 2022 [29] - which summarises the UK government's plan to improve the health and wellbeing of women and girls in England over the next ten years - are overdue but should provide a drive for more research for women's health, especially in utilizing new and emerging technologies such as 3DP.

Therefore, this review provides a comprehensive evaluation of 3D printed implants as drug delivery devices, and how these respond to the requirements of personalised medicine and local drug delivery in clinical condition related to women's health. Whilst 3D printed drug-loaded medical devices provide many clinical benefits, the integration of novel technologies into healthcare systems will pose several regulatory challenges. Thus, an insight into global regulatory environments will also be provided.

2. Implantable drug delivery devices and 3D printing

Implantable drug delivery devices can be broadly classified into two main categories: passive implants and active implants (Fig. 5).

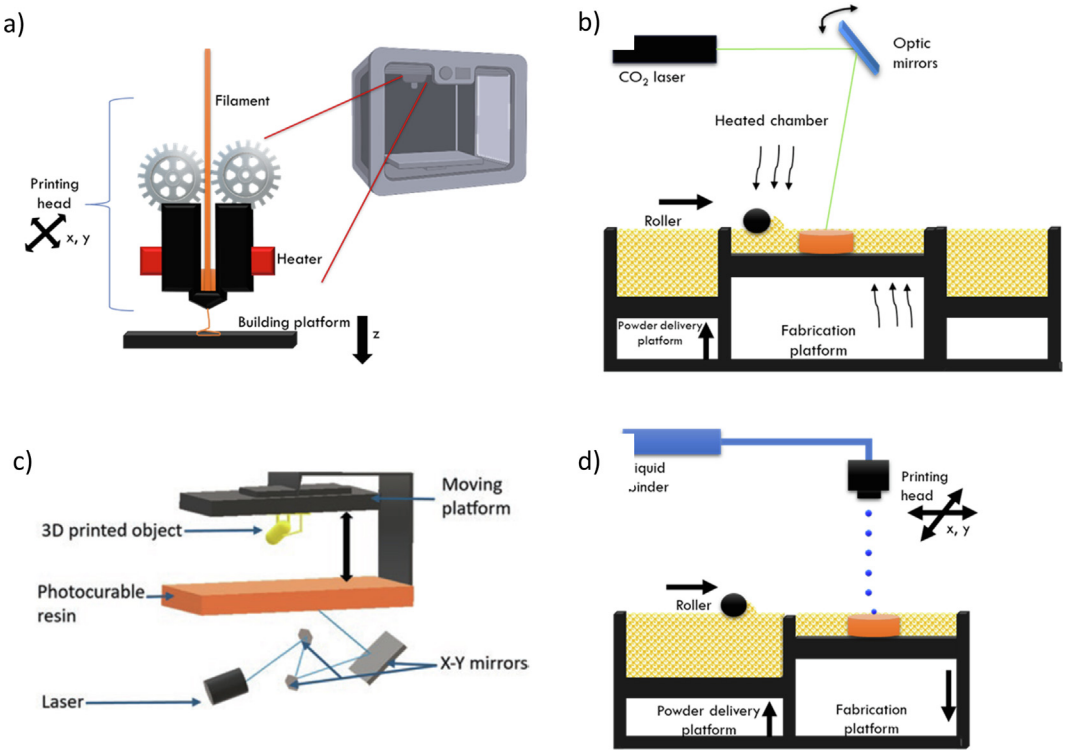

Fig. 3. Illustration of 3DP technique and their main components: a) FDM 3DP b) SLS 3DP c) Vat photopolymerisation 3DP, d) binder jetting 3DP.

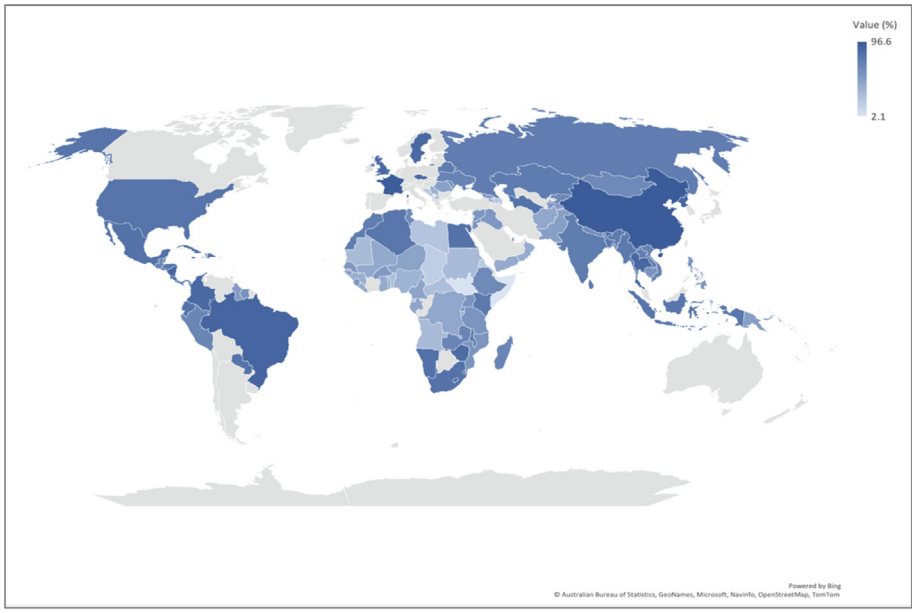

Fig. 4. Distribution of women of reproductive age (aged 15–49 years) who have their need for family planning satisfied with modern methods (based on data from Reference [28] plotted using Microsoft© Excel).

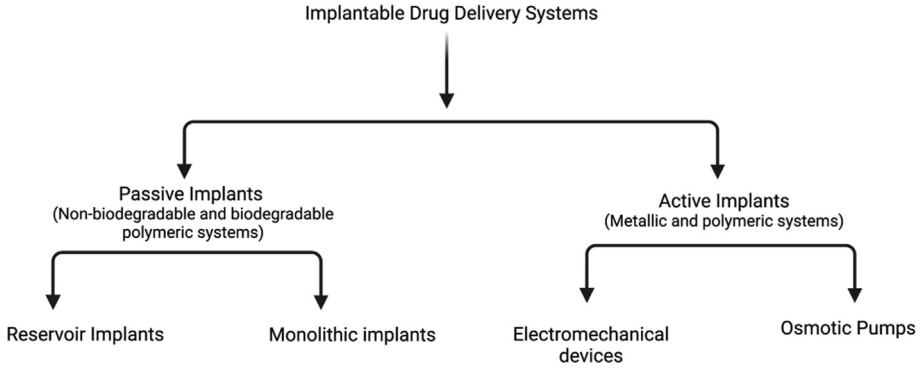

Fig. 5. A broad classification of active and passive implantable drug delivery systems. Based on information from Stewart et al., 2018[26] Created with BioRender.com.

Passive implants include both biodegradable and nonbiodegradable polymeric implants, where drug release is pre-determined. Active implants include systems relying on energy-dependent methods to control drug release. Whilst most active implants consist of metallic electronic systems, polymeric osmotic pumps are also present (consisting of a semi-permeable membrane surrounding a drug reservoir and an orifice), where drug release through the membrane occurs at a constant rate due to pressure changes [26]. Active devices require the replenishment of drugs through an access port [31]. It is noted that passive systems without the need to resupply are most commonly used while rare examples of active implants present and thus this review will focus on printing passive implants.

Regulatory classification systems, such as those implemented by the European Commission in the Medical Device Directives, classify medical devices based on parameters such as the degree of invasiveness, duration of bodily contact and whether the exerted effects are localised or systemic. This includes devices ranging from hospital beds and corrective glasses (Class I) to prosthetic heart valves and catheters (Class III), where higher classes have the highest perceived risk [32,33]. Classifying implantable drug delivery devices can be a difficult task due to the lacking presence of a medical classification system devised specifically for drug delivery devices [26].

Furthermore, international regulatory requirements differ regarding the approval, manufacture and distribution of 3D printed drug products [34]. In 2017, the FDA became the first regulator worldwide to provide technical frameworks and guidelines for manufacturers producing 3D printed medicinal products [35]. However, the European Commission still lack specific regulatory guidelines for 3DP medical devices and pharmaceuticals [36,37]. while the UK's Medicines and Healthcare products Regulatory Agency (MHRA) has become the first to announce in January 2023 the introduction of a new dedicated framework for the manufacture of innovative medicines at the point of care [38].

Passive devices are comprised of drug substances packed within a biocompatible polymer and rely on passive diffusion for drug release. 3DP technologies enable complex tailored dosage forms with sophisticated release profiles and drug-loading capacities to be formulated based on the choice of polymers, implant structure design, surface properties and drug concentrations [11,39]. A wide variety of both non-biodegradable and biodegradable polymers

have been investigated for the development of 3DP implants, including both reservoir systems and monolithic systems. However, with non-biodegradable implants, once the drug load has been fully depleted, they require invasive removal procedures by trained personnel, thereby contributing to issues surrounding patient compliance. In contrast, biodegradable implants do not require removal, as polymer degradation occurs under physiological conditions [40]. A recent review article by Utomo *et al.* [41] provide a detailed overview of the classification and material types and designs of implantable drug delivery systems.

3. Application of 3D printed implantable drug delivery devices in women's health

3.1. Current research landscape

To assess the current landscape of research involving 3D printing of implantable drug delivery devices, an electronic database search for PubMed and Web of Science was conducted using appropriate keywords and Boolean Operators. Additional words were added with every subsequent search to further limit publication search results regarding polymeric implants specifically. The search results in both databases for the combinations of keywords in the search terms are summarised in Fig. 6.

The search terms "3D print" AND "Implant" resulted in an abundance of search outcome in both databases. Articles in this category showed the most prominent application fields to be patient-specific orthopaedic implants (bone screws, plates and scaffolds) and prostheses, not for the purpose of drug-delivery. 3DP is rapidly gaining speed in the healthcare sector, particularly within the surgical and dental fields 33. As the term "implant" can include several medical devices such as orthopaedic prosthetics, artificial teeth, cochlear devices and drug delivery devices, a search exclusive to drug delivery products was required.

Results for the search terms "3D Print" AND "Drug Delivery" showed broader application categories (cell-based therapies, tissue engineering and oral drug delivery applications). Upon conducting a more exclusive search using the terms "3D Print" AND "Implant" AND "Drug Delivery", fewer articles were found, suggesting a clear gap in research surrounding implantable devices specifically for drug delivery, particularly using polymeric materials. In this category, articles published in earlier years (2015–16) mostly consisted of cell-based therapies, particularly for bone tissue engineering applications, whereas interest surrounding drug-loaded implants increased over the years, particularly after 2017. The term "additive manufacturing" was also used in the same combinations of terms and gave in lesser number of results than the term "3D Print". The term appeared to show more results with the term "implant" in Web of Science than in PubMed compared to "3D Print". The terms additive manufacturing (AM) has been reserved for industrial application of the technology and exclusively used by those in engineering or manufacturing fields while 3D printing was used for entry level types of AM such as FDM. However, the terms are used interchangeably now and that separation is not valid and related to more the preference of the user [42].

Since the approval of Spritam® in 2015, increased opportunities have been uncovered to researchers in the formulation of 3DP oral drug delivery systems. Oral dosage forms are highly conventional as they are the least invasive form of drug administration, therefore extensive research efforts have focussed on this regarding improving patient compliance. However, increased clinical opportunities in response to the needs of personalised drug therapies are emerging in research surrounding 3DP drug delivery devices.

Cancer therapies were the most suggested clinical applications for drug-eluting implants, with a wide variety of non-biodegradable and biodegradable drug delivery implants being formulated [40,43–47]. The search also uncovered results for applications to women's health, which are summarised in Table 1 and will be discussed in more details. It is noted that in both applications for cancer therapies and women's health applications, drug delivery implants are commercially available as products, including subcutaneous, intravaginal and intratumoural implants (most commonly in prostate cancer treatments and contraceptive methods) [26].

Unlike research into 3DP implantable devices for cancer applications, those suggested for women's health applications have not yet conducted in vivo studies and are therefore at the stage of proof-of-concept. Nevertheless, extended drug release profiles were demonstrated from a range of implant shapes, showing 3DP to be an applicable method in formulating custom implant designs for long-term drug delivery [48–50]. 3DP implants for women's health applications include hormonal drug delivery for both contraceptive, obstetric and gynaecologic purposes. Implantable drug delivery devices such as intrauterine systems (IUS) and subcuta-

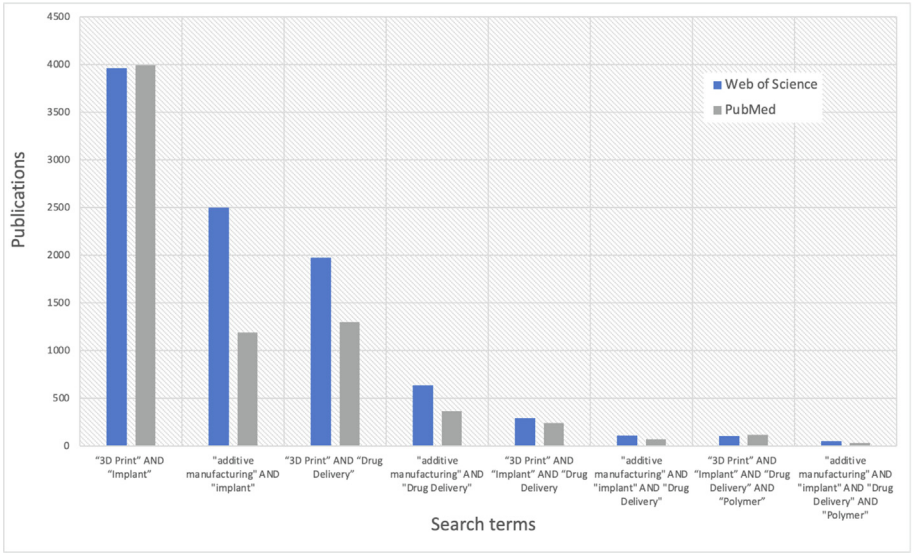

Fig. 6. Number of publications on 3D printing (2015–2022) generated from the number of articles available from Web of Science and PubMed using the indicated search terms.

Table 1
Summary of 3D printed implantable device used in women's health applications.

Implantable Device Type	Polymer(s)	API(s)	Printing Technology	Clinical condition	Reference
T-shaped IUS	EVA copolymers	indomethacin	FDM	NA (model drug)	[49]
	PCL	indomethacin	FDM	NA (model drug)	[50]
		Estrogen and/or progesterone	FDM	Obstetric and gynaecologic	[51]
	Polyethylene	Progesterone and fluorouracil	SLS	Endometrial and ovarian cancers	[53]
SR	EVA copolymers	indomethacin	FDM	NA (model drug)	[49]
SR	PCL	Estrogen and/or progesterone	FDM	Obstetric and gynaecologic	[51]
Surgical Mesh					
Pessary					
Intravaginal rings	PLA and PCL	Progesterone	FDM	Obstetric and gynaecologic	[54]
	Polyurethanes (HP-60D-35 and ATPU-75A)	Hydroxychloroquine, IgG, gp120 fragment and coumarin 6-loaded nanoparticles*	FDM	Protection against sexual transmission of HIV	[55]
	Thermoplastic Polyurethane	Dapivirine	FDM	Protection against sexual transmission of HIV	[56]
	Thermoplastic Polyurethane	Clotrimazole	FDM	Vaginal candidiasis	[57]
Cervical implant	Polyurethane	Anti-HPV protein*	LDM	Cervical cancer	[58]
Urogynecological mesh	Polyurethane	Estradiol	FDM	Pelvic floor disorders (Pelvic organ prolapse and stress urinary incontinence)	[59]
Pessary Implant	EVA or TPC	Progesterone	FDM	Obstetric and gynecologic	[60]

Not applicable (NA), Poly-L-Lactic acid (PLLA), Polylactic acid (PLA), Poly (lactic-co-glycolic acid) (PLGA), Polycaprolactone (PCL), Ethylene vinyl acetate (EVA), polyester-based thermoplastic elastomer (TPC), human immunoglobulin G (IgG), Intrauterine system (IUS), Subcutaneous rod (SR), Human papillomavirus (HPV), Low Temperature Deposition (LDM). *Loaded post-printing.

neous rods (SR) are already commercially manufactured using well-established methods, including injection moulding, extrusion and compression moulding [48]. However, these manufacturing methods produce implants in bulk, with fixed hormone dosages and shapes, therefore cannot account for individualised patient requirements [50]. According to a study from the Women's Health Initiative, clinical and biological characteristics may modify health responses to hormonal therapies, therefore optimal doses, formulations and delivery routes must be tailored on a personalised basis to remove adverse effects and unfavourable outcomes [51,52]. Utilising 3DP technologies in the manufacture of such implants enables factors including patient-specific anatomies, hormone dosages and required periods of hormone release to be accounted for, hence meeting the requirements of individualised therapies. Achieving this requires careful selection of suitable materials and formulation strategies. The key formulation challenges to developing 3DP drug-loaded devices are discussed below.

3.2. Formulation challenges

The main formulation challenges arise from the nature of the original purpose of the technology. As 3DP was initially for producing plastic models, adapting the technology to be used for incorporating pharmaceuticals continues to be a key challenge. APIs usually are sensitive to many factors such as high temperatures, visible and ultra-violet light, sheer pressure. Physical and chemical compatibility with excipients is also an important consideration when formulating pharmaceuticals. Most studies so far have focused on proof of concept that the technology can be used for loading medical devices with drugs, which is reflected in the selection of 'model drugs' in many studies. More research should be built on this to focus on using material that can be taken to the clinical testing stage. A crucial ingredient is the polymer and the main two categories of polymers used are non-biodegradable and biodegradable polymers.

3.2.1. Non-biodegradable drug delivery implants

Several studies have utilised non-biodegradable polymers in the formulation of drug delivery implants. Genina et al. investigated the use of ethylene–vinyl acetate (EVA) copolymer grades to produce IUS and SR prototypes. Hot melt extrusion (HME) was used to produce filaments loaded with 5% and 15% indomethacin, and 5 of 12 EVA copolymer grades were successfully printed at temperatures between 145 and 155 °C and 210–215 °C, respectively. Column strength and viscosity measurements showed that although EVA exhibited a lower flexural modulus and therefore increased bending characteristic in comparison to polycaprolactone (PCL), no deformation occurred during the filament loading process. EVA-5 (16% vinyl acetate content and 28 g/10 min melting index) was selected as an optimal matrix former due to its ideal melt index and molecular weight, resulting in superior printing qualities. In vitro drug release testing showed 5% indomethacin implants to have faster release than 15% indomethacin, where an initial drug burst was observed in the first 2–3 days followed by controlled release. The printed implants exhibited higher drug release than HME filaments. EVA drug release was observed to be directly proportional to the amount of amorphous and/or supersaturated drug present, where indomethacin was predicted to be in this state based on the potential amorphization of the drug due to printing temperatures being performed above its melting temperature [49].

The FDM printing process utilised temperatures exceeding indomethacin's melting point (around 162 °C), causing it to become partially amorphous and release faster than in the HME extruded filaments [49,50,61]. In response to the main constraint of the high temperature requirements of FDM, dynamic supramolecular polyurethane (SPU) has been investigated as a polymeric candidate for 3DP drug delivery implants. Due to its self-assembling ability through hydrogen bonding and pi stacking, lower temperatures are required to disassemble the polymer network for its deposition in the printing process [62].

Salimi et al. formulated SPU drug-loaded implants with varied weight percentage (wt %) SPU and polyethylene glycol (PEG) and 16 wt% paracetamol, where PEG was added as an excipient to alter the drug release rate and improve printability. A higher flexural modulus was found in SPU before the addition of PEG, where this resulted in a 20% reduction in mechanical properties due to interrupted hydrogen bonding and reduced self-assembly. Regardless, the resulting properties of SPU with PEG were still within the optimal parameter ranges to form well-defined structures. Bar-shaped

implants were successfully printed at a temperature of 100 °C, and X-ray diffraction (XRD) identified no phase transitions of paracetamol in the formulations post-printing (it remained as its most stable monoclinic form I) [62]. Implants formulations with varied weights of polyurethane and PEG showed low release levels over 7 days, with the formulation contained a higher amount of PEG showing slower drug release. However, there is an overlap in standard deviation error bars of the release profiles of the two formulations, indicating that the results may not be statistically significant as the data shown is an average of only 5 repetitions. Therefore, a limitation of this study is the lack of statistical testing to draw a valid conclusion in comparing the release profiles overall, it was predicted that full drug release would occur over 5 to 8.5 months [62]. This was significantly longer than the EVA copolymer implants, where full drug release occurred within 30 days, rendering them as unsuitable for drug release in conditions requiring controlled delivery over longer periods. Although this was not intended for a specific therapeutic application but general implantable drug delivery device, this could have been potential candidate for women's health application based on its improved mechanical properties and the tailoring possibilities of the polymer but have the limitation of limited sustained release ability.

Tiboni et al. and Welsh et al. used Thermoplastic polyurethane (TPU) to fabricate 3D printed intravaginal rings. Tiboni et al. incorporated the antifungal agent clotrimazole in TPU-based intravaginal rings at two concentrations (2 and 10 %) using HME at 190 °C. They extruded the polymer and drug mix twice to ensure homogenous distribution of the drug in the filaments. This was done by pelletising the resulted filaments from the first HME and processed them again with HME. They resulted filaments were then printed the rings using FDM at 220 °C. Only the rings with the higher drug concentration showed initial growth inhibition in anticandidal assay in agar plate. The in vitro drug release study showed a release of just over 13% of the drug after one week and the amount released was above the calculated minimum inhibitory concentration needed for Candida albicans. This was also consistent with the results from the in vitro effectiveness of 3D printed rings against the pathogen [57]. 46 On the other hand, Welsh et al. used Arburg Plastic Freeforming (APF) printing technology to fabricate their rings. In this technique thermoplastic droplet are generated at high temperatures and pressures (>300 °C and 400 bar, respectively). Nonetheless, the rings produced were made at 165 °C, which contained depivirine, a nonnucleoside reverse transcriptase inhibitor that is used in the form on vaginal rings to reduce the infection of HIV (type I) through vaginal intercourse. The drug release from rings printed with varying infill density (10, 50 and 100%) was compared with that from rings made with inject moulding, with an increased drug release as the infill decreased [56].

Koutsamanis et al. developed a new polyester-based thermoplastic elastomer (TPC) and used it to prepare implants loaded with progesterone using FDM. The loading of the printed drug-free implant was achieved by solvent immersion method using solvents such as tetrahydrofuran, dichloromethane or ethanol. The novel TPC polymer showed superior printability to EVA as shown in Fig. 7 (I and II). Although the implants were loaded with relevant drug (progesterone), the loading was done post-printing by solvent impregnation [60].

A personalised cervix tissue implant with protein release function was printed using polyurethane. An extrusion-based printing method called low-temperature deposition manufacturing (LDM) was used which allowed printing at sub-ambient temperatures of −30 to −40 °C. The implant was designed in cone-shape with hierarchical porous structures and an anti-human papillomavirus (HPV) protein was incorporated post-printing also by immersion [58].

Different to the above studies, Salmoria et al. used SLS to fabricate IUD that contain progesterone and 5-flurouracil intended for endometrial and ovarian cancers. They investigated the impact of

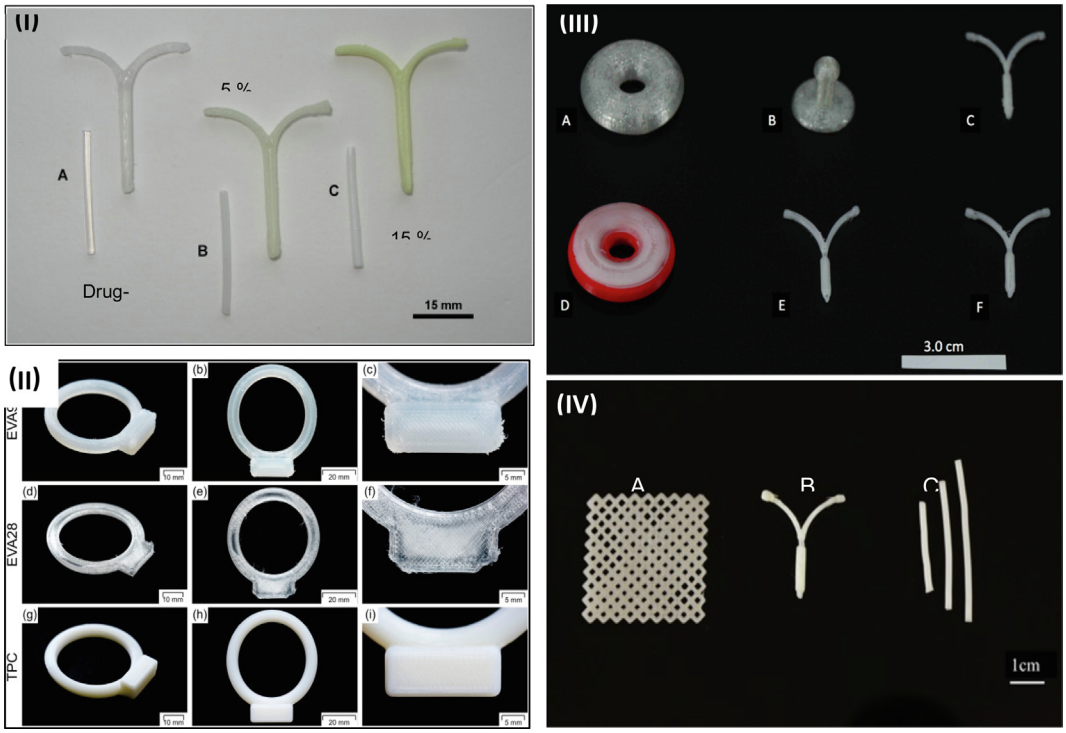

Fig. 7. (I): Images of filaments and 3D printed IUD using EVA 5: (A) drug-free, (B) and (C) 5% and 15 % indomethacin. Reproduced with permission from Genina et al., 2016 [49], Elsevier, 2023, (II): Images of 3D printed implants using FDM technology with EVA and TPC showing visible difference in the quality of the printouts (Reproduced with permission from Koutsamanis et al., 2021[60], Elsevier, 2023, (III): Images of 3D printed constructs of passerines (A, B and D) and IUD (C, E and F) and (IV): Images of 3D printed estrogen mesh (A), PCL-Progesterone IUD (B), and Subdermal implant (C). (Reproduced from Tappa et al., 2017[51] under Creative Commence Attribution Licence CC BY 4.0).

using different laser powers (to melt the polyethylene polymer powder they used) on drug release profiles. It was observed that faster drug release for both drugs was achieved with lower laser power which could be related to higher porosity produced compared to when using higher laser power. Analysis of the drug release profiles pf progesterone suggested it followed a zero-order model, which is favourable for achieving a controlled drug release [53].

The research using different polymeric materials and extrusion-based printing technologies has shown the importance of the selection of polymers based on material characteristics, as well as the compatibility of both polymer and drug melting temperatures with 3DP temperature requirements [13,48,61]. It highlights the main formulation challenge which is drug loading, which is done in most cases post-printing, and the need to demonstrate more prolonged drug release as current hormonal IUS for example last between 3 and 5 years [63].

3.2.2. Biodegradable drug delivery implants

Polycaprolactone (PCL) and polylactic acid (PLA) have been frequently investigated in the formulation of biodegradable implants. Similar to Genina et al., Holländer et al. also explored the production of indomethacin loaded IUS systems using FDM printing. 5%, 15% and 30% drug loaded PCL filaments were produced by HME; like the EVA copolymer implants produced above, the printed prototypes showed a lower degree of crystallinity than the corresponding HME filaments, hence faster drug release. Lower drug loading resulted in faster drug release, and an initial burst release phase followed by slower sustained release was observed in the filaments. This was corroborated by the scanning electron microscopy and XRD analysis; a clear impact of the amount of drug loading on solid-state properties of prototypes was observed, with recrystallisation occurring in both 5% and 15% implants on storage, therefore where slow drug release is required, higher drug loading should be chosen [50].

Another proof-of-concept study showed the applicability of estrogen and progesterone in PCL-based hormone-eluting constructs (Fig. 7 III and IV), where hormone thermal stability was retained throughout the printing process. In vitro biological activity was maintained with no apparent harmful effects of the printing process, and drug release was successful over one week, although almost half of the hormone was released with this first two days. This clearly demonstrates the benefits of customising constructs to individualised needs and anatomies using FDM printing. Nonetheless, the researchers needed to coat the PCL pallets with silicon oil to be able to disperse the hormone of the surface of the polymer pellets before extrusion [51].

It can be deduced that formulations using PLA would have shorter drug release profiles than PCL implants, therefore providing suitability in different clinical conditions depending on the required period of treatment regimens. PCL has a longer degradation time ranging from several months to years [26], and so its use in long-term women's health applications such as hormonal contraceptive delivery would be highly appropriate. The development of a biodegradable implant is yet to reach the hormonal contraceptives market, where currently available products are made of non-biodegradable materials and therefore require removal around every three years. Biodegradable polymers, PLA and poly (lactic-co-glycolic acid) (PLGA), have been widely used in FDA-approved products, such as Lupron Depot® (advanced prostatic cancer) and Zoladex® (locally confined prostate cancer), demonstrating their promising applications in drug delivery systems [25,64]. Nonetheless, a key factor in determining utilising biodegradable polymers for hormonal contraceptives would be the impact on the lack of reversibility of contraception, which is otherwise achieved by removing the implant.

In the discussed examples, various studies include application-specific implant designs incorporating APIs relating to the proposed clinical application, such as hormones for obstetric and gynaecological applications, whereas some utilise model drugs such as indomethacin. Application specific implants enable the therapeutic efficacy of implants to be determined, in turn enabling researchers to further extrapolate the clinical benefits in meeting the requirements of localised and personalised drug delivery. Research into implant formulations using nonbiodegradable and biodegradable polymers showed an immense focus on extrusion-based printing (HME with FDM). Very few studies utilising SLA printing methods to produce implantable devices (none for women's health), and drugs were loaded into printed polymer prototypes such as by soaking in drug mixtures as opposed to incorporation together via melting and extrusion [65]. However, utilising HME prior to the printing process is particularly desirable in drug delivery applications due to its ability to introduce thermostable drugs into polymers and to incorporate various mechanisms of controlled drug release [17,66].

FDM has displayed a significant price reduction since its patent expiry in 2009, and its capacity in rapidly building constructs with suitable mechanical properties and minimal post-processing steps leads to growing interests amongst drug delivery research [67,68]. Nonetheless, the main limitations of FDM would be the added pre-printing processing step of HME and the potential degradation to temperature sensitive drugs especially when exposed to hight temperature in the two steps of HME and printing. As noted with polymers used in above discussed studies, printing temperatures used with FDM ranged from 100 to 215 °C. This limits the drugs that can be incorporated using these polymers to those that are thermally stable at these temperatures and thus, excludes advanced therapeutics such as antibodies, proteins, and peptides. For examples, the two studies reviewed here that attempted loading such therapeutic agents resorted to loading them after printing of the implants [55,58].

However, recently direct powder/pellet extrusion and Melt Extrusion Deposition (MED™) printing technologies have been developed, which are single step technologies as they do not require filament preparation [69,70], although there might be some concerns regarding compromise on the resolution compared to FDM [71]. Another way to utilize 3D printing techniques that uses or generate high temperatures such as SLS can be by creating 3D printed moulds which are then used to produce drug-loaded implants. Long et al. [72] demonstrated using SLS to create nylon moulds of pessary rings, which were then used to make silicon-based estriol eluting pessaries intended to treat pelvic organ prolapse. This approach would allow for various biocompatible materials such silicon. However, formulation challenges for making these 3D printing-enabled implants would differ to those made by directly 3D printing of the drug-loaded formulations.

On the other hand, vat photopolymersiation 3D printing technology requires no pre-printing step, do not use high temperatures, has a much higher printing resolution compared to extrusion printing technologies [5] and can generate geometrically complex designs [73]. This translates into smoother surfaces of the printed objects which would reduce the risks of tissue damage and adsorption of contaminants. Although the use of this printing technology for drug-loaded drug delivery systems seems to be lagging behind that of FDM, there has been an increase in the number of studies employing the technology such as for intravesical [74] and ocular drug delivery [75]. Nonetheless, its use for women's health drug-eluting implants is very limited with such as a study using commercial acrylate-based resin to print progesterone-loaded intrauterine system [76].

More work is needed to explore the advantages of vat photopolymerisation using biocompatible materials. For example, the

formation of hydrogels by this technology could open the prospect to benefit from auxetic hydrogels. Auxetic materials exhibit the unique property of expanding laterally when stretched while densify when compressed (known as having negative Poisson ratio) [77]. Chansoria et al. [78] demonstrated a framework for a rational design of hydrogel patches with anisotropic and auxetic properties. Photo-projection printing was employed to create a new class of photocrosslinkable acrylate-based patches. The biocompatible patches had anisotropic and auxetic characteristics and were tailored to conform to the mechanics of different organs such as the lung, heart, stomach, bladder, intestines, and skin, while Tsegay et al. fabricated auxetic hydrogel for wound healing using vat photopolymersiation 3D printer [79]. Auxetic designs provide the opportunity to overcome limitations of material choice and mechanical properties of implantable devices while reduce tissue stress [78,79] and would be best suited to be employed for implantable drug-eluting drug delivery devices for women's health application.

3.2.3. Characterisation of printed implants

The variety of implantable devices that could be preprepared for women's health applications are evident even with the limited number of studies as shown in Table 1. Nonetheless, there appear to be lack of standardised tests to assess them. A summary of characterisation tests performed in the literature for 3DP implants for women's health are given in Table 2.

It can be noted that although mechanical properties are crucial for the proposed applications, there were not assessed in almost half of the studies reviewed, with tension test being the most common test. Meeting regulatory requirements remains a hurdle impeding the introduction of 3DP implantable drug delivery devices to the market due to the novelty of the manufacturing methods [5]. Successful implementation within clinical settings, research must involve the optimisation of process parameters to improve prediction of the quality of drug delivery implants. Mechanical properties of these devices are critical in preventing their failure once inside the body, which require careful selection and understanding of process parameters. Drug release from printed devices has been shown to be affected by the device designs [80] and internal structure design [25,81]. These would provide an innovative way to personalise the drug release from devices, but very limited work has been done to develop a model to relate them to drug release. Although viscoelastic properties are crucial for the proposed applications, there are either not assessed or assessed in "dry" conditions using static tests, which does not reflect conditions inside the body. Testing mechanical properties in environmentally relevant test conditions would allow for better correlation to drug release in vivo [82].

Solid-state characterisation was performed in most of the studies to evaluate the physical form of the API, using Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction (PXRD), and the thermal stability of the formulation using Thermogravimetric Analysis (TGA).

A key test is the in vitro drug release test, which was performed in all the studies. However, there are variation in how they are performed as there is no official test for testing these devices. The tests included in the British Pharmacopeia for example are limited to vaginal preparations only while there is no section for other prepa-

Table 2
Summary of tests performed for the characterisation of 3D printed devices.

Implantable Device Type	Mechanical properties	Physical properties	In vitro drug release	References
T-shaped IUS SR	NR	SEM, PXRD, DSC, IR,	Medium and volume not specified, 250 mL bottles in shaking water batch, 37 ± 0.2 °C. Metal setup to prevent floating was used. Sample size taken at each time point was not specified. Test carried out for 30 days	[49]
T-shaped IUS	NR	SEM, PXRD, DSC	Medium was 200 mL 0.9% sodium chloride in 250 mL bottles in shaking water batch (100 rpm) at 37 ± 0.2 °C. Metal setup to prevent floating was used. Sample size taken at each time point was not specified. Test carried out for 30 days	[50]
T-shaped IUS Surgical Mesh Pessary	NR	SEM, PXRD, TGA, DSC	Saline used as medium, details of volume, temperature, sample size were not provided	[51]
T-shaped IUS	Quasi-static flexural tests using DMA	SEM, DSC, IR	Phosphate buffer (pH 7.4) (20 mL) was used as medium in a horizontal shaking at 37C and 60 rpm. Sample volume and sampling intervals were not provided.	[53]
Intravaginal rings	NR but hardness was measured (using tablet hardness tester)	SEM, PXRD, DSC. TGA	Sodium dodecyl sulphate (0.25 %, 200 mL) was used as medium kept at 37 °C in a thermostat oscillator. The full medium volume was replaced every 24 h for 7 days.	[54]
	NR	SEM	Vaginal simulated fluid at pH 4.2 (5 mL) in 20-mL scintillation vials was used as medium and an incubating orbital shaker at 37 °C and 60 rpm (25 mm orbital throw). Sample size was 5 mL withdrawn every 12hrs for 14 days.	[55]
	Compression test: test speed of 2 mm/s	TGA, DSC	Water containing 0.2% Tween 80 (250, 500 or 1000 mL) were used as medium and an incubating orbital shaker at 37 °C and 100 rpm. Sample size was 1 mL withdrawn every 24hrs for 14 days.	[56]
	NR	TGA, DSC, IR	Vaginal simulated fluid with 1% sodium lauryl sulphate (100 mL) in an incubating orbital shaker at 37 °C and 100 rpm. Sample size was 1 mL withdrawn every hour for the first 6 h and then 12hrs for 7 days.	[57]
Cervical implant	- Compression test: uniaxial at loading rate of 0.5 mm/s - Tensile test: stretched at 20 mm/min at break	SEM	Medium was 15 mL phosphate buffer saline on a shaker (60 rpm) 20 h. Sample size taken at each time point was not specified.	[58]
Urogynecological mesh	Tensile test: stretched up to 200 mm at a 5 mm/s	SEM, IR, TGA	Phosphate buffer saline (pH 7.4) was used as medium, 2 mL in Eppendorf's tube kept at 37 ∘C shaking incubator (40 rpm). The meshes were removed every 24 h by removing and placed in fresh tube with fresh medium repeated over 14 days.	[59]
Pessary Implant	NR for device (tensile test for filaments)	DSC	Acetate buffer (pH 4.5) containing 1 wt-% SLS was used as Medium using incubator shaker (37 ± 0.5 ∘C and 130 rpm). Pessary was tested in 30 mL medium in glass vials Implants were tested in 400 mL in Duran® flask Sampling was performed every 24 ± 0.5 h for 28 days	[60]

Not reported (NR), Differential Scanning Calorimetry (DSC), Scanning electron Microscopy (SEM), Thermogravimetric Analysis (TGA), Powder X-ray Diffraction (PXRD), Infrared spectroscopy (IR), Intrauterine System (IUS), Subcutaneous rod (SR), Dynamic Mechanical Analysis (DMA).

rations for women's health such as intrauterine systems. The compendial tests for vaginal preparations include uniformity of dosage units, contents and mass, and dissolution. There is no specific dissolution test for vaginal preparations in the BP but instead a suitable test intended for other dosage forms such as dissolution test for solid dosage forms or dissolution test for lipophilic solid dosage forms are indicated to be used as appropriate. It is clear from the information in Table 2 the limited use of relevant simulated media for drug release studies although there have been research into the development of simulated genital tract fluids [83] including simulated uterine fluids [84]. The selected media in the reviewed studies varied from buffer solutions (phosphate or acetate) to unbuffered solutions (e.g., saline) while surfactants (tween 80 or sodium dodecyl sulphate) were added in some cases. This would particularly be important for drugs with low aqueous solubility that is affected by pH or presence of surfactants. An inconsistency in the selected volume for the release studies is also noted. For example, in the reviewed publications the volume varied from 2 mL to 1L.

These inconsistencies make comparing the release results from various studies difficult and in turn, it is challenging to deduce the impact of printing parameters on the performance of printed implants. It is critical when designing in vitro tests to consider critical factors of the clinical relevance such as fluid volume, secretion rate/discharge and composition. This is especially important for implants as they are usually intended to stay in the body for several weeks to months or years and thus require a good understanding of the impact of physiological factors on drug release. For example, when testing vaginal inserts with contraceptive, microbiocides or spermicides, it might be relevant for the test to reflect the impact of mixing vaginal simulated fluid with simulated seminal fluid. This could result in changes such as temporary shift in the pH and increase in the buffer capacity of the vaginal contents, which would influence the dissolution of drugs with solubility that is dependent on pH [83].

This is in clear contrast to studies of in vitro testing of 3D printed oral dosage forms where compendial dissolution apparatus is usually used, which allows for better understanding of various factors such as printing infill level, excipients used and internal microstructure on drug release [85]. This would not be possible for 3D printed drug-eluting implants for women's health applications if the in vitro release tests are not consistent.

It appears that a key limitation for performing relevant dissolution studies for drug-eluting implants for women's health application is the lack of suitable compendial tests. What is more, not selecting relevant dissolution medium could be due to the lack of awareness of their existent, especially that they are not yet included in the compendial tests. For example, simulated vaginal fluid was used in one study to test intravaginal devices but none of the studies for intrauterine systems used simulated intrauterine fluid. It is noted that vaginal preparations are mentioned in pharmacopoeias although not the specific details of the drug release test.

A recent critical review by Deon et al. [85] provides a comprehensive evaluation of characterisation techniques and approaches used to study 3D printed oral dosage forms. It reveals the various tests and techniques that can be applied 3D printed implants and demonstrates how using consistent testing conditions allowed to draw better conclusions relating printing parameters and techniques to the performance of the printed dosage forms.

3.3. Regulatory perspectives

Whilst 3DP technologies are becoming increasingly utilised in the manufacture of medical devices, its use is still widely underdetermined for producing custom drug delivery devices. Meeting regulatory requirements remains a hurdle impeding the introduction of 3DP implantable drug delivery devices to the market due to the novelty of the manufacturing methods [5].

An important consideration in product development is whether the product would be administered to a single patient or a group of patients. This would impact design considerations and printing processes. If commercial-scale manufacturing levels are implemented, then traditional manufacturing standards (chemistry, manufacturing and control (CMC) standards in the U.S., good manufacturing practice (GMP) in the UK and EU, are applied, therefore every dosage form unit must be identical in the formulation and required to meet target shelf-life specifications [34,86]. However, as seen in the literature reviewed above, the main benefits of applying 3DP technologies to this novel drug delivery approach are the ability to produce devices with individualised dosage and release requirements, therefore presenting difficulties in establishing uniform quality standards and tracking largely variable product data [47].

Although the approval of Spritam® has represented a breakthrough in the vision of 3DP as a pharmaceutical manufacturing method, its production is done in fixed-dose units, and therefore is not intended to be a fully personalised product. Such is the case of Triastek's T19 and T20 3D printed drug products, which are delayed release tablet aimed for the treatment of rheumatoid arthritis and cardiovascular disorders, respectively. T19 is fabricated using Melt Extrusion Deposition (MED™) 3D printing technology and composed by three different layers that allow a delayed release mechanism to act as a chronotherapeutic delivery system. T19 was granted Investigational New Drug (IND) approval from the U.S. FDA in early 2021 and T20 earlier this year [87], however, just as in the case of Spritam, T19 and T20 take advantage of the fabrication method to achieve a modified release, rather than meeting individual patient needs [1,34].

The regulatory approval for personalised implantable drug delivery devices and dosage forms would have to cover additional aspects to ensure the quality, safety and efficacy of these products, particularly when they are manufactured at the point of care (PoC). PoC can be informally defined as just-in-time creation of 3D printing of diagnostic anatomic model, instrument for surgery, patient medical imaging at the place of patient care or health care organisation owned facility [88]. In this regard, regulatory bodies are working towards the standardisation of guidance to regulate personalised devices produced by 3DP technologies.

The U.S. FDA is actively exploring 3DP in their Emerging Technology Team to promote the regulatory evaluation of innovative technologies, which may help to bridge the gap between the formal requirements of regulatory policies and their implementation in practice. In 2016, the agency issued the "Technical considerations for additive manufactured medical devices" draft guidance which covered initial thoughts on the technical considerations for 3DP processes, as well as recommendations for the characterisation, testing and premarket submissions of devices fully or partially manufactured by a 3DP technology, or that have at least one 3D printed component in them [89]. It is important to mention that the FDA has clarified in workshops and reference guidelines that the agency does not regulate raw, final printing or any printing process for the purpose of 3DP but specific devices for specific clinical indication [90].

A discussion paper was also produced last year by the U.S. FDA Centre for Devices and Radiological Health (CDRH) to discuss device safety, effectiveness and to identify challenges of 3D printed medical devices at the point of care (PoC) [91]. Similarly, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK launched the "Consultation on Point of Care manufacturing" to request input for a draft regulatory framework for medicinal products manufactured at the point of care, including those

fabricated using 3DP. The consultation aims to identify the required regulatory changes to enable the use of innovative technologies in the fabrication of new therapies [92].

Likewise, Health Sciences Authority (HAS), Singapore produced a guidance document "Regulatory guideline for 3D printed medical devices" in July 2021 with the objective of clarification for 3D printed medical devices as well as regulatory approach and regulatory requirement for these devices [93]. In March 2020, the International Medical Device Regulators Forum (IMDRF) published a document titled "Personalized Medical Devices-Regulatory Pathways". The document provides a harmonized approach for application of existing regulatory pathways to medical devices that are intended for a particular individual and to identify special considerations for the regulation of each identified category of personalised medical device [94].

Technical aspects that should be considered by a quality system for 3D printed medical devices are covered by the U. S. FDA's Technical Considerations for Additive Manufactured Medical Devices guidance. Each step in the printing process must be clearly identified, as well as the critical manufacturing steps, process parameters and output specifications. However, since the additive manufacturing technologies are different in the nature of raw materials, processing, and final object, the applicable appropriate considerations per each technology should be determined and justified to ensure their fit of purpose [89].

The UK's MHRA new framework for POC manufacturing announced at the start of 2023 [38] following the public consultation conducted in 2021 paves the way for developing the needed legislation to implement the framework allowing for easier manufacturing of innovative highly personalised medicines such as those produced by 3DP near the made near the patient, providing quick access to such interventions.

In summary, 3DP at the PoC would be a promising tool to manufacture personalised medical devices to meet individual needs and increase patient compliance, as well as to improve clinical outcomes, however, regulations need to be established relatively soon to keep pace with the latest technology developments. The regulatory frameworks must ensure the safety, quality and efficacy of the patient-tailored devices which at the same time present the big challenge as described in this review due to the novelty of the 3DP technologies applied in this field.

4. Conclusion and future directions

Despite growing interests in formulating drug delivery devices using 3DP, there is a clear gap in the research of implantable drug delivery devices for women's health applications in comparison to oral drug products and drug-free medical devices. Nevertheless, the latest research achievements of novel drug delivery implant formulations have shown the unprecedented abilities of 3DP in meeting the clinical needs of localised drug delivery and individualised patient requirements. In the prominently suggested applications of women's health, research has successfully shown the capabilities of 3DP in producing implants with customised designs, drug loading efficiencies and controlled release profiles. Extrusion-based printing methods have shown promising applications in the manufacture of non-biodegradable and biodegradable drug delivery implants, where investigations utilising different polymers have demonstrated variable controlled drug release profiles. These findings can be supplemented to the suitability of different implants in a range of clinical conditions and required treatment lengths. Despite the formulation achievements of 3DP observed so far, regulatory challenges must be overcome to fully explore its potential in pharmaceutical manufacturing of customised and innovative implantable dosage forms.

For successful implementation of 3DP implantable drug delivery devices within clinical settings, future research must go beyond investigations surrounding the design, drug loading and release characteristics to involve more defined therapeutic uses. Standardised in vitro tests are needed along with conducting in vivo studies on the safety and efficacy of such devices. Using drugs typically used in the treatment of the suggested clinical application is also needed to demonstrate the suitability of the selected printing technology and formulation for any study. It is noticed that formulation of 3DP drug delivery systems for women's health lacks behind other clinical applications. For example, smart and functionalised materials have not been investigated yet while the use of machine learning to optimise formulation and design has not been explored in opposite to 3DP oral drug delivery systems.

Future perspectives also include the optimisation of process parameters to improve the pharmaceutical quality of drug delivery implants. The lack regulatory guidelines for 3DP as a pharmaceutical manufacturing method remains a significant obstacle to its industrial application. However, the newly announced framework for POC manufacturing by the UK's MRHA and the working document of the U.S FDA provides a move in the right direction to facilitate commercialisation of 3DP drug delivery systems.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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