Universidade de Lisboa
Faculdade de Farmácia

Drug delivery systems obtained by 3D-printing

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Monografia orientada pela Professora Doutora Ana Francisca de Campos
Simão Bettencourt, Professora Associada com Agregação

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Resumo

Desde a sua introdução no final do século XX, a impressão tridimensional (3D) tem sido objeto de contínua compreensão e aperfeiçoamento, o que resultou num aumento significativo da robustez e credibilidade desta tecnologia. Dadas as suas aplicações em vários domínios da medicina, incluindo a ortodontia e a ortopedia, tem-se verificado um interesse crescente na sua implementação na indústria farmacêutica. O potencial para uma manipulação mais precisa de diferentes materiais é considerado uma mais-valia, tornando esta tecnologia particularmente atrativa particularmente no contexto da investigação e fabrico de sistemas de veiculação de fármacos. Adicionalmente, um benefício importante da impressão 3D é a possibilidade de desenvolver sistemas precisos e personalizados que consigam ultrapassar os desafios de formulação. Estes sistemas podem simplificar casos de polimedicação, promover a adesão dos doentes ao tratamento, aumentar a eficácia terapêutica e reduzir os efeitos adversos.

Esta revisão procurou fornecer uma visão abrangente sobre os vários aspetos da produção de sistemas de veiculação de fármacos utilizando a impressão 3D. Foram analisadas as vantagens e desvantagens desta tecnologia inovadora na indústria farmacêutica, incluindo uma visão geral dos métodos de impressão mais utilizados, dos biomateriais apropriados e dos compostos mais promissores.

Os estudos revistos foram agrupados de acordo com a escala dimensional (nano, micro e macroescala), apresentando exemplos de diferentes aplicações terapêuticas e formas farmacêuticas. As substâncias ativas mais promissoras na produção de sistemas de libertação de fármacos por impressão 3D foram também consideradas, com destaque para os antibióticos, dada a importância desta classe farmacológica e a necessidade de controlar os seus perfis de libertação. Em cada secção, foram identificadas as principais caraterísticas dos estudos, com o objetivo de fornecer uma fonte de referência que facilite a consulta das publicações por outros investigadores e permita a identificação de novos campos de investigação. Além disso, foi realizada uma análise das aplicações futuras desta tecnologia, incluindo uma avaliação das potenciais implementações a curto prazo e dos desafios que possam surgir.

Palavras-chave: Impressão 3D; Sistemas de libertação de fármacos; Antibióticos; Microagulhas; *Scaffolds.*

Abstract

Since its initial introduction at the end of the 20th century, the three-dimensional (3D) printing has been the subject of ongoing understanding and refinement, which has resulted in a significant increase in robustness and credibility of this technology. Given its applications in various fields of medicine, including orthodontics and orthopedics, there has been a growing interest in its implementation in the pharmaceutical industry. The potential for more precise manipulation of robust biomaterials is seen as an added value, making this technology particularly attractive in the context of research and development of drug delivery systems. Additionally, an important benefit of 3D-printing is the ability to develop accurate and personalised systems that can overcome certain formulation challenges. These systems can simplify cases of polypharmacy, enhance patient adherence to treatment, increase therapeutic efficacy, and reduce adverse effects.

This review aimed to provide a comprehensive overview of the various aspects of the production of drug delivery systems using 3D-printing. The advantages and disadvantages of this innovative technology in the pharmaceutical industry have been outlined, along with an overview of the most commonly used printing methods, suitable biomaterials, and the most interesting compounds.

The reviewed studies were grouped according to dimensional scale (nano-, micro- and macroscale), presenting examples of different therapeutic applications and pharmaceutical forms, which are also presented in summary tables. The most promising active substances for the production of drug delivery systems by 3D-printing were also considered, with a particular focus on antibiotics, given the importance of this pharmacological class and the need to control their release profiles. In each section, the main characteristics of the studies were identified, with the aim of providing a reference source that facilitates the consultation of publications by other researchers and allows for the identification of new areas of investigation.

Furthermore, an analysis of the prospective applications of this technology has been conducted, including an evaluation of potential near-term implementations and the challenges that may arise.

Keywords: 3D-printing; Drug delivery systems; Antibiotics; Microneedles; Scaffolds.

Abreviaturas

3D	Three-dimentional
API	Active pharmaceutical ingredient
BCP	Biphasic calcium phosphate
CIJ	Continuous Inkjet
DDS	Drug delivery system
DOD	Drop-on-Demand
DWA	Direct write assembly
EBM	Electron beam melting
FDA	Food and Drug Administration
FDM	Fused Deposition Modeling
HA	Hidroxyapatite
HME	Hot Melt Extrusion
HPMC	Hydroxypropyl methyl cellulose
MH	Minocycline
MN	Microneedle
MNA	Microneedle array
PA12	Polyamide 12
PCL	Poly(ε-caprolactone)
PEG	Polyethylene glycol
PLA	Polylactic acid
PLGA	Poly(lactic-co-glycolic) acid
PU	Polyurethane
PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone
SLA	Stereolithography
SLM	Selective laser melting
SLS	Selective laser sintering
SPIONs	Superparamagnetic iron oxid nanoparticles
SSE	Semi-solid extrusion
U.S.	United States
UV	Ultraviolet

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1 Introduction

1.1 Drug delivery systems

A drug delivery system (DDS) is defined as a formulation or device that allows an active substance to be introduced into the body for therapeutic purposes, with the objective of improving efficacy and safety or performance by controlling the rate, time and site of drug release (1). The objective of drug delivery is to modify the pharmacokinetics and specificity of the drug by developing a formulation comprising different excipients, carriers and devices. This significantly improves the bioavailability and duration of action of the drug in the body, thereby enhancing its therapeutic effect (2).

Additive manufacturing, otherwise known as three-dimensional (3D) printing, is emerging as a pivotal technology in the development of novel drug delivery systems. It enables precise and personalized manufacturing, which in turn facilitates the simplification of polymedication cases, the promotion of patient cooperation, an increase in efficacy, and a reduction in adverse effects (3,4). This technology has the potential to transform the fields of medicine and drug delivery. Since the U.S. Food and Drug Administration (FDA) approved the first 3D-printed tablet, Spritam®, there has been a notable increase in interest in utilising this technology for drug delivery and biomedical applications. These developments bring us closer to the realisation of personalised medicine, which challenges the traditional 'one size fits all' approach (5).

1.2 3D-printing methods

A variety of 3D-printing techniques have emerged that may be applicable to the fabrication of DDSs. These methods entail the deposition of material or substrate through the use of computer-aided design software to achieve the desired outcome. The most prevalent techniques include:

- inkjet system;
- extrusion system;
- laser system.

A comprehensive overview of the fundamental aspects of 3D-printing techniques is presented in Table 1.

Table 1 – Overview and examples of applications and type of biomaterial of some 3D-printing technologies

(Adapted from: (6–23))

3D-Printing Technology		Overview	Applications	Biomaterial
Inkjet-Based	Drop-on-Demand	Ejects droplets only when needed using actuators (thermal or piezoelectric).	Additive manufacturing for complex structures Bioprinting cells and biological materials.	Hydrogels Ceramics Bioinks
	Continuous Inkjet	Continuously ejects a stream of ink droplets, directing or recycling them.	Applying drug coatings Orodispersible films for personalized drug delivery	Hydrogels Thermoplastics
Extrusion-Based	Fused Deposition Modeling	Extrusion of thermoplastic filament through a heated nozzle, printing layer by layer	Drug-loaded implants and stents Sustained-release drug formulations	Thermoplastics
	Hot Melt Extrusion	Heating a material until it melts and extruding it through a nozzle	Sustained drug release systems Implants	Thermoplastics Drug-polymer blends
	Semi-Solid Extrusion	Extruding materials in a semi-solid state, often with a syringe-based system	Biomedical implants Tissue scaffolds	Bioinks Pastes and gels
Laser-Based	Selective Laser Sintering	Uses a laser to sinter powdered material layer by layer Commonly used to create durable and functional parts	Biodegradable implants with controlled drug release Scaffolds for tissue engineering with loaded drugs	Ceramics Polyamide Metals
	Stereolithography	Uses a UV laser to cure liquid resin into hardened plastic layer by layer. Known for high precision and smooth surface finish.	Highly detailed drug delivery microdevices Microneedles for transdermal drug delivery	Photopolymers Ceramics

Subsequently, the techniques that are more frequently used in reviewed papers will be next detailed.

1.2.1 Inkjet systems

Inkjet systems have emerged as a key technology in the domain of 3D-printing, particularly in the context of DDS. This printing technique involves the deposition of tiny droplets of a material in a controlled manner to create a three-dimensional object, allowing for precision and versatility in the fabrication of intricate drug delivery structures due to its high resolution and capacity for precise control over the deposition of bioactive substances (6,7). Inkjet technology is applicable to a number of printing techniques, including Drop-on-Demand (DOD) and Continuous Inkjet (CIJ).

In DOD, droplets are ejected only when necessary, which makes the system less rigid in terms of ink requirements. The droplets are ejected from a reservoir through the nozzle by acoustic pulses that are thermally or piezo-electrically generated (8). CIJ technology involves the pumping of ink through a nozzle to form a liquid jet, with the droplets being controlled through the periodic introduction of perturbations to the jet that overcome the liquid surface tension. This results in the generation of a continuous stream of liquid drops, even in the absence of a printing requirement (9,10).

1.2.2 Extrusion systems

Extrusion-based three-dimensional printing represents a further noteworthy technology in the field of drug delivery system development. The versatility of this method is evidenced by its extensive use, which is attributable to its capacity to accommodate a diverse range of biomaterials, including thermoplastics, hydrogels, ceramics, and bioinks. This adaptability renders it an optimal choice for the fabrication of intricate drug delivery structures (11,12). There are numerous extrusion-based printing techniques, with the most prevalent being Fused Deposition Modeling (FDM), Hot Melt Extrusion (HME), and Semi-Solid Extrusion (SSE) (13). Despite their differences in extrusion biomaterials and conditions, these techniques adhere to a similar fundamental premise.

FDM is a method that entails the continuous deposition of a heated and extruded filament material, which is then built up layer by layer to create the desired product. HME is the only reliable technique for drug incorporation into filaments for FDM (14). In HME materials at the required temperature are pumped with rotating screws on a shaft through an extruder barrel, then the mixture is passed through a die extruding and printing the desired product (14,15). SSE involves the sequential deposition of layers of gel or paste and in comparison, with other extrusion-based technologies, employs low printing temperatures (16).

1.2.3 Laser based systems

Laser-based 3D-printing employs the use of a high-energy light source, namely a UV laser beam, which is focused on the surface of the material in order to form the layers that comprise the 3D shape. Two distinct categories of laser-based 3D-printing techniques are based on the principles of liquid and powder solidification. The two main techniques are stereolithography (SLA) and selective laser sintering (SLS) (17). These technologies employ laser beams to selectively harden or fuse biomaterials in a layer-by-layer process, thereby forming solid structures.

SLA employs the use of photopolymerizable biomaterials, which undergo a solidification process upon exposure to light, particularly UV light (18). In this manner, the high energy cures and solidifies the resin by polymerizing the liquid and forming a solid layer. Thereafter, the reservoir containing the liquid resin is lowered to allow the laser to form the subsequent layer, thus building the 3D shape. This process is repeated until the result is achieved (17,19,20).

SLS can be used to print metal, plastic, and ceramic with a high degree of detail, which is dependent on the precision of the laser and the fineness of the powder. This enables the creation of structures with a high level of detail and delicacy (21,22). The laser serves as the power source, selectively fusing the powdered material through the scanning of cross-sections generated from a 3D digital description of the part on the surface of a powder bed. Following the scanning of each cross-section, the powder bed is lowered by one layer thickness, and a new layer of material is applied on top. This process is repeated until the desired structure is complete, resulting in a solid object (23).

1.3 Characteristics and impact of 3D-printed drug delivery systems

1.3.1 Benefits and advantages

As this is a highly promising technology, it is important to highlight its advantages for both the pharmaceutical industry and individual patients. A variety of advantages are enumerated and subsequently summarized in Table 2.

The use of 3D-printing systems on an industrial scale presents a plethora of advantages. From an economic standpoint, this technology is advantageous despite the initial setup costs. The affordability and simplicity of 3D-printing systems significantly enhance the efficiency of DDS, accelerating production timelines (12). It is noteworthy that the reduced necessity for manual labor serves to minimize operational costs, thereby rendering it a cost-effective solution (24). Furthermore, the intrinsic precision of 3D-printing technology mitigates the probability of human error during production (25).

The additional benefit of the decentralized nature of 3D-printing is that products can eventually be manufactured closer to their point of consumption or on-site, for example in pharmacies or hospitals, which improves access to medications. This could facilitate the production of drugs on an as-needed basis, obviating the necessity for large-scale manufacturing, reducing waste, and optimizing resources through the precise deposition of material. A reduction in storage and transportation costs could result in a concomitant reduction in environmental impact (24).

Furthermore, the production of pharmaceutical forms can be tailored with precise doses to specific needs, including various shapes, sizes and intricate drug geometries, which are difficult to achieve with traditional manufacturing methods. The combination of multiple drugs into a single dosage form is also a highly attractive proposition, particularly in the context of complex treatment regimens. The possibility of printing multiple layers for combination therapies or sequential release represents a significant advantage (2). Such a system has the potential to simplify the administration of medication, thereby improving patient adherence and compliance, particularly in the case of pediatric, geriatric, or chronically ill patients.

3D-printing, due to its increased customization, enhances drug bioavailability and is compatible with formulations of DDS with precise control over drug release kinetics (such as immediate, delayed, or extended release) and specific target areas. Another favorable aspect is the reduction of systemic exposure, which can minimize adverse effects (26).

Moreover, the automation and computerization of 3D-printing technologies streamline production, quickening the development and testing of new drug formulations and delivery systems, allowing for the rapid prototyping and speeding up possible modifications or adjustments to drug designs without the need for extensive retooling (25,27).

Currently, 3D-printing technology is going beyond traditional manufacturing. Researchers are exploring groundbreaking avenues, aiming to produce organs with patient-specific characteristics, revolutionizing the field of healthcare (28).

In conclusion, the seamless integration of 3D-printing technology in industrial processes not only optimizes production efficiency and reduces costs but also unlocks a realm of possibilities in customization, healthcare, and job creation, heralding a new era of innovation and progress.

Table 2 - Advantages of 3D-printing in the pharmaceutical field

(Adapted from: (2,12,24–28))

Category		**Advantage**
Customization and Personalization	Personalized Dosage	Tailored medications to each patient needs, ensuring precise dosage and improved therapeutic outcomes
	Complex Drug Release Profiles	Design drugs with specific release patterns, such as immediate, delayed, or extended release
Enhanced Drug Efficacy and Safety	Improved Bioavailability	Customizable drug forms can enhance the bioavailability of medications
	Reduced Side Effects	Minimized adverse effects by controlling drug release rates and targeting specific areas
	Minimize Errors	Precision of 3D-printing technology reduces the probability of human error during production
Innovative Applications	Complex Geometries	Creation of elaborated drug geometries difficult to achieve with traditional manufacturing methods
	Multi-Layered Structures	Capability to print drugs with multiple layers for combination therapies or sequential release
	Combination Therapies	Combine multiple drugs into a single dosage form, improving patient adherence to complex treatments
	Targeted Delivery	Targeted drug delivery systems, reducing systemic exposure and focusing treatment on specific sites

Table 3 - Advantages of 3D-printing in the pharmaceutical field (cont.)

Category	Advantage	
Cost Efficiency and Waste Reduction	On-Demand Production	Reduction in waste and cost by producing drugs as needed, eliminating the need for large-scale manufacturing and storage
	Material Efficiency	Precise deposition of biomaterials minimizes waste and optimizes resource usage
	Manual Labor	Reduced requirement for manual labor minimizes operational costs
Rapid Prototyping and Production	Accelerated Development	Quicker development and testing of new drug formulations and delivery systems
	Flexibility in Design	Easy modifications and adjustments to drug designs without the need for extensive retooling
Accessibility and Convenience	Remote Manufacturing	Potential for localized or on-site drug manufacturing in pharmacies or hospitals, improving access to medications
	Ease of Use	Simplified administration and improved compliance, especially for pediatric, geriatric, or chronic patients

1.3.2 Disadvantages and challenges

While 3D-printing offers numerous advantages for drug manufacturing, such as personalized dosages and complex formulations, it also presents several disadvantages and challenges listed below and summarized in Table 3.

The adoption of 3D-printing technology poses a threat to traditional manufacturing jobs due to reduced labor costs and workforce demand, potentially leading to a decline in job opportunities and consequently increased unemployment, resulting in economic slowdown (28). In addition, implementing 3D-printing in pharmaceutical production requires expertise in both pharmaceutical science and additive manufacturing, requiring training personnel and establishing robust manufacturing processes that can be time-consuming and resource-intensive (29,30).

3D-printing also offers flexibility in producing personalized or small-batch medications, but scaling up production for mass manufacturing may be challenging due to constraints such as printing speed and equipment capacity (27,31). Ensuring consistent quality and efficacy, as well as chemical and physical stability of 3D-printed drugs across different batches, during and after production is also challenging due to variability in printing processes (32).

The availability of compatible raw biomaterials for 3D-printing is also an obstacle. Currently, there are few suitable bioprinting biomaterials presenting excellent bioprintability, biocompatibility and desired mechanical and degradation properties, being challenging to ensure that 3D-printed drugs are bioavailable and effective when administered (33,34). Achieving precise and predictable release profiles with this technology is also desirable, requesting further research and development alongside with investigation of suitable polymers and other biomaterials.

Another issue with the advancement of 3D-printing technology, is the risk of copyright infringement through the production of counterfeit products or replicas, posing significant security threats. This could lead to a surge in cases of intellectual property violations, posing challenges for legal frameworks and enforcement agencies (35). Besides, the lack of more clear guidelines, weakens the regulatory landscape, leading to uncertainties, delays in approval processes and possibly intellectual property disputes (30,36,37). Contributing for a complex and time-consuming process, with concerns around the consistency and quality of 3D-printed medications (38).

In summary, while 3D-printing technology offers numerous benefits, including increased efficiency and customization, it also presents challenges and concerns related to employment, production limitations, material constraints, copyright infringement, regulatory aspects and the production of hazardous items. Addressing these challenges will be essential to achieve the full potential of 3D-printing while mitigating the risks.

Table 4 - Disadvantages and challenges of 3D-printing technology

(Adapted from: (30,36–40))

Category		**Challenge**
Legal and Regulatory	Regulatory Approval	Regulatory landscape for 3D-printed drugs with unclear guidelines and approval processes
	Quality Control	Difficult to guarantee quality, safety and effectiveness consistently between batches
	Intellectual Property	Complex patent landscape and potential for intellectual property disputes

Table 3 - Disadvantages and challenges of 3D-printing technology (cont.)

Category		Challenge
Technical Limitations	Material Limitations	Limited availability of biomaterials suitable for drug printing and biocompatible
	Precision and Reproducibility	Precise dosage and consistent reproducibility in each print batch is technically demanding
	Drug Stability	Guaranteeing chemical and physical stability of drugs during and after the printing process
Economic and Production	High Initial Costs	Significant initial investment for 3D-printing equipment, technology and professional expertise
	Scalability	Difficulty in scaling up production from lab-scale to industrial-scale while maintaining cost-effectiveness and efficiency
	Production Speed	Slower production rates compared to traditional mass manufacturing techniques
Pharmacokinetic and Pharmacodynamic	Drug Release Profiles	Designing drugs with precise and predictable release profiles requires extensive research and development
	Bioavailability	Ensuring that 3D-printed drugs are bioavailable and effective when administered
Ethical and Social Concerns	Ethical Use	Potential for misuse of 3D-printing technology to produce illicit drugs or counterfeit medications
Supply Chain and Distribution	Logistics	Establishing a supply chain for raw biomaterials and distribution can be complex
	Storage and Handling	Ensuring proper storage and handling of 3D-printed drugs to maintain their integrity and efficacy

1.3.3 Biomaterials and types of 3D-printed drug delivery systems

Many biomaterials are currently available to be used in the fabrication of 3D DDS, the most frequently used are natural and synthetic polymers, ceramics and metal alloys.

In the context of polymers, synthetic or thermoplastic polymers, including polylactic acid (PLA), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polyurethane (PU) and polyvinyl alcohol (PVA), exhibit exceptional physicochemical properties, offering a cost-effective solution with established interactions with drug molecules. Additionally, they are easily synthesized, abundant in resources, straightforward to process, demonstrate resilience to stress and are lightweight (41). Synthetic polymers possess the requisite mechanical properties (tensile strength, elastic modulus and fracture toughness) to resist internal and external tensions during 3D-printing processes (42). The origin of natural polymers is, as might be anticipated, in natural sources such as microorganisms, plants, or animals. In contrast to synthetic polymers, natural polymers have a diminished likelihood of triggering adverse effects and produce fewer toxic reactions in humans. They exhibit enhanced biocompatibility, biodegradability, availability, and capacity for chemical modification. It is noteworthy that two categories of natural polymers are particularly relevant in the context of 3D-printing: polysaccharides (chitosan, hyaluronic acid, cellulose) and proteins (collagen) (43).

Another category of biobiomaterials that is frequently employed in biomedical applications is bioceramics. These biomaterials are used in a multitude of applications, including the fabrication of hip joints for orthopedic applications, dental fillings for dentistry, and scaffolds for tissue engineering, which support the process of osteogenesis. The most used bioceramics are alumina, zirconia and hydroxyapatite. These biomaterials are distinguished by their exceptional biocompatibility and bioactivity potential, as well as their inherent characteristics of hardness, brittleness, wear resistance and corrosion resistance, which are typical of ceramics (44,45). The use of metallic biomaterials in medical treatments has also demonstrated considerable potential, with applications including implants, prosthetics, stents, scaffolds, and drug delivery systems. Examples of metallic biomaterials employed in these applications include iron, stainless steel, magnesium, titanium, zinc, and cobalt, which are used in alloys or as standalone biomaterials. These biomaterials have been shown to possess the dual capacity of delivering drugs and providing mechanical support (46,47).

Furthermore, in addition to traditional forms such as tablets or suppositories, 3D-printing has enormous potential to produce more complex forms such as implants, patches and microneedles. For example, as mentioned above, 3D-printing of delivery systems has sparked interest and research in the fields of orthopedics and orthodontics; it could also have an impact on conventional medicine through personalized dosages for acute or chronic diseases and applications in bone regeneration, treatment of wounds or infections. In addition, as will be next discussed, this technology allows the development of medicines and devices with different dimensional applications, whether at the nano, micro or macro scale.

2 3D-Printed Drug Delivery Systems

2.1 Nano to macro scale

3D (three-dimensional) printing is driving growth from a production point of view, both on a nano and micro scale, as well as on a macro scale (48). Following this, several articles on 3D-printing applications in the production of drug release systems will be presented according to dimensional scale, with the information summarized in Tables 4, 5 and 6, respectively.

2.1.1 Nano scale

The meticulous creation of complex structures on a nanometric scale (dimensions of the order of 100 nm or less), enables the development of nanomedicine and the production of functional tissues and organs and is a revolutionary advance in the pharmaceutical sector. Due to the tiny size of their particles, nanomedicines provide more precise and effective administration, enabling therapies with controlled release mechanisms or precise and targeted administration to specific cells, increasing efficacy and reducing toxicity (2). These advances are relatively recent. As a result, the studies are fewer than in other dimensions. Summarized information on some examples incorporating nanoscale DDS can be found in Table 4.

Table 5. Examples of 3D-printed nanoscale drug delivery systems

3D-Printing Method	Components	API	DDS	Application	Reference
Material Extrusion	PVA, PA12	Silver nitrate	Nanoparticle Filaments	Antibacterial activity	(49)
Inkjet-based	Alginate–gelatin Nanocomposites with niosomes	Doxorubicin	Nanocarriers	Breast cancer therapy	(50)
SSE	HPMC	Indomethacin	Nanocrystals for Film Formulations	Fast-dissolving oral film	(51)
	caproyl 90, octanoic acid, PEG 400, poloxamer 188 and PEG 6000	Dapagliflozin	Self-nano--emulsifying solid dosage forms	Tailored doses for diabetic patients	(52)

Note: Polyvinyl alcohol (PVA), Polyamide 12 (PA12), Hydroxypropyl methyl cellulose (HPMC), Semi-solid extrusion (SSE), Polyethylene glycol (PEG).

As mentioned before, synthetic polymers, present excellent physicochemical characteristics are cost-effective and their interactions with drug molecules is favorable (41).

The studies reviewed involving 3D-printing at the nanoscale have applications in various fields, including anti-tumour and diabetes therapy, tissue regeneration, as well as advances in the production of orodispersible films and the study of antimicrobial activity. The preferred printing method in these studies was extrusion-based. Therefore, Vidakis et al. used material extrusion method to develop 3D-printed nanoparticle filaments. In this study PVA, a synthetic polymer, was used as a reducing macromolecular agent with good results, contributing to the release of silver nanoparticles through reactive melt mixing during the extrusion process to produce nanoscale composites with silver nitrate salt. The resulting composite showed satisfactory results, while having sufficient antibacterial performance against *S. aureus* and *E. coli* strains, with potential for biomedical applications (49).

Semi-solid extrusion (SSE) is another example of extrusion-based 3D-printing technology. It can also be used in nano applications, as demonstrated by Germini et al. (51) and Algahtani et al. (52). For the printing gel solution Germini et al. diluted indomethacin nanosuspensions with water and used hydroxypropyl methyl cellulose (HPMC) as film-forming polymer, this research obtained fast-dissolving oral polymeric film preparations which are a very promising option to produce formulations with immediate release and improved solubility, also 3D-printed films showed less variation in the measured properties when compared to film-casted (51). Algahtani et al. prepared a semi-solid paste for 3D-printing by fusion method, taking advantage of the biopharmaceutical properties of dapaglifozin, which provides the possibility to deliver tailored doses for diabetic patients. The 3D-printed self-nanoemulsifying tablet showed an immediate release drug profile, and this technique provides an alternative to design and develop self-nanoemulsifying solid dosage forms for poorly water-soluble drugs (52).

Using inkjet-based printing, another research successfully combined nanocarriers and 3D-printing to develop breast cancer therapy. Zaer et al. developed a 3D-printed alginate-gelatin nanocomposites associated with niosomes (vesicular nanostructures composed of non-ionic surfactants and cholesterol compounds) loaded with doxorubicin, resulting in pH-dependent DDS. The study obtained nanocarriers with excellent cytotoxicity against breast cancer cells. This study helped to promote further research on 3D-printed DDS applied to cancer therapies, as the designed nanocarriers showed efficacy for these pathologies. Furthermore, the use of 3D-printing to produce smart DDSs on a large scale seemed feasible (50).

2.1.2 Micro scale

Although the microscale (scale less than 1 mm) is an order of magnitude larger than the nanoscale, it has also several advantages and specificities, and is highly relevant to produce for example microneedles, which have been shown to be effective in tissue regeneration. Summary information on some micro-scale applications of 3D-printing is provided in Table 5.

Table 6. Examples of the 3D-printed microscale drug delivery systems.

3D-Printing Method	Components	API	DDS	Application	Reference
Extrusion-based	PU, spidroin hydrogel, EGaIn nanoparticles	Aloe Vera Gel	Microneedles	Wound healing	(53)
FDM	PLA, almond oil, PEG, silicon dioxide	Estradiol Valerate	Transdermal microneedle arrays	Hormone therapy	(54)
	PLA, carboxymethyl Cellulose	Rhodamine B	Microneedles	Not specified	(55)
SLA	DETAX Freeprint ortho biocompatible resin, collagen	Gentamicin	Coated microneedle patches	Tissue repair	(56)
DLP	Flexible resin and ENG hard resin	Ciprofloxacin, Fluocinolone	Hearing aids loaded with antibiotics	Ear infections	(57)

Note: Polyurethane (PU), Eutectic Galium-Indium (EGaIn), Fused Deposition Modeling (FDM), Polylactic acid (PLA), Polyethylene glycol (PEG), Stereolithography (SLA), Digital light projection (DLP).

The microscale articles under review are predominantly examples of microneedle development. A microneedle device is comprised of needles of micron size, arranged on a small patch. This DDS facilitates enhanced drug delivery through the stratum corneum layer of the skin, and overcomes the various issues associated with conventional formulations (58). It has a range of therapeutic applications, including wound healing (53), tissue regeneration (56) and hormone therapy (54).

Zhang et al. (53) produced multifunctional microneedles (MNs) using customized extrusion process for 3D-bioprinting. This MNs were projected to accelerate skin wound healing, resulting in the prevention of infection, persistent pain, and systemic injury. A hybrid emulsion containing spidroin, aloe vera gel, polyurethane and eutectic cerium-indium was prepared as primary material and used as bioink. Thanks to this formulation, the MNs obtained high flexibility, stretchability, biocompatibility, and self-healing characteristics, which are crucial for wound management and other possible biomedical applications (53).

In the field of hormone therapy, Khosraviboroujeni et al. incorporated estradiol valerate into transdermal microneedle arrays (MNAs) and produced MNAs with a high drug-loading capacity, uniform drug content, and a sustained drug release manner. Despite the restricted resolution of FDM, which limits the ability to print fine needles for MNAs, the 3D-printed PLA MNAs were successfully produced. They demonstrated effective penetration into the skin without reaching the dermal nerves or puncturing blood vessels (54). Another noteworthy aspect of this formulation is the selection of the polymer. PLA is a renewable and biodegradable polymer (41,59), rendering it an appealing biomaterial for use in dissolvable microneedle arrays. The authors optimized this aspect by using PLA, which can degrade through hydrolysis (54). Additionally, Wu et al. incorporated PLA into the fabrication of microneedles (MN) with customized architectures utilizing Rhodamine B as a model pharmaceutical agent through FDM. Due to its biocompatibility and bioabsorbability, PLA is frequently used in a variety of applications. Furthermore, its high melting temperature (210°C) makes it compatible with FDM techniques (60,61). Wu et al. demonstrated this by showing that, within the temperature range that the FDM printer and PLA filament can withstand, increasing the thermal parameters during the FDM process improves the interfacial bond strength and reduces the void density of the PLA layers when producing MNAs. Furthermore, increasing the concentration and temperature of the etchant can improve the efficiency of chemical etching, which provides a method for fabricating MNs structures for various biomedical applications without the need for expertise in microfabrication (55).

The use of antibiotics at the microscale is also a topic of interest, with two of the papers reviewed developing DDS with antibacterial activity. Still in the field of MNs production, Mutlu et al. successfully produced 3D-printed biocompatible MN patches for transdermal drug delivery using stereolithography (SLA) with the aim of evaluating the coating capacities of microneedles on skin tissue applications. The MNs were coated with collagen-gentamicin loaded nanoparticles via the electrospray method, as gentamicin can be readily loaded into type I collagen. Due to collagen's natural protein properties related to scar development, it was revealed to be an important component in connective tissue repair. These patches could therefore be a successful tool in such treatments (56). Vivero-Lopez et al. established a correlation between the extended use of hearing aids and an increased incidence of ear infections. They further proposed that the loading of the device with antibiotics could serve to reduce the number of infections. The study employed VAT polymerization to fabricate patient-specific medical devices with antibacterial properties. The 3D-printed hearing aids were composed of a layer thickness of 25 µm, thereby ensuring a compact and lightweight device. The antibacterial drugs (ciprofloxacin, fluocinolone) were dissolved in a resin ink, which produced a flexible printed device. The high precision and resolution of the printing technique permitted the creation of a hearing aid that was tailored to the patient's individual needs and considerably more comfortable than standard hearing aids, which are typically limited in size and shape and produced on a large scale (57).

2.1.3 Macro scale

At the macro scale (classical optical scale, greater than 1 mm), the utilization of 3D-printing also presents a multitude of advantages. In addition to the meticulousness of the forms that can be obtained using this technology, it also offers advantages when applied to more traditional therapies due to its ability to effectively reproduce techniques such as combining layers of multiple drugs. At present, there is a considerably larger body of research at the macroscale than at the nanoscale or microscale. A summary of the applications of 3D-printing at the macroscale can be found in Table 6.

Table 7. Examples of 3D-printed macroscale drug delivery systems

3D-Printing Method	Components	API	DDS	Application	Reference
Extrusion-based	Methylcellulose, nHA	Vancomycin	Implantable scaffolds	Bone tissue engineering	(62)
	Gelatin based hydrogels	Manuka honey	Patches	Wound healing and skin regeneration	(63)
	Chitosan	Sophorolipids	Hydrogel mesh to coat medical devices	Prevent infection	(64)
Micro--extrusion	GelMA	SPIONs	Nanoparticles	Soft and hard tissue regeneration	(65)
FDM	PVA, xylitol, Chitosan	Dexamethasone acetate	Buccal patches	Recurrent oral ulcer	(66)
	PLA, PEG, Poloxamer® 188, and EVA	Paliperidone palmitate	Implantable dosage forms	Schizophrenia	(67)
	PVP 40, Eudragit® RSPO mixture	Quercetin	Medicated skin patches	Destructive pulmonary tuberculosis	(68)
	PU	Chloramphenicol, Metronidazole	Vaginal ring	Bacterial vaginosis	(69)
	Anionic cellulose nanofiber hydrogel, PLA	Nadolol, metoprolol	Implantable Capsules	Hypertension	(70)
	PLA, collagen, citrate-HA nanoparticles.	Minocycline	3D-printed scaffolds	Bone Regeneration	(71)
	PCL, meniscus extracellular matrix, PLGA	Kartogenin	Implantable scaffolds with loaded microspheres	Repair meniscus defects	(72)
	PU	Zinc Oxide, Heparin	Zein nanospheres to coat 3D-printed stents	Stent to prevent thrombosis and infection	(73)
	PLA, collagen, nHA	SPIONs, Minocycline	3D-platform with nanoparticles	Antibacterial activity with potential application in bone diseases	(74)

Table 6. Examples of 3D-printed macroscale drug delivery systems (cont.)

3D-Printing Method	Components	API	DDS	Application	Reference
SLM	Magnesium alloy (Mg-Nd-Zn-Zr), butyl acetate and polysilazane	Zoledronic acid	Scaffolds with loaded ceramic coating	Repairing osteoporotic bone defects	(75)
SSE	Gelucire® 44/14; Coconut oil	Budesonide, Tofacitinib citrate	Suppositories	Acute severe ulcerative colitis	(76)
DWA	BCP powders, chitosan, genipin	Levofloxacin	Scaffolds made of a mesh of ceramic rods	Local bone regeneration and infection treatments	(77)
EBM	pyridinium *p*-toluenesulfonate, PEG-OH, Titanium	Paclitaxel	Titanium alloy implants loaded with nanoparticles	Prevent osteosarcoma recurrence	(78)

Note: Nanohidroxyapatite (nHA), Gelatin methacryloyl (GelMA), Superparamagnetic iron oxid nanoparticles (SPIONs), Polyvinyl alcohol (PVA), Polylactic acid (PLA), Polyethylene glycol (PEG), Ethylene–vinyl acetate (EVA), Polyvinylpyrrolidone (PVP), Polyurethane (PU), Poly(lactic-co-glycolic) acid (PLGA), Fused deposition modelling (FDM), Selective laser melting (SLM), Semi-solid extrusion (SSE), Direct write assembly (DWA), Biphasic calcium phosphate (BCP), Electron beam melting (EBM).

A review of the studies in question, particularly those conducted at the macroscale, reveals a clear preference for the 3D-printing technique known as fused deposition modelling (FDM). As mentioned earlier, HME is the only reliable technique for incorporating drugs into filaments for FDM (14), and an example of this application was given by Chaudhari et al. in the production of medicated skin patches with possible application in mitigating destructive pulmonary tuberculosis (DPTB). Quercetin-PVP extruded filaments were prepared by hot melt extrusion (HME) together with Eudragit® RSPO and tri-ethyl citrate and then printed using fused deposition modelling (FDM) based 3D-printing technology. The resulting patches exhibited remarkable properties, including a stable formulation with prolonged efficacy, as well as zero moisture content and low moisture absorption properties, effectively preventing microbial contamination (68).

As previously stated, PLA is a widely used polymer. One of its key benefits is its non-toxic nature, which allows it to be used safely by humans, as approved by the FDA (79).

Manini et al. emphasized this aspect and employed PLA as a polymer due to its favourable mechanical properties, ease of preparation of adapted filaments for FDM and the capacity to facilitate sustained release of paliperidone palmitate over time (67). Furthermore, this polymer facilitates the fabrication of biomaterials. Consequently, PLA has been employed in Europe and in the USA as an alternative to stainless steel in the development of a novel orthopaedic fixation material. By employing this methodology, Martin et al. developed a 3D-printed a PLA scaffold that was successfully multifunctionalized with collagen, minocycline, and citrate hydroxyapatite nanoparticles. This resulted in a combination of antibacterial/antibiofilm and osteogenic properties, while maintaining morphological and mechanical properties compatible with those of trabecular bone (71). Auvinen et al. also employed a novel method, namely 3D-printing via FDM, to create PLA capsules filled with a drug-loaded anionic cellulose nanofiber (CNF) hydrogel. This approach offers the dual benefit of biocompatibility and biodegradability, which are inherent properties of both PLA and the CNF hydrogel. The hydrogel formulations were prepared by mixing anionic CNF hydrogel with the model compounds (nadolol and metoprolol). As the capsules are injected with the hydrogel formulations post-printing, without undergoing heating, this method can be compatible with compounds such as proteins and liposomes. Additionally, this formulation offers the advantage of personalization, as the release of any CNF-compatible drug can be modulated simply by adapting the inner geometry of the PLA capsule and regulating the open surface area. The authors also discussed the potential future addition of nitrofurantoin to prevent biofilm formation and the actual injection of the hydrogel formulations, which could be performed automatically by 3D-printers (70).

Similar to PLA, PVA possesses characteristics that render it an attractive material for various applications. It exhibits thermoplastic properties, high temperature stability, low reactivity, and is biocompatible with high potential for biological degradation and minimal toxicity. The most effective method for the production of PVA drug delivery filaments is HME, with FDM being the preferred technique for the 3D-printing of drug delivery devices. The most common format for PVA-based drug delivery is that of oral disposables (43,80). In light of these characteristics, Chen et al. employed PVA as a drug carrier for dexamethasone acetate and a primary excipient in the development of buccal patches, underscoring its mucoadhesive properties. PVA demonstrated excellent adhesion performance, forming a paste in contact with water that enabled the drug-loaded layer to maintain its shape and adhesion. The success of this formulation can be attributed to the properties of PVA, including its excellent printability. Moreover, the experimental results demonstrated that the 3D-printed patch exhibited superior performance compared to commercially available alternatives. (66).

There’s also an example of PU applied as polymer, Wang et al. studied the application of Zein Nanospheres (ZN) to coat 3D-printed Polyurethane (PU) stents to prevent thrombosis and infection. PU was selected as polymer due to characteristics such as being a kind of block copolymer with good biocompatibility, biodegradability, mechanical properties, non-toxicity and reasonable price (81,82). The PU stents were printed via FDM and Zein Nanospheres loaded with Zinc Oxide nanoparticles were prepared by a phase-isolation, the stents were coated through spraying process and then soaked into a heparin solution. PU also presents excellent thermoplasticity, contributing to possibly fabricate functional medical devices with anti-coagulation and anti-infection properties (73).

Bioinks are frequently compatible with 3D-printing methods being normally associated with FDM technique. Saraiva et al. used superparamagnetic iron oxide (SPIONs) and hydroxyapatite nanoparticles, combining for the first time with minocycline. Using FDM technology 3D-printed PLA scaffolds were obtained and subsequently loaded with (SPIONs) and minocycline. The scaffolds obtained showed potential bone treatment applications where bacterial infection is of concern, having activity against *S. aureus* as well as cytocompatibility and osteogenic effects on immortalized and primary bone cells (74).

Using the polymeric gelatin methacryloyl (GelMA) bioink and superparamagnetic iron oxide nanoparticles (SPIONs) Theus et al. produced a 3D-printed nanoparticle-laden hydrogel scaffolds with enhanced antibacterial and imaging properties. The scaffolds were printed with microextrusion based 3D-bioprinting and presented the ability to be used in a variety of soft and hard tissue engineering applications (65).

Using Extrusion-based 3D-Printing technique Iglesias-Mejuto et al. printed implantable scaffolds for advanced bone tissue engineering. Methylcellulose (MC) was employed as graft matrix endowed with nanohydroxyapatite (nHA) to confer bioactivity. MC-nHA aerogels were obtained through the 3D-printing of hydrogel-based scaffolds followed by scCO2 drying and were loaded with vancomycin. Obtained results showed that the scaffolds promoted the intended two-in-one effect (bone repair and infection management simultaneously) in a personalized way, regulating formulation design, drug dose, and porosity (62). Also through extrusion, Brites et al. used gelatin-based hydrogels as ink, obtaining Manuka-Gelatin based patches for wound healing applications. The incorporation of Manuka Honey improved the printing process, the printing accuracy and quality of the 3D-printed patches, having also appropriate antibacterial and biocompatible properties (63). Narciso et al. applied the same 3D-printing technique and investigated the potential of antimicrobial chitosan-biosurfactant hydrogel mesh, utilizing chitosan gels loaded with biosurfactants. The 3D-printed structure was designed to coat polydimethylsiloxane-based (PDMS) medical devices for infection prevention purposes. The hydrogel inks produced showed appropriate printability, and the developed 3D-printed coatings demonstrated a solid capability to be used as antibacterial for the designed purpose (64).

Apart from the use of polymers, the incorporation of alloys and 3D-printed DDS is relevant in the pharmaceutical field. The use of metal implants as a means of providing mechanical support for the healing and regeneration of bone tissue is a long-established practice in the field of orthopedic surgery. However, recently, titanium alloy-based implants have demonstrated the capacity to deliver drugs in addition to providing mechanical support (46). Fan et al. developed 3D-printed titanium scaffolds loaded with pH-responsive paclitaxel (PTX) nanoparticles (NPs), which demonstrated excellent mechanical support, good biological safety, and favorable physical-chemical properties. The porous scaffold was produced using electron beam melting (EBM) technology in a layer-by-layer fashion and subsequently loaded with PEG–acetal–PTX (PAP) NPs (a previously synthesized modified PTX prodrug). This research permitted the examination of a 3D-printed porous titanium alloy implant with a high antitumor efficiency and a controllable release system, thereby demonstrating the potential for it to serve as an effective solution to prevent local recurrence of osteosarcoma after surgery. Consequently, it shows great potential for the cure of bone tumors and the provision of a new research direction in the treatment of tumor-related bone complex diseases (78).

As previously stated bioceramics are also a very interesting material due to their mechanical stability and biocompatibility (44). In this field, Marques et al. investigated the production of 3D-printed biphasic calcium phosphate (BCP) scaffolds consisting of a mesh of ceramic rods, printed layer by layer via direct write assembly (DWA) a technology developed for ceramics that uses extrudable aqueous ceramic inks at room temperature. BCP powders were synthesized using CaP-based powders with different proportions of hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP) phases. The BCP powders were then added to chitosan and genipin (crosslinking agent) producing the ceramic ink. The obtained 3D-printed scaffolds were loaded with levofloxacin exhibiting an early and fast drug release, opening a path for local bone regeneration and infection treatment, allowing a more direct administration of drug (77).

In addition, a study conducted by Ran et al. employed the use of both alloys and ceramics aiming to develop a novel method for theoretical research and clinical treatment of osteoporotic bone defects. This entailed combining the osteogenic effect of magnesium through the production of 3D-printed biodegradable magnesium alloy (Mg-Nd-Zn-Zr) scaffolds and the osteoclast inhibition effect of zoledronic acid (ZA) through the loading of the drug into a ceramic composite and the coating of the scaffold surface. The magnesium alloy scaffolds were fabricated via selective laser melting (SLM) and subsequently coated with polysilane coating materials containing ZA. The coating markedly reduced the degradation rate of the Mg alloy substrate *in vitro* and facilitated a controlled and gradual release of loaded drugs, resulting in scaffolds with a biological function of regulating osteoblast/osteoclast differentiation. (75).

Another interesting application of 3D-printing at a macro level is the production of suppositories, which are classical pharmaceutical forms. Although, this manufacture technology enables more detailed and robust formulations for more specific administrations. Awad et al. developed 3D-printed suppositories for acute severe ulcerative colitis application. The suppositories were printed using semi-solid extrusion (SSE) and contained tofacitinib citrate and budesonide in varying doses. This combination treatment can provide a possible option if the patient is unresponsive to steroid treatment, which is common in this disorder, becoming more manageable (76).

2.2 Active Pharmaceutical Ingredients

The variety of active pharmaceutical ingredients (APIs) available for incorporation into 3D-printed DDS is relatively large, making it possible to take advantage of this methodology in various treatments, with more specific, personalized formulations and greater bioavailability. Among the pharmacological classes addressed in the formulations mentioned in this review, categories of high therapeutic importance have been addressed, namely in the field of tissue and bone regeneration, wound management, chronic diseases and infection treatment. It is also worth noting that within the 3D-printing of pharmaceuticals it is possible to generate formulations with APIs with different characteristics.

Since 3D-printing allows better control over drug release profiles, enhancing therapeutic outcomes and personalized production of DDS tailored to patient-specific needs, this benefit stands out in the treatment with antibiotics. Another concern in the formulation of DDSs is the formation of biofilm, and antibiotics are also incorporated for this purpose. Minocycline (MH) is commonly tested in 3D-printed DDSs, being an antibiotic with tunable properties, multistimuli response and activity against *Staphylococcus aureus*. MH was combined by Saraiva et al. for the first time with superparamagnetic iron oxide and hydroxyapatite (HA) nanoparticles in a 3D-printed platform for potential bone treatment applications where bacterial infection is of concern, assuring anti-*S. aureus* activity (74). Also, in the field of bone treatment, this antibiotic was incorporated by Martin et al. in a novel 3D-multifunctional PLA-Col-MH-cHA scaffolds to prevent the formation of biofilm during bone repair treatment (71).

As referenced, Vivero-Lopez et al. aimed to treat and prevent biofilm formation, combining ciprofloxacin and fluocinolone acetonide into 3D-printed hearing aids, due to its common use in ear drops to address ear infections and showed effects against *P. aeruginosa* and *S. aureus* (57). Iglesias-Mejuto et al. loaded aerogels with vancomycin, as it is an antibiotic employed in the management of bone infections. The loaded aerogels showed inhibition of *S. aureus* (62). Marques et al. loaded 3D biphasic calcium phosphate (BCP) scaffolds with levofloxacin exhibiting an early and fast drug release as well as bacterial growth inhibition (77).

A further application of local antibiotic delivery was investigated by Arany et al. To treat bacterial vaginosis, the researchers developed 3D-printed vaginal ring loaded with metronidazole and chloramphenicol. The use of these drugs is limited by a number of concerns, which are overcome when applied to local administration. This represents a significant benefit in the treatment of patients using this DDS. The addition of chitosan to this formulation also enhanced the antibacterial effect of the drugs against *E. coli.* (69).

Other drugs were considered for 3D-printed DDSs for orthopaedic purposes. Li et al. used kartogenin to repair meniscus defects, as this is a small bioactive molecule that has been reported to promote chondrogenic differentiation of mesenchymal stem cells. Kartogenin enhances the expression of collagen II and aggrecan, improving the development of cartilage nodules and synovial joint (83). The resulting scaffolds showed a prolonged release profile, demonstrating that the incorporation of this drug into poly(lactic-co-glycolic) acid (PLGA) microspheres used to load scaffolds holds great promise for future meniscal tissue engineering (72). To repair osteoporotic bone defects Ran et al. analyzed zoledronic acid, as a third-generation, nitrogen containing bisphosphonate, zoledronic acid shows high affinity for the surface of bone mineralization, acting on osteoclasts, promoting osteoclast apoptosis, and inhibiting bone resorption positively (75).

The use of chemotherapy drugs in conjunction with 3D-printed DDSs is an intriguing avenue of research. This technology has the potential to facilitate the development of targeted nanoparticles, which can be used to deliver drugs directly to cancer cells. This approach has the advantage of reducing off-target toxicity and enhancing the therapeutic efficacy of the drugs (84). By employing this strategy, Zaer and colleagues were able to synthesize nanocarriers loaded with doxorubicin, which exhibited favorable cytotoxicity against breast cancer cells and maintained good cell viability (50). Localized DDSs contribute to the direct delivery of high-concentration drugs to tumor sites, thereby improving the medication effect and reducing systemic side effects. Paclitaxel, another chemotherapeutic drug, was incorporated by Fan et al. into nanoparticles for this reason. The objective of this research was to address the adverse effects associated with the systemic administration of chemotherapeutic agents, including weight loss, anorexia, diarrhea, and bone marrow suppression, which can potentially lead to patient mortality (78).

The incorporation of natural molecules with healing properties into the manufacturing of DDSs through 3D-printing is also a promising avenue of research. These molecules offer enhanced biocompatibility and non-toxicity, which are crucial factors in the development of safe and effective medical devices. Given that Manuka honey displays characteristics such as microbial growth inhibition, enhanced fibroblast activity, increased oxygenation and induction of angiogenesis, Brites et al. investigated its potential use in the development of wound healing patches. The resulting patches demonstrated efficacy in wound healing and skin regeneration, which provides a foundation for future research into the potential applications of Manuka honey in modelling the removal of wound exudates or in improving tissue regeneration (63). Similarly, Zhang et al. incorporated aloe vera gel into microneedles for the same therapeutic applications, resulting in microneedle patches composed of a breathable scaffold backing layer. The incorporation of aloe vera gel provided excellent biocompatibility and self-healing ability due to the presence of aloe polysaccharide, the main ingredient of the gel (53).

The examples of APIs cited in the reviewed papers provide an overview of the potential applications of 3D-printing in developing DDSs. These examples demonstrate that 3D-printing is a versatile technology with applications across various therapeutic fields. Moreover, they highlight how this approach can help overcome challenges related to systemic intolerance, as well as issues in drug development and formulation.

3 Conclusions and future perspectives

Due to the expansion of research in three-dimensional printing, there has been a notable increase in the number of documented biomaterials with well-defined characteristics. Presently, synthetic and natural polymers, bioceramics, and metal alloys are among the most relevant printing materials in the pharmaceutical and medical sectors. Consequently, a variety of tools are available for producing products tailored to diverse therapeutic needs. Among the pharmaceutical forms discussed, microneedles, implants and patches are particularly noteworthy.

The incorporation of active substances, particularly antibiotics, marks a significant advancement in drug delivery systems (DDSs). DDSs that utilize 3D-printing to formulate new therapeutics present a promising approach to reducing the common adverse effects associated with medications. Many drugs, when administered systemically, can cause severe side effects; however, by enabling different release profiles and localized release systems, this technology holds great potential for overcoming these challenges.

To develop these systems, several printing methodologies are available, with extrusion-based techniques being the most commonly used for 3D-printing DDS. Among these, FDM is the most prevalent across the reviewed papers due to its ability to accommodate a wide range of biomaterials, including thermoplastics, hydrogels, ceramics, and bioinks.

Among the DDSs reviewed, nanoscale and microscale systems are less explored when compared to macroscale. The development of 3D-printed formulations at these scales these dimensions is still in its early stages and requires further investigation, with only a limited number of tangible outcomes in recent years. Nevertheless, the overall outlook is promising, as all research contributes to a deeper understanding and the potential future integration of these technologies into smaller, more precise systems.

Overall, the benefits of 3D-printing technology in the the manufacture of drug delivery systems make this an attractive area for future research, despite some short-term barriers that need to be overcome. These barriers include the lack of standardized protocols and guidelines, as well as the need for legislation and cybersecurity measures.

Although this is not yet a reality in the pharmaceutical sector, 3D-printing is already being used in orthodontics and orthopaedics. Antibiotics are particularly noteworthy in this context, as they can be used in the printing of coating structures to improve the management of infections, including those affecting dental or orthopaedic prostheses.

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