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Review article

Rising role of 3D-printing in delivery of therapeutics for infectious disease

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ABSTRACT

Modern drug delivery to tackle infectious disease has drawn close to personalizing medicine for specific patient populations. Challenges include antibiotic-resistant infections, healthcare associated infections, and customizing treatments for local patient populations. Recently, 3D-printing has become a facilitator for the development of personalized pharmaceutic drug delivery systems. With a variety of manufacturing techniques, 3D-printing offers advantages in drug delivery development for controlled, fine-tuned release and platforms for different routes of administration. This review summarizes 3D-printing techniques in pharmaceutics and drug delivery focusing on treating infectious diseases, and discusses the influence of 3D-printing design considerations on drug delivery platforms targeting these diseases. Additionally, applications of 3D-printing in infectious diseases are summarized, with the goal to provide insight into how future delivery innovations may benefit from 3D-printing to address the global challenges in infectious disease.

1. Introduction

1.1. Infectious diseases represent a healthcare burden

Resistance of infectious diseases to established medications pose a significant economic impact globally, both in terms of direct medical costs and broader economic effects [1]. Infectious diseases in general can lead to significant healthcare costs, with hospitalizations and long-term care often required for severe cases. CDC data show national healthcare costs from multidrug-resistant pathogens infections in the United States exceed $4.6 billion annually [2]. Furthermore, antibiotic resistance and lack of patient adherence to prescribed medications contribute to the estimated 300,000 cases of methicillin-resistant *Staphylococcus aureus* (MRSA) in the U.S. alone in 2017 [3,4], and to the recurrence of bacterial vaginosis (BV) in women [5,6]. On a global scale, an estimated 13.7 million deaths were determined to be infection-related deaths in 2019 [7]. The emergence of drug-resistant pathogens in infectious disease has underscored the need for new technology and treatment to combat these challenges.

1.2. Overview of infectious diseases

Infectious diseases encompass viral particles, fungi, and pathogenic bacteria that enter the human body and alter the course of healthy, physiological function. These foreign agents often cause communicable diseases, which can be transmitted to others and affect all of society. Infectious diseases include, but are not limited to, tuberculosis (TB), *Staphylococcus aureus* (*S. aureus*) and MRSA infections, non-sexual viral infections such as influenza and SARS-CoV-2, sexually transmitted infections (STIs), human immunodeficiency virus (HIV) infection, malaria,

Abbreviations: API, Active Pharmaceutical Ingredient; CLIP, Continuous Liquid Interface Production; DNA, Deoxyribonucleic Acid; FDM, Fused Deposition Modeling; FFF, Fused Filament Fabrication; HIV, Human Immunodeficiency Virus; HME, Hot Melt Extrusion; HPMCAS, Hydroxypropyl Methylcellulose Acetate Succinate; INZ, Isoniazid; LCD, Liquid Crystal Display; MRSA, Methicillin-Resistant *Staphylococcus aureus*; PAM, Pressure-Assisted Microsyringe; PCL, Poly-ε-caprolactone; PEG, Polyethylene Glycol; PEGDA, Polyethylene Glycol Diacrylate; PPE, Personal Protective Equipment; RFC, Rifampicin (a.k.a. Rifampin); SLA, Stereolithography; SLM, Selective Laser Melting; SLS, Selective Laser Sintering; SNEDDS, Self-Nanoemulsifying Drug Delivery Systems; STD, Sexually Transmitted Disease; STI, Sexually Transmitted Infection; TB, Tuberculosis; UV, Ultraviolet.

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and oral infections. STIs, caused by various bacteria, viruses or parasites acquired through sexual contact, include chlamydia, trichomoniasis, syphilis, and human papillomavirus, which influence fertility, childbirth, susceptibility to other viruses such as HIV, and immunity [8]. HIV, a retrovirus generally acquired through sexual contact or through exposure to blood, attacks CD4 cells, weakening the immune system and thus increasing susceptibility to other infections and certain cancers [9]. Variants of HIV have spurred the development of antiretroviral therapy cocktails to contain infection; these variants have had substantial impact on immune health and childbirths in regions of Africa. Malaria continues to induce high mortality in children in sub-Saharan Africa due to high mosquito transmission and less developed immunity that leads to parasite *Plasmodium falciparum* transmission that results in anemia and blocked blood vessels [10]. As the recent pandemic abates, SARS-CoV-2 and influenza cases continue to encumber healthcare systems worldwide seasonally. MRSA is a threatening infection due to its resistance to antibiotics and becomes a point of concern for surgical sites and skin infections which, if untreated, could cause sepsis and the need for amputation if infections reach bone tissue [11]. TB is acquired via airborne transmission of *mycobacterium tuberculosis* and through blood, and can spread from lungs to kidney, spine, and brain [12]. Oral infections caused by pathogens *Candida albicans (C. albicans), Porphyromonas gingivalis,* and *Fusobacterium nucleatum* contribute to oral mucosal disease, periodontal disease, and pulp and periapical disease, respectively [13].

1.3. Alternative solutions are needed to tackle infectious diseases

The multi-faceted nature of infectious diseases encompassing various modes of transmission and affecting different microbiomes have prompted the need for alternative solutions. Additive manufacturing has garnered attention due to its adaptable workflow to locally customize medicinal treatment. Additive manufacturing refers to combining materials to create a construct layer-by-layer and is, most generally, used to classify manufacturing through 3D-printing. With the challenge of antibiotic-resistant infections, 3D-printing enables the development of drug delivery systems that mitigate the spread of infections by fine-tuning drug release [14]. Through 3D in vitro cultures to advance vaccine development and individualized, 3D-printed implants loaded with antibiotics, infections can be further controlled. The everchanging landscape of infectious diseases has prompted this review paper to focus on 3D-printing for delivery of therapeutics for these diseases.

1.4. 3D-printing can efficiently tackle infectious diseases

With the rise of personalized medicine, 3D-printing offers the potential for developing drug-specific doses with tailored release kinetics customized to meet specific patient needs. Global challenges due to differences in incidence of infectious diseases in underserved populations are further compounded by differences in age, genetics, and underlying health conditions [15–17]. For infectious disease applications, 3D-printing offers cost efficiency, high throughput methods, and customization [18–20]. In the field of pharmaceutics, the FDA has approved the first 3D-printed oral disintegrating tablet, Spiritam®, an antiepileptic medication available in a range of dosage strengths and use for seizures for adults and children [16,19,21–23]. Furthermore, 3D-printing has been employed for developing localized drug delivery systems for treatment of HIV, STIs, respiratory infections, *staphylococcus aureus* infections, as well as for vaccine development against infectious diseases [24–29]. Specifically, in bioprinting, 3D-printing has led to development of accurate in vitro testing platforms for drug development [30]. This work has demonstrated that as is the case with drugs, growth factor release can also be temporally modified [31], which brings great potential to further customize and devise 3D cultures in vaccine development.

1.5. 3D-printing facilitates application customization

Orally administered drugs are classified by the Biopharmaceutics Classification System (BCS) contingent on aqueous solubility and intestinal membrane permeability. However, different drug dosages are needed to meet the needs of patients with specific underlying conditions, different ages, body masses and genetic differences [16,17,32]. 3D-printing facilitates personalizing treatment through localized delivery at the site of infection, providing an avenue to fine-tune permeability thresholds [33]. With localized delivery, architectures can be optimized for targeting and interacting with particular tissues. Furthermore, specific drug concentrations can be loaded into the printing materials to meet various medical needs. With computer-aided design (CAD) software, 3D-printing aims to personalize treatment through architectures designed for customized drug release profiles. These favorable attributes enable 3D-printing applications to span a spectrum of dentistry, orthopedics, biomedical device development, personal protective equipment (PPE), pharmaceutics, and bioengineering [22,23,34–44]. Customized architectures for individualized patient care are 3D-printed via the formulated inks [45–47]. Personalization through customization is made possible by converting CAD architectures into Stereolithography (STL) files that are translated into printing. The versatility of 3D-printing thus enables innovative solutions to complex medical treatment challenges for individual patients in a high throughput manner.

1.6. 3D-printing facilitates therapeutic customization

Variants of viral infections have different incidences of infection depending on global region [48–52]. A previous study found that HIV subtypes have a genetic variation between 17 and 35% contingent on subtype and genome regions evaluated, and a genetic variation between 8 and 17% within the subtype resulting in the need for alternative drug treatments [48,53,54]. These circumstances give rise to new challenges where treatments are not as easily mass scaled in production. High prevalent HIV subtypes A and C and moderate prevalent intersubtype recombinants of subtype A1 and D in East Africa display differences within smaller geographic regions [55–58]. Within the Eastern African region, a previous study found a diverse composition of pure subtypes A and C and numerous intersubtypes within Kenyan cities, underscoring the difficult task of customizing treatment for patients [57]. Likewise, compared to North America, MRSA exhibits greater clonal diversity in other continents [59]. Furthermore, genetic differences require different drug treatments for patient populations, as commonly seen with antiviral medications in HIV [60–63]. Challenges in infectious disease treatment arise from inequalities in treatments for different populations [64,65]. With shortcomings in fixed dose combinations of antibiotics, as seen for treatments in infectious diseases such as MRSA, patient-targeted local production utilizing 3D-printing could have advantages [66]. Regardless of the healthcare system, 3D-printing in drug delivery presents novel opportunities to mitigate the burden of specializing treatment for specific patient cases.

1.7. 3D-Printing has progressed into clinical applications

Recently, 3D-printed molds aided in the development of antibiotic bone cement-coated intramedullary nails that demonstrated infection control within patients [67]. Antibiotic-loaded polymethyl methacrylate bone cement was utilized to create a radial head prosthesis with the assistance of 3D-printing in which patients exhibited high restoration of elbow function with high bone preservation [68], exemplified by the precision of 3D-printing. In addition to these examples, a 3D-printed tibial component was designed with porosity to enhance osseointegration to prevent aseptic loosening [69], in which only one patient acquired infection after the procedure. Through the use of CAD and 3D-printing, bone reconstruction was designed for implementation at the site of the bone defect, where the customized devices exhibited fewer

infections in patients compared to the conventional device [70]. Other bone defect cases led to creation of 3D-printed polycaprolactone (PCL) and tricalcium phosphate scaffolds for bone formation [71]. With these advances in orthopedic-related clinical studies, 3D-printing has shown promise to become customizable and highly individualized to meet patient needs in clinical applications with focus on implementing greater biomechanical support while reducing infection.

1.8. Motivation for current review

A previous review pertaining to infectious disease and 3D-printing focused on the role of bioprinting in manufacturing 3D in vitro models, therapeutics, and vaccination strategies [72]. Additionally, the convergence of bioprinting with vaccination therapeutics, and its potential through microfluidic organs-on-chips and organoids has been reviewed [73]. In comparison, our current review covers the influences of different types of 3D-printing (not limited to extrusion printing) on drug delivery applications for an array of infectious diseases (not limited to virological applications). Our review also focuses on the interrelations between the type of 3D-printing, drug delivery design, and the targeted infections, evaluating the advantages and disadvantages for each application.

2. 3D-printing design considerations for targeting infectious diseases

2.1. Versatility in manufacturing

Differences in manufacturing through 3D-printing have established, novel drug delivery platforms for various uses. Fused deposition modeling (FDM) has improved poor solubility and lipophilicity of drugs via the development of self-nanoemulsifying drug delivery systems (SNEDDS) [74]. Recently, the use of hot melt extrusion (HME) in conjunction with FDM has been shown as an effective continuous process for Active Pharmaceutical Ingredient (API) incorporation into polymers. Fig. 1 exemplifies the process of drug-loading into a filament as feedstock for subsequent FDM printing. Due to the need of enhancing bioavailability of APIs, HME has become an effective technique for improving the solubility of poorly water-soluble drugs [75]. Depending on the polymer properties, shear stress and residence time in the extruder are adjusted to produce die in forms such as powders, flakes, tablets, filaments or pellets [76]. A large portion of FDM printed drugs

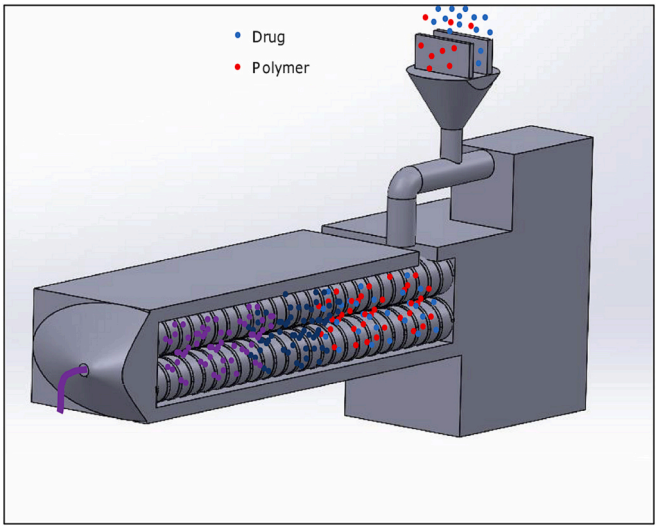

Fig. 1. A SOLIDWORKS developed part with an isometric assembly of a twin-screw hot melt extruder at cross section to provide insight of drug and polymer additions to create a homogenous drug-loaded filament for FDM printing.

are classified with poor dissolution and solubility characteristics; principles such as acid-base supersolubilization during HME have been utilized to enhance these properties when using FDM printing [77].

By eliminating the need for high temperature and thus maintaining physiologically relevant temperatures, pressure-assisted microsyringe (PAM) printing has enabled the bioprinting of cells for tissue engineering applications; however, limitations arise in regards to shear stress on cells and implications on viability during extrusion [78]. An advantage of PAM printing compared to other 3D-printing types is that a wide variety of materials can be utilized as matrices whereas other printers are limited to curable resins, powders, and filaments to achieve the desirable deisgn [79]. Extruding layer-by-layer leads to potentially compromising the design depending on the viscosity of the material because many prints in PAM printing depend on post-processing such as curing, crosslinking, or drying to retain structure [80]. In contrast, inkjet printing in both 2D and 3D provides promising potential to be used more adjunctively with other types of additive manufacturing as drug loaded films or distinctive elevated surfaces for altering release profiles.

Selective laser sintering (SLS) uses laser sintering to create a construct from powdered materials, which offers an advantageous expedited process with powders [81]. Due to high energy and temperatures, SLS has had limited impact in pharmaceutics because of the degradation of APIs through this manufacturing process [82].Stereolithography (SLA) printing uses thermoset polymers, in contrast to thermoplastics in FDM, which are irreversibly hardened from liquid state during printing. Selective laser melting (SLM) uses lasers to selectively melt powdered metals layer-by-layer to produce the desired three-dimensional design, and it is often used on biomaterials for implants due to its high precision and reproducibility of microarchitectures [83]. Due to high intensity of the laser, API incorporation in powdered metal is not feasible; however, SLM printed implants have previously incorporated antibiotics and nanoparticles on their surface [84–86].

In contrast to SLA, Continuous Liquid Interface Production (CLIP) enables a faster approach to printing by reducing time between layers for photopolymerization [87]. CLIP benefits from higher resolution and more manufacturing efficiency by exposing UV light through an oxygen permeable window to photopolymerizable liquid resin to selectively polymerize with precision while mitigating the need for repositioning by having unpolymerized resin that is oxygen-inhibited above the window [88].

The main types of 3D-printing for drug delivery are summarized in Table 1.

2.2. Machine learning in formulation development

Machine learning (ML) has been a recent area of growth for 3D-printing in drug delivery. With formulation development, manufacturing through 3D-printing has challenges that include printability, creating desired drug release profile or dimensions. ML can reduce research and development costs by determining optimized formulations contingent on drug delivery platform design considerations varying from material characteristics like mechanical strength to 3D-printing processing parameters like extrusion speed. Challenges arise often in HME and the subsequent FDM printing of the filament, which has spurred the development of ML models to accurately predict printability, filament mechanical characteristics, and processing temperatures [95]. ML provides insight into how improve formulation development for desired drug release profiles. ML has been employed for targeting manufacturing parameters and release for 3D-printed formulations, and more broadly for drug formulations, stability, particle size, drug loading and delivery efficiency [96]. In the realm of 3D-printing, ML models that extracted formulations from >900 drug delivery systems from FDM to SLS to inkjet printing acquired predictions for dissolution times depending on material and drug as well as printability and extrusion temperature [97]. With complications in HME and FDM printing processes, ML software

Table 1
Summary of main types of 3D-printing applicable to target infectious diseases.

3D-Printer Type	Means of Printing and Processing Parameters	Drug Delivery Advantages
FDM	Extrusion of thermoplastic filaments; nozzle diameter, air gap, raster width and angle, build orientation, temperature, printing rate, layer thickness, infill density, infill pattern, contour width, and number of contours [89]	Lowest cost for production, versatility in altering dissolution of drug, great compatibility for use with HME for API incorporation, and dual layer capabilities
PAM	Extrusion based printing; pressure, temperature, needle gauge, layer thickness, printing rate, infill density/spacing, and infill pattern [90]	Biologic incorporation capabilities, multi-layered drug constructed scaffolds, wide variety of materials can be used as inks, higher drug stability due to less temperature dependence, and higher range of drug concentration incorporation in inks
Inkjet	Drop on demand or continuous technique; frequency, entrance driving speed, coverage percentages, dots per inch (dpi) resolution, layer number [91]	High processing times, drug loaded films, distinctive elevated surfaces, pattern adjustments to tune release profile, adjunctive use with other 3D-printers
SLS	Laser sinters powder; part bed temperature, fill laser power, scan size (determines speed), scan spacing, and slice thickness [92]	Expedited process through sintering polymeric powders, porosity alteration to influence release profile, great for rapid release of drug
SLA	Liquid, photosensitive resins are cured through exposure to UV light; layer thickness, build orientation, support touchpoint size, support structure density, layer height, lift speed, exposure time, anti-aliasing (smoothening of curvature) [93]	Multi-layered drug incorporation, versatility in modifying drug concentration and controlled drug delivery
CLIP	Exposes UV light through an oxygen permeable window to photopolymerizable liquid resin; UV intensity, print speed, exposure time/layer thickness [88,94]	High resolution and manufacturing efficiency

M3DISEEN was designed as a predictive tool for drug and material selection, in which characteristics such as drug dissolution time or printability is further projected [98]. Furthermore, in ML applied with FDM formulations, rheological data was used to develop a model to evaluate printability of particular formulations as well as dissolution of formulations based on viscosity measurements [99]. In SLS printing, the Fourier-transform infrared spectroscopy, X-ray powder diffraction, and differential scanning calorimetry (DSC) were extracted from formulations for a ML model to predict printability using SLS printing [100]. With inkjet printing, ML has enabled the ability to streamline the development workflow of orodispersible films [101] and printability and drug dosage [102]. Infectious diseases have considerable hurdles such as antibiotic resistant infections that are compounded by poor dosing. Overall, the application of ML in the 3D-printing workflow is a promising approach to streamline and more efficiently tackle the challenges with therapeutic development for infectious diseases.

2.3. Design parameters

This section evaluates key design parameters for 3D-printing targeting infectious diseases, as illustrated in Fig. 2.

2.3.1. Infill density

Infill density is adjusted to modify the strength, printing duration, material usage, or, in the case for drug delivery, the release kinetics. Design parameters that are directly affected by changing the infill percentage are the weight, thickness, and volume of the scaffold as well as

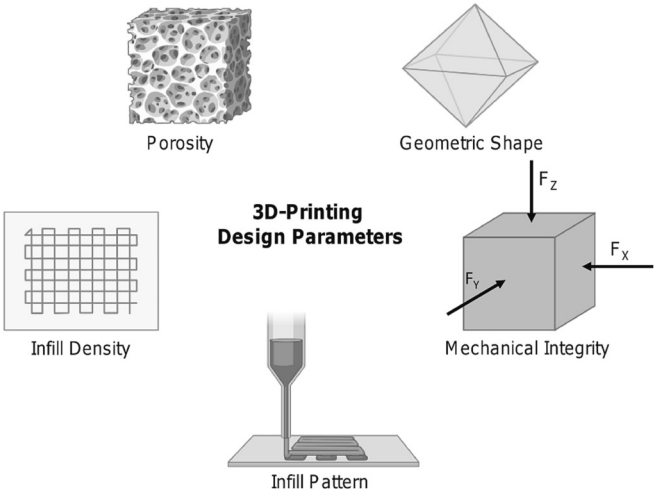

Fig. 2. Key design parameters for 3D-printing targeting infectious diseases. These parameters include infill density, geometric shape and infill pattern, mechanical integrity, and porosity. (Schematic was created with the use of Biorender).

the drug load [103,104]. Change in surface area due to infill density change enables control of the release by achieving either rapid burst or sustained, prolonged release [103,105,106]. Additionally, adjusting the infill percentage, adjunctively with the pattern, affects the scaffold mechanical strength [103].

Challenges with antibiotic-resistant infections are augmented by varying therapeutic windows for different antibiotics. Modifying infill densities helps to optimize drug delivery systems to meet the necessary therapeutic indices while simultaneously streamlining manufacturing alterations through 3D-printing. Most drug delivery systems utilizing low infills are classified as BCS Class I drugs with both high aqueous solubility and intestinal permeability, as drugs with poor solubility represent a challenge to achieve similar release kinetics. Lumefantrine (BCS Class IV)-loaded scaffolds using EUDRAGIT® E PO for matrix formation, xylitol as a plasticizer, and maltodextrin for pore formation were FDM-printed, with drug loads from 0% to 30% as well as different infill percentages from 65% to 100%, with the 65% infill being the highest infill percentage to meet the rapid release criteria of >85% of drug dissolved within 30 minutes [107]. Statistically significant parameters included increase in accessible porosity, increase in specific surface area, and reduction in relative density, all due to lowering the infill percentage [107]. This example underscores the potential of 3D-printing to facilitate the release of poorly soluble or less permeable medications.

A previous study [104] demonstrated extended release from scaffolds with an additional insoluble shell surrounding the drug in the core. Having a higher infill reduced the initial release whereas no shell surrounding the drug increased the release, with dissolution of only the core taking an estimated 20 h for complete release compared to 48 h for insoluble shell with core scaffolds [104]. Delayed release has been achieved by applying covering layers by fabricating a bilayer tablet containing isoniazid in one layer and rifampicin (RFC)in the other, with hydroxypropyl cellulose (HPC) as a matrix for the INZ layer and hydroxypropyl methylcellulose acetate succinate for the RFC layer. Covered tablets exhibited slower INZ drug dissolution of 32% in 45 min and slower RFC release of <10% in 60 min. With regards to a core shell design utilizing 100% infill parameters, an immediate release followed by sustained release of theophylline further demonstrated the role of layers and highlighted how geometry can alter release, as observed with the different sustained release profiles due to the geometry [108].

2.3.2. Geometric shapes and infill patterns

Geometry and infill pattern influence the surface area and thickness layers, which in turn influence the release profile. Profiles of drug release can be controlled by altering the geometric patterns with inkjet printing as observed with the release of fenofibrate from inkjet-printed honeycombs, in which a cell size of 0.20 mm and cell sizes >0.41 mm showed distinct release profiles while having the same formulation [109]. Various geometries complemented with hydrophobic and hydrophilic layered formulations have been developed to exploit surface area changes, multiple kinetic models, and physicochemical interactions [110]. With altering tablet sizes at fixed concentration, increased tablet size corresponded to decreased surface area to volume ratio, which extended the drug release time and, similarly, a fixed drug amount in different tablet sizes demonstrated a trend of decreased rate of drug release due to increased tablet size and decreased surface area to volume ratio [111]. In instances of pH changes such as passaging through the stomach, higher surface area to volume ratios provide a more effective release as observed in evaluation of release profiles of ring, cylindrical, and spherical tablets, where shift in pH demonstrated that rings with higher surface area to volume ratio had theophylline release of 95% compared to 60% release from cylindrical and spherical tablets [112], exemplifying the influence of geometric shape in environment-dependent drug delivery. From another perspective, the design of a 3D-printed lens-shaped scaffolds enabled localized delivery as a patch for vaginal wall delivery of nanoparticles to treat cervical cancer patients [113].

Dependent on selected infill percentages and geometric design, the amount of ink consumed per layer as well as exposed surface is contingent on the infill pattern. Fig. 3 displays the visually distinct surface areas and designs that could be implemented to control drug release from drug-loaded materials for localized delivery targeting infectious disease. As an example of infill pattern influence on drug release, amlodipine-loaded tablets were FDM printed with various infill patterns, showing that a zigzag infill pattern provided the highest release regardless of formulated composition [114]. Depending on the polymeric matrix, infill patterns printed per layer may also contribute to the factors affecting drug release such as diffusion, disintegration, swelling and erosion [115].

2.3.3. Mechanical integrity

Mechanical strength becomes an important aspect for localized delivery systems as they are subjected to mechanical forces, e.g., as is the case with drug-eluting implants and intravaginal rings. In general, constructs with higher infill densities are mechanically stronger than those with lower densities due to more area to distribute applied loads. Studies have shown that increasing infill densities while maintaining the

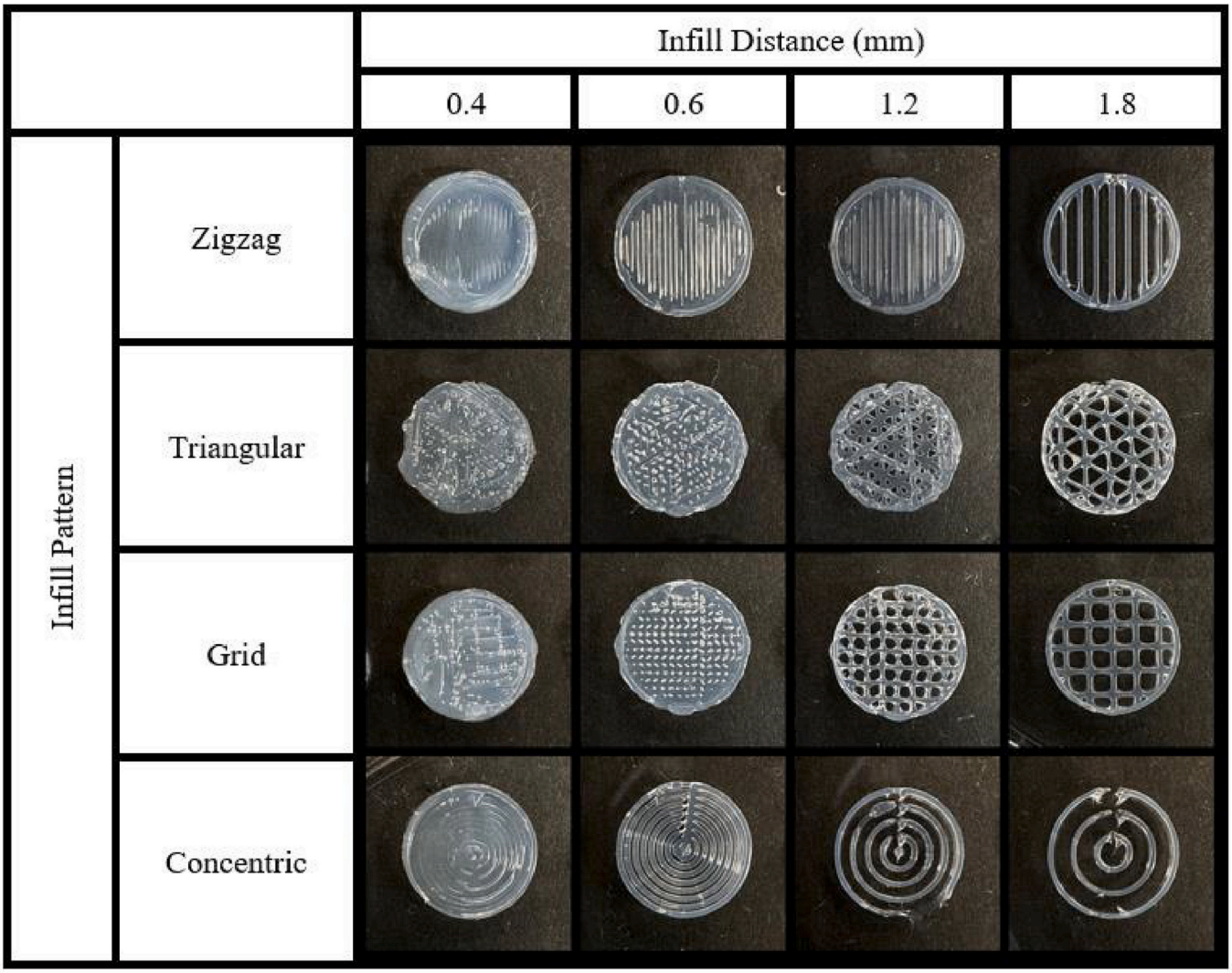

Fig. 3. Distinct surface areas and designs that could be implemented to control drug release for localized delivery targeting infectious disease. PAM printed silicone discs were printed at different infill distances and patterns to underscore visually evident differences in surface area, which pose implications for drug delivery.

same printing material and pattern can lead to a significant increase in mechanical strength [116–118]. Increasing infill density may also lead to decreased porosity and decreased drug release; therefore, it is crucial to find an optimal infill density that balances mechanical strength with adequate porosity [116].

Additionally, the type of material used in the 3D-printed construct plays a crucial role in determining mechanical strength, as the elasticity of the material leads to differences in resistance while keeping parameters like pattern and infill densities constant. For example, scaffolds made from PCL have been shown to have higher resistance and mechanical strength than those made from polylactic acid (PLA) [116,119].

Another important factor to consider when choosing printing material is printability. For extrusion printing, materials that are easily printable will typically have low viscosity and surface tension, which allows them to flow through the printing nozzle with less resistance and be deposited in a precise and controlled manner. Additionally, the material should be able to solidify quickly after printing, without deforming or becoming distorted, to ensure the integrity and accuracy of the final scaffold [120,121]. Common biomaterials used in 3D bioprinting such as hydrogels, polymers, and ceramics have been shown to have good printability and can be used to create scaffolds with high mechanical strength, biocompatibility, and porosity [120,122]. For example, PCL and liver decellularized extracellular matrix (ECM) bioink exhibited differences in viscosity and in dynamic modulus when concentration was increased compared to collagen hydrogels [123], which underscores the mechanical difference between natural and synthetic hydrogels while also demonstrating suitable biomechanical microenvironments through 3D-printing. Bioprinted heart tissue-derived decellularized ECM was bioprinted with 2 layers of PCL to retain mechanical support [124], further underscoring the need for synthetic polymers to maintain structure. In the case of hydrogels, the printability is enhanced by the use of crosslinkers, which increases strength, gelation time, and capability of printing more complex structures [125]. Efforts at combining hydrogels with synthetic biomaterials demonstrated enhanced cell adhesion and proliferation while retaining 3D structure and support [126]. Supplements added to biomaterials or bioinks for 3D-printing have been a useful strategy to optimize ink rheology and strengthen print mechanical integrity [127], which with creation of 3D cultures fabricated through 3D-printing can be utilized to assess efficacy of therapeutics.

Modifying bioink behavior also depends on softness or hardness of target tissue. For example, bioprinted alginate solutions were infused into PCL constructs and displayed osteoblast and chondrocyte proliferation for 7 days [128]. Like this study's case for osteochondral regeneration, bioinks must consider additives in inks, especially as hydrogels from natural derivatives like chitosan, alginate, gelatin and collagen that cannot always retain shape fidelity. Given the target such as adipose tissue [129] or bone regeneration [130], bioink composition is altered for these tissues. Methods like a two-step process of sequential vitamin B2-induced UVA crosslinking and thermal gelation for decellularized bioink further show how to alter bioink strength [131]. These advances are particularly promising for research and development of in vitro 3D cultures to assess efficacy of therapeutics.

Managing printability can be done through elasticity. The elasticity of a material and 3D-printing are interdependent, as the ideal elasticity leads to smoother printing with a reduced likelihood of nozzle clogging and fewer surface flaws. It is crucial to find a balance between elasticity and mechanical strength, so that the filament is strong enough to be extruded through the nozzle. To enhance elasticity, changing the solid plasticizer concentration has been found to be effective [132,133].

Different printing patterns can have a significant impact on both drug release and mechanical strength. The microarchitecture of the scaffold, including the shape, size, and orientation of the individual components, can affect the scaffold's ability to withstand external loads and stresses [134,135]. For example, scaffolds with specific geometries, such as a honeycomb or lattice structures, can have improved mechanical strength due to the added support provided by the interconnected structures [136]. Also, pattern affects the scaffold disintegration rate due to differences in exposed surface area. In a recent study, sharkfill, linear, and hexagonal infills all exhibited swelling and bursting from the center, possibly due to the more porous internal structure of these infill patterns, which made it easier for water to be taken up and increased the internal pressure that caused the scaffolds to disintegrate from the center [133]. In contrast to extrusion printing, SLS printing of drug tablets has exploited laser speed rates to enhance porosity for rapid release though disintegration at the expense of mechanical strength.

In conclusion, infill density plays a crucial role in determining the mechanical strength of 3D- printed scaffolds. Also, the type of material used in the scaffold, the additives added, and the printing pattern are all crucial factors in determining mechanical strength.

2.3.4. Porosity

Altering porosity to control release or for advancing physiologic functionality presents another parameter in 3D-printing that can be exploited. Porosity of 3D-printed drug delivery systems is introduced either from a particular polymer used as a matrix, characterized by its porosity, or by the type of 3D-printing, such as the customized laser speed of SLS and SLA. As point defects accumulate, unintentional pores can have critical consequences for drug delivery for systems that depend on mechanical integrity [137]. Porosity increases the exposed surface area, affecting drug release profiles and the scaffold dissolution mechanism. As laser speed increases, there is typically a trend towards increased porosity within the 3D-printed structure due to inconsistent powder deposition and incomplete melting of particles [138]. With less laser focus on particular areas of powder or a weaker laser, these printing parameters have implications on porosity and mechanical integrity. Hydrogels with highly porous networks exhibited sustained delivery of doxorubicin, with an increasing release through 13 days, whereas non-porous hydrogels exhibited an initial burst followed by slow release through the initial 10 days [139]. Via drug entrapment in a polymeric matrix, SLS printed tablets were subjected to dissolving media, resulting in dissolution and leaching of povidone that formed channels, permitting drug diffusion through the channels and enabling sustained release [140]. With disintegrating tablets, increased porosity increases surface area exposed to the surrounding medium, which induces higher physicochemical interactions. Recently, fluconazole-containing filaments were FDM printed into orodispersible tablets with infill density to yield porosity that reduced disintegration time compared to basic-shaped tablets [141].

Although porosity can be used as an advantage to control drug release, it comes mostly at the expense of mechanical integrity, which can be undesirable for localized delivery vehicles such as vaginal suppositories or drug-eluting bone implants. Lastly, from dynamic mechanical analysis of porosity in 3D scaffolds, it has been deduced that an increase in pore size along the compression axis would result in a weaker construct, while an increased planar surface area (less pores) subjected to compression would provide larger contact area to decrease local stress [142].

2.3.5. Summary

3D-printing design parameters for targeting infectious diseases are summarized in Table 2.

3. Applications of 3D-printing in infectious disease

3.1. Tuberculosis

Isoniazid for treatment of TB has been developed into the form of 3D-printed oral tablets. Due to faster acetylators of isoniazid that result in subtherapeutic plasma exposure levels, personalized dosing was developed through HME and FDM printing with tunable printing parameters to control release [143]. In conjunction with HME, FDM printed

Table 2
Overview of key 3D-printing design parameters relevant for targeting infectious diseases.

Design Considerations	Advantages	Disadvantages
Infill Density	Enhances controlled drug delivery and drug solubility, modifies printing time and material usage	Lesser density increases susceptibility for a mechanically weaker construct
Geometric Shape	Suited for localized delivery to best accommodate the localized site of infection; increased surface area alters drug release profile	May decrease surface area to volume ratio contingent on construct shape, and may hinder mechanical integrity
Infill Pattern	Ink usage and surface area alter drug release profile	Affects mechanical strength of system, reduces infill density and geometry resolution
Mechanical Integrity	Higher mechanical strength enhances drug delivery capability at localized sites that exert physiological forces	May decrease capability for enhanced drug release profiles
Porosity	Enhanced surface area to volume ratio, suitable for rapid release	Poor mechanical integrity, susceptible to biofilm formation and pathogenic niches

transdermal patches have been developed as localized treatment to prevent necrosis in healthy tissue during tuberculosis [144]. With consideration for adults, children, or patients with suboptimal drug absorption capabilities, the numerous parameters for adjustment of release in 3D-printing enable its use for a wide array of patients affected by specific ailments. In contrast, SLS printed isoniazid-loaded tablets were made to disintegrate within 3 s with dissolution in 2 min, which provides simple administration for pediatric patients and facilitates dose-flexible development [145]. Alternative treatments for extrapulmonary tuberculosis, specifically osteoarticular tuberculosis, are needed due to poor patient compliance and drug resistant *Mycobacterium tuberculosis*. For post-surgical applications, 3D-printed isoniazid and rifampicin-loaded mesoporous scaffolds exhibited co-sustained release for over 80 days and good osteogenic capabilities from implantation in rabbits [146]. Similarly, SLM printing of porous tantalum surface followed by coating with isoniazid and rifampicin was used for implantation to treat osteoarticular TB [84]. Note that SLM is less effective to use for printing drugs because it fully melts powders to form layers whereas SLS heats powders to an extent that they can be fused together.

The development of a layer by layer 3D-printed drug-loaded implant designed with isoniazid release for elimination of rapidly dividing mycobacteria, in tandem with rifampicin to prevent transcription and translation of pathogenic DNA, exploits their different mechanisms to improve pharmacodynamic action [147]. The versatile capabilities of pressure-based printing such as PAM printing offers a wide variety of material incorporation to formulate mesoporous structures that exhibit biomechanically relevant strength with controlled release of anti-TB drugs as a prophylactic measure. Although the conventional route for TB drug delivery is oral, TB drugs are susceptible to low bioavailability and inadequate therapeutic index [148]. Fabrication and investigation into different delivery routes using 3D-printing such as transdermal delivery [144] are an appealing alternative, especially in the case of latent TB where compliance with medications is difficult due to the lengthy treatment duration (e.g., 600 mg of Rifampicin taken daily for 4 months) [149]. Latent TB has been targeted through PAM printing of soft tablets for simple pediatric mastication with majority of drug released within an hour [150]. For delayed drug release and absorption, a dual compartment, composed of isoniazid and rifampicin encapsulated in a hollow PLA shell and a PVA cap, was manufactured through 3D-printing to modulate the release kinetics [151]. Exploiting layer-by-layer 3D-printing and polymer and drug concentrations, bilayer tablets have been developed with isoniazid and rifampicin resulting in fast isoniazid release in acidic media and delayed rifampicin release in alkaline conditions; thus, the design enabled a delay between the release of the two drugs when orally administered [106]. From latent to osteoarticular TB, and from pediatric to adult patients, 3D-printing has demonstrated its capabilities in improving pharmacodynamics of TB treatments.

3.2. Wound healing infections

Infections that impede tissue wound healing are often due to the presence of *S. aureus,* which can become antibiotic resistant (such as MRSA) and persist in macrophages and epithelial cells [152]. Lack of treatment could further lead to sepsis and bone infections. Measures against *S. aureus* after orthopedic surgeries have been complemented by treatments customized by 3D-printing that implement prophylactic measures such as drug-eluting implants. For example, 3D-printing custom parameters aid in the fabrication of composites with optimal mechanical strength suitable for implant applications and prolonged release in drug-eluting screws [153]. Capabilities with mechanical integrity and prolonged release of API using FDM have been displayed with development of ciprofloxacin-containing implants to treat bone infections [154]. In other orthopedic applications, controlled release for two weeks was demonstrated from 3D-printed spacers with exceptional mechanical strength with drug loaded formulation [155]. 3D-printed porous implants with different biomaterials intended to enhance cell signaling and growth have been investigated for unintended detrimental consequences such as bacteria adhesion and proliferation, as has been the case for SLM-created porosity on 3D-printed titanium implants [156]. In other applications, SLM 3D-printed porous titanium alloy implants with reduced graphene oxide and silver nanoparticles demonstrated a significant increase in zone of inhibition (the area in which pathogenic bacteria are unable to grow) against MRSA [86]. Silver nanoparticles as a therapeutic have been attached as a layer to 3D-printed polymers to fight against drug-resistant pathogens in healthcare settings [157]. SLM printed porous implants containing magnesium have been developed as a defensive measure against MRSA biofilms due to their ability to downregulate expression of biofilm-related genes, as demonstrated with magnesium implants that showed a decrease in biofilm formation compared to the control [158].

3D-printing has extensively demonstrated and sparked innovative methods to prevent infections after surgical operations. Through adjusting parameters such as laser rate in SLS printing, the extent of porosity can be altered, and architectures such as channels can be designed to elute drugs. Multiple drug-eluting studies have investigated the effect of vancomycin release from implants as post-surgical precaution against infections [85,159,160]. Inkjet printing enabled the development of vancomycin-loaded alginate aerogels for wound healing treatment and defense against *S. aureus,* in which sustained release was demonstrated as the various formulations had >60% of vancomycin release after 3 days [161].With regards to adjusting porosity, FDM printing has been utilized with PCL and porogen ink to create interconnected pores on the printed construct with the intent of localized delivery of antibiotic and chemotherapeutics for regenerating diseased tissue [162].

With the ability to print hydrogel materials, PAM has been used for wound healing and tissue remodeling applications through the development of mesh-like hydrogels composed of chitosan-pectin loaded with lidocaine hydrochloride in which a moist environment optimal for wound healing is retained and controlled release of lidocaine hydrochloride occurs for up to 5 h [163]. Alternatively, 3D-printed rapamycin-loaded hydrogels filled micropores of titanium alloy to create a bioactive prosthetic interface produced a strong inhibitory effect on *S. aureus* proliferation, and bacteria elimination was evident in viability assays [164]. Hydrogels assist with tissue remodeling and healing by retaining an increased water uptake, porosity, and moisture

balance at the site of infection, enabling effective drug delivery for hydrogels. Exploiting these advantages, 3D-printed implants complementary to drug-loaded hydrogels as well as solely 3D-printed hydrogels have been developed with capabilities of slowed and sustained release as antibiotic or antibacterial agents against *S. aureus* and MRSA [165,166]. Other gels, such as aerogels, have also been utilized as vehicles for localized delivery to chronic wounds [161]. Microspheres have been utilized to enhance prolonged sustained release as seen with FDM printed vancomycin-loaded scaffolds to treat bone infections [167].

Several scaffold fabrication studies have exploited the advantages of 3D-printing for localized infection treatment and tissue regeneration at the site of delivery [168–170]. As a prophylactic antibiotic treatment after surgery, 3D-printed femoral implants with reservoirs and microchannels to release doxycycline to combat deep bone infections demonstrated the role of geometric shape for mechanical functionality and release efficacy of the implant [171]. Interestingly, bioprinted scaffolds utilized antibacterial defense capabilities of macrophages and antibiotics incorporated into the ink to demonstrate clearance of *S. aureus* during craniotomy-associated biofilm infection [172]. PAM printing has been used to develop 4 mm thick biofilms of pathogens, *Escherichia coli* and *S. aureus,* to examine 3D models and morphology of clinically relevant antibiotic-resistant pathogens, as 3D constructs have been shown to offer greater drug resistance than 2D biofilms [173]. Bioactive glasses and bioceramics have also been incorporated in formulations for 3D-printing to retain similar compression behavior and strength to natural cancellous bone tissue for orthopedic applications. With formulations that foster an anti-MRSA response, such studies are further complemented by wound healing capabilities as observed by evidence of apatite-forming potential supported by surface morphology relative to mineralized hydroxyapatite [174], regulation of osteogenic and osteoclastic activity based on scaffold influence to induce osteogenic differentiation of cells [175], and sustained release of antibiotics to reduce infection-induced bone loss [176]. With similar drug concentrations as commercial eye drops, the PAM-printed patches exhibited strong anti-microbial effects on high densities (10^8 cells/dish) of bacterial strains such as *S. aureus,* and dissolution tests determined that the majority of levofloxacin was released within 2 h [177]. Lastly, 3D-printed meshes for pelvic floor repair applications have been developed with prophylactic measures against *S. aureus* for post-surgery healing [178,179].

3.3. Non-sexually transmitted viral infections

Safety and efficacy of vaccine development have recently garnered attention during the SARS-CoV-2 pandemic. Under so much scrutiny, it comes to no surprise that innovation in research and development of vaccinations have utilized 3D-printing to further advance this research. 3D-printing has contributed to the role of customizing precise particle shapes of antigen nanoparticles for shape-dependent immune induction as a vaccine delivery strategy [180]. Bioprinting, adjunctively with a method to stabilize size and morphology of particles, has resulted in the development of protein-loaded chitosan nanoparticles as an alternative vaccine therapeutic carrier [181]. Transdermal delivery using microneedles has been an innovative alternative for vaccine and drug delivery. Using FDM and LCD, an additive manufactured sub-assembly with microneedles provided potential insight on how drug delivery through microneedles can be adjusted contingent on personalized patient dosing [182]. With the advantages of safety and less painful administration, microneedles are an alternative administration method compared to hypodermic needles, which has led to preclinical and clinical studies of their application in infectious diseases including poliomyelitis, rabies, TB, measles, adenovirus, SARS-CoV-2, HIV, and influenza [183]. As an example, CLIP printed, ovalbumin and CpG oligonucleotide-coated microneedles demonstrated efficient vaccine delivery evident by in vivo humoral immune responses indicated by the still detectable response of IgG after 196 days [184]. Through SLA and CLIP printing, precise needle diameters can be designed accurately, and 3D-printing can modify the size of microneedles contingent on the shear stress subjected by the delivered treatment during application, with the nozzle tip sizes that do not reach threshold of pain. A study of SLA printed microneedles made use of these design considerations when extruding human hepatocellular carcinoma cells [185].

Bioprinting provides a means to fabricate tissue models to study responses to viral exposure. 3D-bioprinted biomimetic organization that maintains apical and basolateral cell polarity, which affects cell adhesion, signaling, and paracellular diffusion, creates a realistic, physiological microenvironment advantageous for viral infection investigations [186]. Although they are not drug delivery applications, model designs foster research and advance vaccine development as well as the understanding of viral activity in physiological mechanisms. For example, honing the layer-by-layer fabrication of bioprinting, tissue components have been temporarily bioprinted sequentially as ECM, endothelial cells, second ECM layer, and then epithelial cells to construct a proliferating 3D air-blood tissue barrier [187]. Additionally, inkjet printing has been utilized to print layers in the fabrication of an alveolar barrier model [188]. Such advances have enabled the SARS-CoV-2 viral infection process to be investigated through bioprinted tissues spatially similar to those of nasal and bronchial epithelium, cardiac, renal, pulmonary, and hepatic origin [189]. In this manner, bioprinted 3D-models have been used to study SARS-CoV-2 in a more physiological microenvironment and to evaluate how this environment relates to infection mechanism and viral replication [190]. Furthermore, neurotropism as the result of SARS-CoV-2 infection has been investigated utilizing 3D-bioprinted neural-like tissue [191]. Human alveolar cells A549 were bioprinted with gelatin alginate and Matrigel, and infected with seasonal influenza patterns of virus clusters, and the immune response was similar to that observed in natural lung, suggesting the potential for antiviral evaluation in ex vivo systems [192].Other applications such as bioprinted human intestinal tissue have aided in understanding drug permeability [193], bioprinted human HepaRG liver cells transduced by viral vectors [194], and 3D-printed vascular networks integrated with an airway epithelium model with subsequent inflammation response [195]. These applications demonstrate the ranging capabilities 3D-printing may have on 3D-culture model development. Bioprinting also enables easier characterization of permeability and mechanical integrity as observed with bioprinted vasculature conduits [196] and can simplify drug detection/screening observed in vascularized networks [197]. With the aim of advancing pre-screening of drug technology, bioprinted vessels that mimic mechanical and cellular behavior of in vivo blood have helped to develop advantageous angiogenesis models to reduce animal model use [198]. As it pertains to cardiovascular disease, a bioprinted, myocardium model with endothelial cells was developed to provide insight on drug efficacy [199].

Lastly, there have been oral drugs formulated to alleviate influenza symptoms. Through electrohydrodynamic 3D-printing and electrospinning, a multiple layered capsule loaded with paracetamol and chlorpheniramine maleate demonstrated advantageous cumulative release in simulated gastric fluid [200]. With a wide range of applications, 3D-printing, not just in drug delivery, but also in tissue models and microneedles, has demonstrated versatility in virological applications.

3.4. Sexually transmitted infections

The containment of sexually transmitted diseases and infections has been particularly difficult due to the rising number of recurrent cases caused by antibiotic-resistant pathogens [201] Prevention and personalized treatment could be further advanced using 3D-printing. The variety in 3D-printing techniques provides a platform to produce advanced localized delivery vehicles with infill patterns ranging from cylinders to honeycombs for enhanced, controlled release and with compressive load resistance comparable to commercialized products like NuvaRing® and ESTRING® [202]. Similar platforms for localized vaginal delivery such

as suppositories and pessaries have been created through 3D-printing with mechanically relevant strengths [203,204]. For infections arising from vaginal dysbiosis, PAM and FDM printed discs, meshes, and intravaginal rings have been developed as a personalized alternative treatment with metronidazole-loaded devices [205–207]. Furthermore, release kinetics of metronidazole-containing 3D-printed scaffolds have been modeled as a template to advance 3D-printed intravaginal drug delivery systems [208]. Bioprinting has been utilized with live-probiotic incorporation to develop intravaginal rings with antibacterial capabilities [209]. Through the use of FDM, thermoplastic polyurethane filaments have been developed in the form of intravaginal rings filled with jellified metronidazole or chloramphenicol, with demonstrated stability of the drugs and capability to modify the dissolved API amount based on the jellified agent and API used, for bacterial vaginosis treatment [205]. With potential applications for vaginal infections, SLS printlets loaded with clindamycin exhibited rapid disintegration and dissolution, and provided insight on how laser speed may affect porosity, hardness, and dissolution [210]. For pelvic organ prolapse applications, 3D-printing was adjunctively utilized along with electrospinning for the development of PCL prolapse mats with metronidazole-, lidocaine-, and estradiol-loaded fibers [211]. Through the adjunctive use of HME and FDM, acyclovir-loaded intrauterine devices and intravaginal rings exhibited burst release followed by sustained release over a span of 80 days as a localized treatment for herpes [212].

3.5. Human immunodeficiency virus

A strong pathogen presence also increases susceptibility to human immunodeficiency virus (HIV) [213]. These difficulties persist with local challenges on a global scale, making it difficult for a standard treatment, e.g., as exhibited by the global genetic diversity of HIV, especially by the various subtypes in Africa [214]. A variety of subtypes, inconvenient dosing, ineffective viral suppression, and limited treatment concentrations due to toxicity [215] constrain effective antiretroviral therapies. In applications for HIV prevention and viral suppression, FDM printed intravaginal rings were customized with varying infill patterns and densities, where the loaded rings at 50% infill extrusion width showed greater release of both IgG and gp120 fragments compared to the 80% infill extrusion width [216]. Oromucosal delivery is another route of localized delivery for HIV treatment, in which saquinavir (HIV-1 protease inhibitor)-loaded oromucosal patches were fabricated through DIW 3D printing. Contingent on nozzle and layer use, the designed patches incorporated different saquinavir concentrations and demonstrated ability to modulate the microenvironmental pH [217]. HIV antiretroviral protease inhibitors, ritonavir and lopinavir, have both been developed as SLS prints and were characterized by their resulting structure and associated dissolution rate [218,219]. With regards to potential ink formulations, a silver ion loaded zeolite resin significantly reduced the average half-life of HIV-1, exemplifying its potential to be utilized as a 3D-printed resin [220]. Formulations have also been adapted to pediatric dosage forms by HME coupled with FDM printing, which produced minitablets that exhibited advantageous dissolution profiles that enhanced oral bioavailability in the gastrointestinal tract [221]. Combinations of antiretroviral drugs were produced through extrusion printing resulting in a controlled, fixed dosage with evidence of simultaneous delivery and release of multiple drugs that were from different BCS classes [222]. With an ever-increasing option of antiretroviral therapies, 3D-printing holds potential to contribute to the optimization of HIV regimens.

3.6. Malaria

Severe malaria disproportionally affects pediatric patients, who are more likely to suffer fatal consequences; consequently, global pre-referral measures have been implemented, including the administration of rectal artesunate [223]. Rectal suppositories designed via FDM printing sought to improve pre-referral treatments for severe malaria by improving artesunate's half-life and low bioavailability through gradual release [224]. For initial treatment needs, developing different routes of delivery or controlling the release of drug for malaria cases through 3D-printing has a potential role. Although 3D-printing has been utilized for advancing diagnosis transmission research [225–227], it has not yet been extensively utilized with drug delivery and controlled release for malaria applications.

3.7. Oral infectious disease

3D-printing has shown potential to reduce infections related to oral health. Poor oral health such as periodontitis has been linked to diabetes and cardiovascular disease [228]. A 3D-printed dental resin made of polymethylmethacrylate with different concentrations of graphene for reinforcement has been developed to prevent pathogenic colonialization in denture prosthetic applications. Printed disc and bar-shaped specimens using LCD printing were developed, and scaffold antimicrobial properties against *C. albicans* and *Streptococcus mutans (S. mutans)* as well as adhesion to the scaffold surface were evaluated. Growth inhibition of *C. albicans* in various concentrations of graphene after 24 h displayed no recovery after 48 h. The graphene-doped specimens were also able to inactivate *S. mutans* by 1.6 log CFU/mL after 48 h [229]. Another study demonstrated that porous zirconia 3D-printed scaffolds manufactured by using a polymer-infiltrated ceramic network and extrusion-based 3D-printing reduced proliferation of *Escherichia coli* and *Streptococcus salivarius* over 24 h incubation in vitro [230]. Furthermore, vancomycin-loaded chitosan hydrogels have been developed as prophylactics for oral and maxillary defects, and demonstrated sustained release and inhibition of *S. aureus* as a means to prevent oral infectious defects [231].

3.8. Summary

The advantages of 3D-printing in drug delivery for infectious diseases extend into the role of customizing patient treatments. Design considerations of drug delivery platforms manufactured through 3D-printing relate to the therapeutic window of treatment that varies per patient mass and severity of infection. Challenges of antibiotic-resistant infections could be better solved through precise dosing acquired via drug release from intricate architectures. In contrast to systemically administered treatment, local application of medication can significantly alter the course of disease (e.g., applying antibiotic directly on biofilm can disrupt and reduce bacterial growth). Thus, 3D-printing can create localized drug delivery platforms that can exploit surface area exposure to an infected site. Custom parameters that can be modified in 3D-printing such as thickness layers, geometric shape, and surfaces, influence the release kinetics of these drug delivery platforms to benefit local delivery. In surgical outcomes, customized 3D-printed implants enable infection control through antibiotic-loaded materials. Bioprinting aids with the development of 3D cultures that assist in assessing the efficacy of virological applications. The versatility of 3D-printing with drug loading has demonstrated effective outcomes that could be further implemented clinically. From MRSA to STIs, the customization advantages of 3D-printing for manufacturing local delivery platforms holds promise to better contain and eliminate. Infectious diseases.

3D-printed drug delivery applications in infectious disease are summarized in Table 3.

4. Conclusion

As the challenges to tackle infectious diseases continue to evolve, new technology offering flexibility to patient conditions and local adaptation must be utilized to treat patients. From diverse subtypes of HIV and STIs acquired at birth to MRSA infections that threaten limbs and personal survival, these infections become harder to contain with

Table 3
Overview of 3D-printed drug delivery applications in infectious disease.

	3D-Print Drug/Vehicles for Infectious Diseases				
Type of Infection	Types of 3D-Printing	Materials	Drug/ Antibacterial	Route of Delivery	Application
Tuberculosis	HME-FDM	Various polymers and plasticizers for HME, and polylactic acid for 3D-printing	Isoniazid	Oral	Tunable drug release tablets for variety of patients with tuberculosis [143]
	HME-FDM	Polyvinylpyrrolidone, EUDRAGIT® RS PO, tri-ethyl citrate	Quercetin	Transdermal	Maintaining healthy plasma levels in tissues for treatments during tuberculosis infections [144]
	HME-FDM	Polyethylene oxide, polylactic acid, polyvinyl alcohol	Isoniazid, rifampicin	Oral	Delayed and sustained drug release for TB treatment utilizing multiple comaprtments [151]
	HME-FDM	Hydroxypropyl cellulose, hypromellose acetate succinate	Isoniazid, rifampicin	Oral	Bilayer tablets, mitigating drug-drug interaction, for separate drug release at different pH mediums for tuberculosis treatment [106]
	PAM	Mesoporous bioactive glasses and mesoporous silica nanoparticles	Isoniazid	Implant	Post-surgical prophylactic measure for osteoarticular tuberculosis [146]
	PAM	Corn starch	Isoniazid	Oral	Soft, ease of administration tablets for pediatric latent tuberculosis patients [150]
	Inkjet	Poly(DL-Lactic acid)	Isoniazid, rifampicin	Implant	Controlled layer release from implant for enhanced pharmacodynamic actions against bone tuberculosis [147]
	SLS	Kollicoat IR, croscarmellose sodium, and Candurin NXT Ruby Red	Isoniazid	Oral	Disintegrating tablets for rapid release for tuberculosis patients [145]
	SLM	Gellan gum, tantalum	Isoniazid, rifampicin	Implant	Scaffold implantation for site infection for osteoarticular tuberculosis as well as prophylactic treatment against *Staphylococcus aureus* [84]
S. aureus	FDM	PCL mixed with grounded disodium hydrogen phosphate and sodium chloride salts	Doxorubicin, paclitaxel, cefazolin	Scaffold/ Surgery site	Tissue engineering applications for post-surgery by porous networks for drug release [162]
	FDM	PCL, polydopamine, polylactic acid-glycolic acid	Vancomycin	Site of infection	Antibacterial treatment for bone infection applications [167]
	FDM	PCL	Cefazolin	Scaffold for site of infection	Porous scaffold for localized delivery to inhibit *S. aureus* [168]
	PAM	PCL/nano-hydroxyapatite	Vancomycin/ ceftazidime	Composite for surgery site	Drug-loaded implants for various medical application [153]
	PAM	PCL	Levofloxacin	Mesh at pelvic floor site	Drug-loaded meshes for pelvic floor dysfunctions [178]
	PAM	PCL/hydroxyapatite	Rifampicin, daptomycin, macrophages	Site of craniotomy	Treatment against *S. aureus* biofilm infections for craniotomy applications [172]
	Inkjet	Calcium phosphate	Rifampicin, sitafloxacin	Spacer	Biphasic local delivery for reduced bacterial colonies in *S. aureus* osteomyelitis cases [155]
	Inkjet	Calcium phosphate	Rifampicin	Scaffolds/ surgery site	Treatment for implant associated *S. aureus* infections [176]
	SLM	Ti-6Al-4 V	Vancomycin	Implants	Treatment for local drug treatment application for 24 h [85]
	Electron beam melting	Titanium	Vancomycin	Implant	Treatment for surgical site infections against pathogens such as *S. aureus* [160]
	Melt-electro-writing	PCL/polyethylene glycol	Azithromycin	Mesh for implant site	Alternative treatment option for pelvic organ prolapse with antibacterial properties [179]
MRSA	Extrusion-based	Polyethylene glycol diacrylate	Gallium Maltolate	Hydrogels/ surgical Site	Controlled release for inhibiting concentrations of MRSA and *S. aureus* for wound healing [165]
	FDM	Bioactive, glass ceramics	Silver	Scaffolds/ surgery site	Bioactive and antibacterial capabilities against MRSA for orthopedic applications [174]
	FDM	Acrylonitrile butadiene styrene	Silver nanoparticles	Antibacterial coating	Antimicrobial coating used for 3D-printed applications for healthcare associated infections like MRSA [157]

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Table 3 (*continued*)

	3D-Print Drug/Vehicles for Infectious Diseases				
Type of Infection	Types of 3D-Printing	Materials	Drug/ Antibacterial	Route of Delivery	Application
	FDM	Poly(lactic) acid, sodium alginate	Zn^{2+}	Scaffold for site of bone defect	Bone tissue regeneration application with antibacterial activity against MRSA [170]
	PAM	PCL and mesoporous bioactive glasses	Gallium	Scaffolds/ Surgery site	Reparation of bone defects susceptible to MRSA infection [175]
	PAM	Polymerization of caprolactone and lactide	Nano-hydroxyapatite, and epigallocatechin-3-gallate	Scaffold for bone repair/ infection	Alternative to antibiotics for bone tissue repair with resistant capabilities against MRSA [169]
	Inkjet	Alginate	Vancomycin	Site of infection	Aerogel delivery for treatment against common infections acquired from chronic wounds such as from *S. aureus* [161]
	SLM	Ti-6Al-4 V	Reduced graphene oxide, silver nanoparticles	Implant	Porous implant incorporated with antibacterial components as prophylactic measure against MRSA after orthopedic surgeries [86]
	SLM	Mg-Nd-Zn-Zr	Magnesium	Implant	Porous implant as prophylactic measure against MRSA [158]
	SLM	Ti-10Ta-2Nb-2Zr, chitosan-hyaluronic for hydrogel	Vancomycin for hydrogel	Porous implant/ hydrogels	Complementary use with scaffolds and implants to prevent MRSA infection [166]
	SLM	Ti-6Al-4 V	Vancomycin	Implant	Sustained release as treatment against MRSA for orthopedic surgical applications [159]
	(unspecified)	Polyvinyl alcohol, N-carboxyethyl chitosan, agarose, and silver nanowires	Rapamycin	Hydrogels/ surgical Site	Drug-loaded hydrogels to be utilized with implants to fight infections of *S. aureus* and MRSA [164]
Bacterial Infections	SLS	Kollidon® VA64, microcrystalline cellulose, lactose monohydrate	Clindamycin	Oral	Characterized printlets with potential use for bacterial infections [210]
Viral infections	CLIP	Methylcellulose, sucrose, sodium alginate	Ovalbumin, CpG	Transdermal	Custom, microneedle application for delivery of vaccination components with promotion of antigen-specific humoral response [184]
	Multiphoton lithography	Rose Bengal, phosphate-buffered saline	Ovalbumin, bovine serum albumin, gelatin	Antigen nanoparticles	Custom designed antigen nanoparticles for vaccine delivery applications [180]
	PAM	Chitosan, sodium sulfate	Trypsin	Encapsulation	Novel process to modify stabilize formulations and morphology with potential vaccination applications [181]
Influenza	Electro-hydro-dynamic printing	PCL	Paracetamol, chlorpheniramine maleate	Oral	Multilayered capsule for oral consumption with multi-drug release for applications to alleviate influenza symptoms [200]
Sexually transmitted infections	FDM	Ethylene-vinyl acetate	Acyclovir	Vaginal	Prolonged release for herpes infections [212]
	FDM	Thermoplastic polyurethane, polylactic acid, chitosan, hydroxyl ethyl cellulose, agar-agar	Jellified metronidazole or chloramphenicol	Vaginal	Intravaginal ring for localize delivery to treat vaginal infection [205]
	PAM	PCL, copolymer of methyl vinyl ether and maleic anhydride	Metronidazole	Vaginal	Vaginal meshes and discs for localized delivery to treat vaginal infection [206]
	PAM	Mixture of vinyl terminated polydimethylsiloxane (70%) and vinyl, methyl modified silica (30%), methylhydrosiloxane-dimethylsiloxane copolymer, trimethylsiloxane terminated	Metronidazole	Vaginal	Sustained, delivery for vaginal applications [207]
	PAM	Sodium alginate, gelatin	*Lactobacillus crispatus*	Vaginal	Sustained probiotic delivery for vaginal applications [209]
HIV	Extrusion-based	Brown humic acid sodium salt, hydroxyethyl cellulose ethoxylate, quaternized, cellulose acetate phthalate	Efavirenz, tenofovir disoproxil fumarate, emtricitabine	Oral	Fixed dose combination matrix for HIV treatment applications [222]
	FDM	Thermoplastic polyurethane (HP-60D-35 and ATPU-75 A)	Hydroxychloro-quine, IgG, gp120 fragments, coumarin 6 polylactic-*co*-glycolic acid (PLGA)-PEG nanoparticles	Vaginal	Controlled and tunable release of agents for localized delivery treatment for HIV [216]

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Table 3 (*continued*)

	3D-Print Drug/Vehicles for Infectious Diseases				
Type of Infection	Types of 3D-Printing	Materials	Drug/ Antibacterial	Route of Delivery	Application
	HME-FDM	Hypromellose acetate succinate, PEG 4000, magnesium stearate	Ritonavir, lopinavir	Oral	HIV treatment adapted to pediatric dosage form [221]
	HME-SLS	Kollidon® VA64, candurin	Ritonavir	Oral	Enhanced solubility and bioavailability method for applications to drug delivery with example of utilization of an HIV treatment [219]
	SLS	Kollicoat® IR, lactose monohydrate, talc, Candurin® NXT Ruby Red	Lopinavir	Oral	Amorphous printlets with rapid release that demonstrated profile of antiretroviral medication loaded printlets [218]
	DIW	Hydroxypropyl methylcellulose, sodium carbonate, methyl cellulose	Saquinavir	Oromucosal	Flexible patches with potential application for localized delivery treatment against HIV [217]
Malaria	FDM	Polyvinyl alcohol, polyethylene glycol	Artesunate	Rectal	Drug loaded-suppositories for pediatric patients with severe malaria [224]
Oral Infection	PAM	Chitosan	Vancomycin	Oral	Sustained release and inhibition of *S. aureus* in oral and maxillary defects [231]
	Inkjet	Tetragonal zirconia polycrystal (3Y-TZP), Pluronic® hydrogel ceramic paste, bisphenol A glycerolate dimethacrylate (Bis-GMA), and tri(ethylenglycol) dimethacrylate (TEGDMA) copolymer	Surface modification of zirconia	Oral	Reduced the proliferation of *E. coli* and *Streptococcus salivarius* [230]
	LCD	Polymethylmethacrylate, graphene	Graphene-polymethylmethacrylate resin	Oral	Antimicrobial activity of resin inhibits *S. mutans* and *C. albicans* [229]

changes in pathogen genetic makeup and increased population mobility. Challenges in manufacturing platforms to create customizable treatments can be tackled with 3D-printing to address the global burden of infectious diseases. 3D-printed drug delivery platforms have found success in local application and modified release kinetics. Manufactured in the form of suppositories, meshes, implants, intravaginal rings, etc., these alternative platforms provide promising solutions to the global challenges of infectious diseases. Development will need to be cognizant of individual patient genetic susceptibility as incorrect dosing could add to the problem of antibiotic-resistant infections. With the potential of clinics to house 3D-printers, there are challenges to ensure proper production of drug delivery constructs. In terms of equity in healthcare, precise and customized dosing through 3D-printing, previously incapable of manufacturing, may be a viable strategy to level the access to advanced treatments for infectious diseases through streamlined manufacturing and lower input costs. To this point, in-house 3D-printers at clinics for underserved populations have the potential to impact health on a global scale. A future focus of 3D-printing in therapeutic delivery will be on regulating its use with regards to patient safety as well as educating patients about its capabilities in medicine to advance acceptability. From oral medications and localized delivery platforms to implants and prosthesis, 3D-printing is expected to help address the challenges of infectious diseases on a worldwide scale.

Declaration competing of interest

None.

CRediT authorship contribution statement

Anthony J. Kyser: Writing – review & editing, Writing – original draft, Visualization, Investigation. **Bassam Fotouh:** Writing – original draft, Investigation. **Mohamed Y. Mahmoud:** Writing – original draft, Investigation. **Hermann B. Frieboes:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

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