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The potential applications of nanocomposites in 3D-printed drug delivery systems

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Abstract

Additive manufacturing is a renowned technology for producing three-dimensional objects, based on ceramic, metal, and plastic materials for different applications. This review examines and provides a perspective on using nanomaterials along with biopolymeric matrices for 3D printing (3DP) with potential applications in pharmaceutical dosage forms. Many 3DP methods have been developed for the formulation of drug delivery systems, including stereolithography, fused deposition modelling (FDM), selective laser sintering, and bioprinting through droplet- or extrusion-assisted techniques. Polymeric drug-loaded nanocapsules regulated the drug release profiles from 3D-printed tablets with faster drug release from 50% infill tablets. Also, incorporating nanomaterials/micro-ribbons significantly changed the mechanical and flow properties of polymers used in 3DP. For example, the addition of 1% w/w chitosan micro-ribbons to poly-vinyl alcohol powder improved filament mechanical properties for FDM 3DP in terms of flexibility and stiffness, with enhanced disintegration time of 3D-printed oral films. Berberine nanoparticles were integrated into a biodegradable and biocompatible 3D-printed pill, which facilitated sustained drug release and improved gastrointestinal absorption. Furthermore, nanocrystals enhanced the solubility of 3D-printed oral films. In conclusion, nanocomposites improved 3D-printed drug delivery systems in different aspects such as mechanical strength, solubility, and drug release profiles.

Keywords: 3D printing; nanoparticles; pharmaceutical dosage forms; mechanical properties; nano-fibres; fused deposition modelling

Introduction

There is potential for the introduction of three-dimensional printing (3DP) technology into the pharmaceutical sector to lead to a paradigm shift in the process of designing, formulating, and manufacturing medicines, as well as their utilization by the end user [1, 2]. It has also become a focus of research and development in numerous fields [3, 4] including biology and biomedicine, as it could construct any desired 3D model quickly and accurately [5–7]. As a rapid prototyping (RP) technology, one can conceptually define the term 3DP as a direct digital manufacturing method that allows the creation of a broad range of object geometries (including internal channels) using a wide variety of materials [8, 9]. Various methods have been introduced for additive manufacturing (AM), such as fused deposition modelling (FDM), stereolithography (SLA), inkjet printing, and selective laser sintering (SLS) [10]. Among these, the most popular and most cost-effective is FDM [11].

The most direct factors affecting 3DP quality are the various printing strategies and dimensional scales [12]. For example, the FDM 3DP method operates based on the principle of material extrusion, as illustrated in Fig. 1A. In this technique, a thermoplastic polymer undergoes melting (a key requirement) and is subsequently extruded through a nozzle onto a build platform. The nozzle's movement is dictated by the program (g-code) generated by slicing software tailored to a specific design. The melted polymer is deposited layer by layer, forming a three-dimensional (3D) object [13]. Common materials employed in this method include poly(lactic acid) (PLA), acrylonitrile butadiene styrene (ABS), thermoplastic polyurethane (TPU), polypropylene (PP), nylon, polycarbonate, and polyether ether ketone (PEEK) [14]. Key advantages of this method encompass its capability to process a diverse range of materials, low maintenance costs, absence of toxic chemicals, rapid production of thin objects, an overall tolerance of 0.1 mm, and ease of material change. However, notable disadvantages include surface roughness, a relatively slow process, dimensional constraints, the occurrence of voids, and lower mechanical properties [15].

Nanotechnology offers new opportunities in the development of more advanced 3D-printed medical devices and drug delivery systems that have the potential to significantly influence and improve therapeutic effects [16]. Nanomaterials include nanoclusters, nanoparticles (NPs), nanocrystals, nanofibres, nanotubes, nanorods, nanowires, and nanofilms [17]. It has been proven that the use of nanomaterials is favourable

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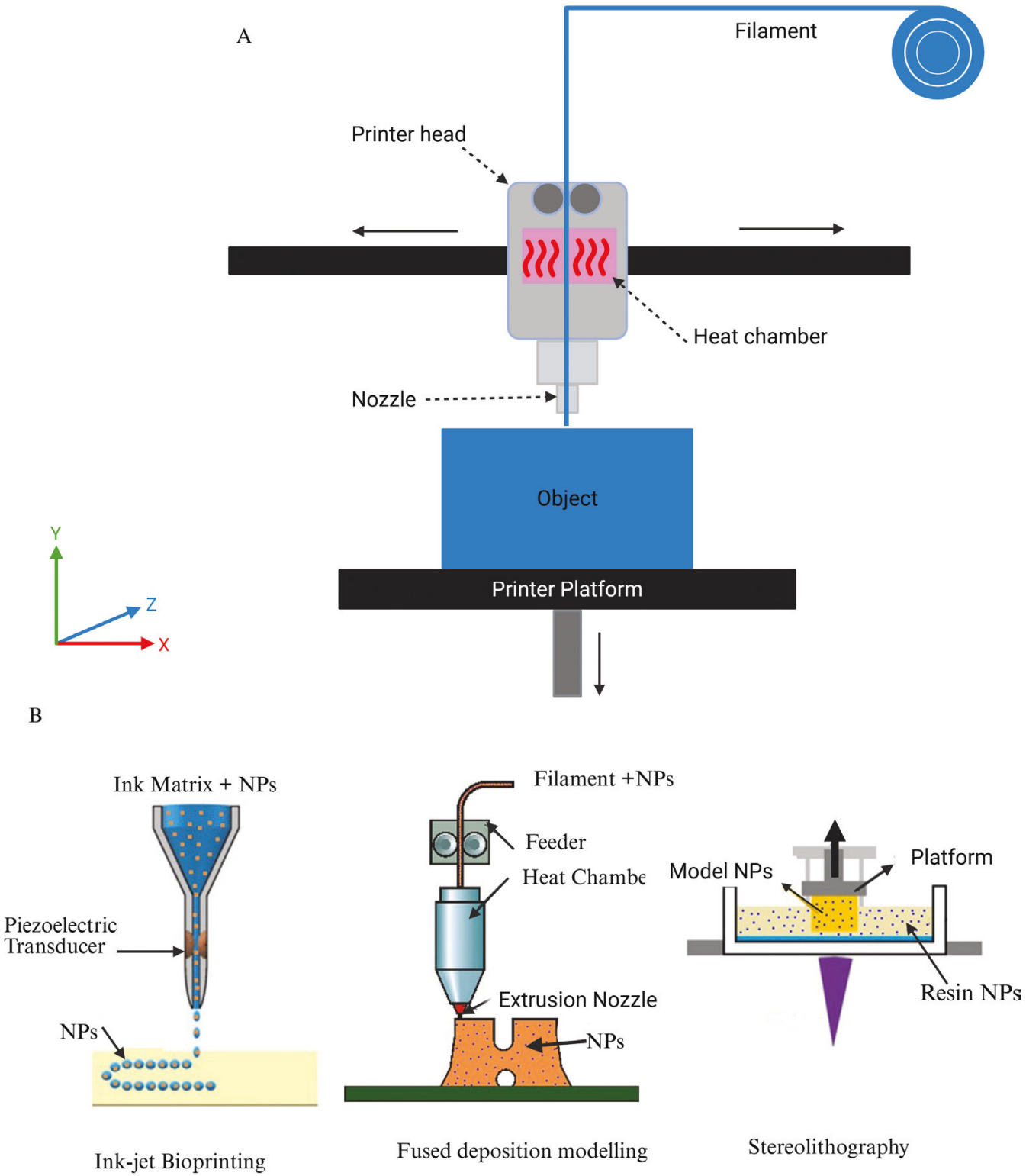

Figure 1. (A) Schematic diagram of fused deposition modelling using composite filament for the 3DP process. (B) Schematic diagram of the incorporation of nanomaterials in three different 3DP methods.

in the fields of *in vitro* diagnostics, drug delivery, and *in vivo* imaging, as well as for the development of implants, biomaterials, and coatings. Nanofillers are more advantageous than macrofillers, since they have a high aspect ratio and an extremely high surface-to-volume ratio. Furthermore, uniform dispersion of these nanofillers into the host matrix allows them to offer a large interfacial area per volume, which in turn improves the polymers' mechanical properties [18]. To date, the combination of nanotechnology and 3DP has led to a new age of conductive tissue engineering scaffolds that possess multifunctionality and optimized properties [19]. The interaction between device- (biomaterial-) and cell has

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promoted broad applications of different nanomaterials in biomedicine and biology [20], such as SiO_2-gold nanoshells [21], water-soluble polymers [22], hydrogels [23], starch-based powders [24], and fibrin gels [25]. Utilization of these biomaterials has been seen in the fabrication of various medical devices, such as neurone-adhesive patterns [26], collagen scaffolds [27], synthetic biodegradable scaffolds [28–30], as well as fibrin channels [23, 31]. Based on all the 3D nanoscale fabrication methods, there is greater adoption of 3DP due to its speed in fabrication and precision in dimensions and geometric shapes [32]. To date, various nanofabrication techniques, including electro-spinning, phase separation, self-assembly processes, thin film deposition, chemical vapour deposition, chemical etching, nano-imprinting, photolithography, and electron beam or nanosphere lithographies, have been developed to create nanomaterials with both ordered and random nanotopographies [33].

Nanoparticles have begun to be employed in the 3DP of pharmaceutical dosage forms with improved mechanical [34] and drug release properties [35]. This review paper inspects and provides a perspective on using nanomaterials along with biopolymeric matrices for 3DP with potential applications in pharmaceutical dosage forms. The ongoing efforts and trends specific to the formulation of nanocomposites have been investigated and summarized concerning additive manufacturing.

Nanomaterials for 3D-printed polymeric composites

When materials are reduced to the nanoscale, there is a substantial increase in the ratio of surface roughness and surface area to volume. This change can lead to heightened surface reactivity and enhanced physicochemical properties, including electrical, mechanical, optical, magnetic, and catalytic characteristics [36]. The advanced properties of nanobiomaterials have given them the excellent potential for numerous biomedical applications, such as utilization in advanced tissue/organ regeneration [37]. Kaynak and Varsavas [38] investigated the mechanical characteristics of three types of composites: neat PLA, glass fibre (GF)-reinforced PLA, and TPU-blended PLA. Both injection moulding and 3DP methods were employed in the study. Using twin-screw extruders, composite filaments were produced for 3DP, containing 10 %w/w TPU and 15% w/w GF in a PLA matrix. Subsequently, dog-bone specimens were 3D printed from these filaments, and their performance was compared with dog-bone samples obtained through injection moulding. Upon conducting tensile and flexural tests, the researchers did not observe significant differences in strength between the specimens from the two manufacturing methods. However, they did note a slight increase in the elastic modulus values of the 3D printed specimens compared to the injection moulded ones. This difference was attributed to the stiffening effect caused by the slightly textured structure formed during the 3DP process.

Both solid and liquid polymers have been used as feedstock for 3DP. Even though 3D printed polymer scaffolds possess customized geometric complexities, the absence of bioaffinity and mechanical integrity still creates hurdles for their use in clinical applications. Further tests need to be conducted on the methods of dispersing and integrating different nanomaterials into biopolymeric matrices to address these problems. Thus, nanomaterials like metals, ceramics, carbon, and polymers are being examined for their potential use in 3D printed biomedical scaffold applications [39, 40]. Figure 1B presents schematically the incorporation of nanomaterials in typical 3DP methods. Table 1 provides a selection of the utilization of natural and synthetic biopolymers that have been incorporated with nanomaterials and processed using a range of 3DP techniques. The addition of nanomaterials improved mechanical and viscoelastic properties.

Polymeric nanomaterials

Over the past decade, nanoscale cellulose nanocrystals (CNCs) and cellulose nanofibers (CNFs) derived from natural resources have been extensively utilized in the biomedical field, including applications in tissue engineering, wound healing, drug delivery systems, implants, and cardiovascular devices. This widespread use is due to their exceptional chemical, mechanical, and biocompatible properties. Recent research has explored the combination of 3DP with nanocellulose and polymers as a promising approach for future regenerative therapies. The printability of nanocellulose hydrogels, attributed to their shear-thinning behaviour, along with their ability to support living cells, enables 3D bioprinting with nanocellulose. This advancement is considered to have significant potential [41].

Often, polymers at the nanoscale level and in a variety of structures (spheres, tubes, fibres, core-shell designs) are mixed with bulk polymeric matrices to improve the functionality of final tissue constructs and processability in 3DP. For instance, when nano-fibrillated cellulose was incorporated into an alginate matrix, an adjustable shear-thinning bioink was produced. The resulting material was then used for printing cartilage tissues of the ear and the meniscus at room temperature and with high structural reliability. As proof-of-concept, the bioink was used to entrap human chondrocytes before printing and resulting in a viability of over 70% [42].

Another application of nanofibers has been in cartilage tissue engineering to facilitate the treatment of patients with congenital or acquired hearing defects. Bioink based on nanofibrillar cellulose and alginate has been utilized to conduct 3DP for the fabrication of hearing structures with appropriate cellular distribution and density. It was observed that the process supports the redifferentiation of cells and the development of components with cartilage-specific extracellular matrix [43]. For the preparation of a hydrogel ink using CNCs and an interpenetrating polymer network (IPN) made up of gelatine and sodium alginate, it was discovered that a vast improvement in the rheological properties was achieved for 3DP. Furthermore, it was observed that the orientation of the CNCs was aligned at about 80% of the printing direction, as proven by the 2D wide-angle X-ray scattering. Moreover, there was a successful optimization of the gradient pore structures for the 3DP of scaffolds. Thus, it was able to demonstrate the potential of CNCs to create scaffolds with controlled pore structure, pore size, and nanocrystal alignment via 3DP [44]. By taking advantage of their inherent stiffness and robust mechanical strength, CNCs were incorporated into composites to lend toughness to the 3D-printed objects. 3DP via SLA was used with the CNC nanocomposite hydrogel to form structures appropriate for tissue engineering [45].

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Table 1. Summary of biopolymers incorporated with nanomaterials utilized in a range of 3DP techniques.

	Nanomaterials	polymers	Printing method	Application	Main outcome	Ref.
1	Nanocrystalline hydroxyapatite (nHA)	Chitosan	Extrusion Bioprinting	Bone tissue engineering	Storage moduli increased for formulations containing nHA	[113]
2	Silver nanoparticles (AgNPs)	Alginate	SLA	Bionic ears	The printed ear showed enhancement in auditory sensitivity for radio frequency reception, and both paired left and right ears capable of stereo audio music listening	[71]
3	Nanocellulose	Alginate	Extrusion printing	wound Dressing	Enable the creation of personalized implant and wound-healing products containing therapeutic agents with gradual release	[47]
4	nHA	Collagen	Extrusion printing	Tissue Vascularization engineering scaffolds	Internal microchannels were created within the model	[114]
5	Single-wall nanotubes (SWCNTs)	Agarose	Extrusion printing	Biosensors, flexible electronics, tissue engineering, and organ printing.	Enhanced electrical conductivity of 3D printed hydrogels, and allowed 3DP of patterned hydrogel structures.	[115]
6	Multi-wall nanotubes (MWCNTs)	Alginate	Extrusion printing	Fabrication process to print vascular conduits directly	Improved tensile strength and elastic modulus, along with reduced ultimate strain, result from greater polymer chain cohesion due to increased physical entanglements.	[116]
7	Nanocellulose	Alginate	Extrusion Bioprinting	Cartilage tissue engineering	Significantly improved shape fidelity	[42]
8	Lidocaine, diclofenac sodium	CMC nano-fibres	Gel extrusion	Wound healing	Sustained release of encapsulated drug (lidocaine) in the nano-fibres	[50]
9	nHA	Polylactic acid	FDM	Bone tissue repair	Improved stem cell adhesion, vascular cell growth, proliferation, and osteogenic differentiation	[55]
10	PLGA nanofibers	Polycaprolactone	FDM	Cell therapy and tissue regeneration	Achieve greater mechanical stability and enhanced cell adhesion	[49]
11	Gold nanoparticles	Polylactic acid	FDM	Bone tissue regeneration	Enhanced mechanical strength, increased stiffness, and improved cell adhesion	[66]
12	nHA	1,6-Hexanediol l-phenylalanine-based poly (ester urea)	FDM	Bone regeneration	Significantly elevated mechanical properties and enhanced scaffold calcium mineralization	[57]
13	MWCNTs	Polycaprolactone	Extrusion printing	Cardiac tissue engineering	CNTs reinforced the alignment of the polymer chains. As a result, improvement in elastic modulus and hardness	[77]
14	Indomethacin nanocrystal	Hydroxypropyl methyl cellulose	Extrusion printing	Fast dissolving oral film	Developed 3D printed film and enhanced solubility	[79]
15	Fe_3O_4 NPs	Polycaprolactone	Paste extrusion	*In vitro* Doxorubicin delivery	Developed osteogenic activity, localized anticancer drug delivery, and magnetic hyperthermia	[80]
16	albendazole nanocrystals	PEG 1500/ propylenegycol	Melting Solidification Printing Process	To improve drug aqueous solubility	3D printed tablets with 25% nanocrystals released 90% of the drug within first 15 min, compared to 25% of commercially available capsules	[81]

3DP using bioinks can be used to print structures that mimic musculoskeletal tissues to create nanofibrous matrices. Polylactic acid nanofibres were therefore integrated within alginate hydrogel before being bioprinted with human adipose-derived stem cells (hASCs). Utilising bioink with nano-fibre reinforcement allowed cells to proliferate in bioprinted parts for over 2 weeks with excellent cell viability. At its peak (day 7), the metabolic activity of the cells with the nano-fibres was 28.5% higher than those without nano-fibres. Regular examination of the bioprinted meniscus along the external areas revealed greater cell density compared to the structure's internal regions. Proteoglycans and collagen were both found in the regions around hASCs, indicating that chondrogenic differentiation and secretion of extracellular matrix had taken place [46]. To examine the behaviour of nanocellulose-alginate hydrogels during the 3DP of the constructs, computational fluid dynamics tools were employed. The composite hydrogel attained enhanced biofunctionality when cellulose

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nanofibrils provided sites where avidin protein was able to anchor covalently. As a result, water absorptivity and tissue compatibility were observed under moist conditions [47]. To collect and sense pore-forming toxins and facilitate detoxification, a poly(diacetylene) (PDA) nanoparticle-based 3D device was devised. Specifically, dynamic optical projection stereolithography (DOPSL) was used to create the bioinspired 3D device. This was done by placing PDA NPs in a polyethylene glycol diacrylate (PEGDA)-based 3D structure possessing a modified liver lobule structure [48].

Two synthetic biopolymers (PCL and PLGA) were used in combination to achieve enhanced mechanical stability of 3D printed scaffolds fabricated from molten PCL filaments and to improve the cell adhesion by using PLGA nanofibres. It was found that the scaffolds were suitable for use in tissue regeneration and cell therapy processes. The synthesized scaffolds consisted of 3D printed PCL with electrospun PLGA nanofibre walls and seeded cells. Tensile tests and SEM were conducted and revealed no loss in fibre integration and mechanical strength within the matrix. Fluorescence and electron microscopy were used to examine the attachment of cells. Further tests revealed insignificant toxicity and cell differentiation into chondrogenic and osteogenic types within the scaffolds. Results showed that adding nanofibers increased the mechanical stability and enhanced cell adhesion [49].

Diclofenac sodium (DCS), a nonsteroidal anti-inflammatory drug (NSAID), and the local anaesthetic lidocaine (LID) were mixed in wound-dressing materials and prepared via two distinct techniques. A comparison was made between the release of these drugs from a 3D bioprinted carboxymethyl cellulose (CMC)-based scaffold and their release from an electrospun CMC-based nano-mesh. LID and DCS had release profiles that were completely distinct for the electrospun materials compared with those obtained from 3D-printed scaffolds. Specifically, for electrospun nanofibres, up to 90% of both drugs were released within the first 30 min, signifying a promising foundation for treating wounds that require quick pain reduction. The latter is notable in LID, whose onset of action occurs within a couple of minutes, with an effect that is measurable in hours [50].

Tablets (printlets) were prepared by the FDM 3DP after soaking poly(ε-caprolactone) (PCL) and Eudragit® RL100 (ERL) filaments with or without a channelling agent (mannitol) in deflazacort-loaded nanocapsules (particle size: 138 nm). Results showed that the drug loading and drug release profiles were dependent on the polymeric material of the tablets and the presence of the channelling agent. In particular, tablets prepared with 50% infill had a higher drug loading (0.27% w/w) and a faster drug release rate [35].

Ceramic nanomaterials

Tissue engineering is starting to utilize nanoscale ceramics, such as bioactive glass (BG), silica (SiO_2), hydroxyapatite (HA), tricalcium phosphate (TCP), zirconia (ZrO_2), and alumina (Al_2O_3) mainly due to their enhanced bioactivity and mechanical strength compared to their bulk counterparts [51]. Nanoceramic materials were added to polymer matrices to simulate composite hard tissues and enhance their degradation profiles, mechanical properties, and biochemical functions [52]. This was achieved by using alkaline ceramics such as hydroxyapatite to neutralize the acid end-products degraded from polymeric scaffolds such as PLA [53]. 3DP has recently improved nanoceramic distribution in polymeric matrices for hierarchically structured scaffolds. Furthermore, nanohydroxyapatite (nHA) is steadily being accepted as a filler material. Almost 70% of the hard tissues in the human body are made of calcium hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) and are clinically utilized for dental and orthopaedic repairs [53]. These nanocomposites facilitated the passage of bone cells and bone ingrowth. However, the main challenges of creating bone-like structures by using the aerosol-based 3DP system are dispersion of nanophase ceramics in the polymer solutions by applying controlled sonication power and adjusting rheological properties of nanocomposite suspensions for ideal aerosolization [54].

PLA-based FDM-printed scaffolds embedded with nHA gained various active sites where human mesenchymal stem cells (hMSCs) could attach, spread, and undergo osteogenic transformation. This eventually led to an enhancement in the vasculature and bone matrix formation compared to pure PLA scaffolds [55]. In 3D printed PLGA constructs, an increase in the content of nHA from 0 to 20 wt.% resulted in a gradual increase in compressive strength and modulus. The results showed that the compressive strength of the scaffolds increased from 1.82 to 32.81 MPa. However, composites started to show signs of brittleness beyond that point [56]. Porous scaffolds (75% porosity) with enhanced compressive modulus (~50 MPa) were obtained when 1,6-hexanediol L-phenylalanine-based polyester urea (PEU) was blended with HA nanocrystal in a layer by layer, fused deposition process. Furthermore, seeding of the MC3T3-E1 pre-osteoblasts achieved >95% cell viability and a composition-dependent improvement of radio-contrast after a week-long incubation in phosphate-buffered saline (PBS) at 37°C. There was a 330-fold increase in bone sialoprotein expression with PEU scaffold containing 30% HA nanocomposite by week 4. A 185-fold increase was also generated within the mineralized extracellular matrix of PEU-nHA. The rarely examined PEU-based nanocomposites have therefore stimulated bone regeneration and were considered suitable to orthopaedics [57]. The addition of nHA and TCP in PCL-based composite scaffolds, with two different synthesis methods, increased the compressive modulus by 130% and 107%, respectively [58]. Cell adhesion was enhanced by the incorporation of glass NPs into a nozzle-based 3D-printed PLA scaffold as it made the surface of the scaffold rougher and more hydrophilic [59]. Another study integrated calcium phosphate NPs (Ca–Ps) into a chitosan and collagen composite that produced a scaffold that mimicked natural bone structure and improved osteo-conductivity and surface area [60].

Recently, there have been attempts to produce composite bioinks using ceramic nanomaterials to enable 3D bioprinting. The hMSCs were suspended in poly(ethylene glycol) dimethacrylate (PEGDMA) inks and used with a thermal inkjet printer. With bioactive glass (BG) and HA NPs undergoing simultaneous polymerization produced substrates having an accurate arrangement in the 3D structure. The interaction between hMSCs and nHA had high cell viability (>85%) and a higher compressive modulus after a 3-week period. Biochemical analysis indicated high production of collagen and elevated activity of alkaline phosphatase in the PEGDMA-nHA group, in agreement with PCR-based gene expression data. This study indicated that nHA has a higher efficiency compared to BG for hMSC osteogenesis

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related to bioprinted bone constructs [61]. To address the challenge of producing an osteochondral arthritic joint interface, a compact stereolithography 3D printer was used to process a nano-ink composite formed by using nHA. The osteochondral scaffold produced higher *in vitro* stem cell proliferation, adhesion, and differentiation due to the hierarchical nano-to-micro structure having spatiotemporal bioactive factor gradients [62].

Synthetic silicate clay is one class of nanomaterials that has various applications in bioprinting. Nanoclays were deemed appropriate for regulating shear-thinning behaviour and pre-gel solution viscosity in bioinks for producing customized tissue constructs. Several shapes, such as a hemisphere, cube, bundle, pyramid, the human ear, and human nose, were created using ternary poly (ethylene glycol) (PEG)-alginate-nanoclay composite hydrogels. The nanocomposite hydrogel of this kind was tough yet appropriate for 3DP and endured cell culture [63]. Novel 3D bone scaffolds were successfully crafted and printed, featuring supporting structures for bone formation and 3D microvascular mimicking channels with a high degree of interconnectivity. These attributes provided better and more efficient osteogenic bone regeneration along with vascular cell growth [55]. By employing a chemical functionalization method, the specimens were conjugated with nHA to produce novel nano- and micro-featured tools for vascularized bone growth [55].

hMSCs mixed in PEGDMA were co-printed with hydroxyapatite (HA) and bioactive glass (BG) through simultaneous polymerization to obtain printed substrates having precise positioning in three-dimensional (3D) locations. This was to evaluate the activity of bioactive ceramic NPs towards the stimulation of osteogenesis in printed bone marrow-contained hMSCs in PEGDMA scaffold. Considering all the groups, those hMSCs that interacted with HA presented the most significant cell viability (86.62 ± 6.02%) and a higher compressive modulus (358.91 ± 48.05 kPa) after 21 days in culture. Biochemical analysis indicated that the PEG-HA group had the highest production of collagen and activity level of alkaline phosphatase, which agreed with quantitative PCR-based determination of gene expression. The poly (ethylene glycol) glycinamide (PEG-GA) scaffold had the highest level of collagen deposition when assessed using Masson's trichrome staining. Hence, HA has better effectiveness when compared to BG, for hMSCs osteogenesis in bioprinted bone constructs [61].

Metallic nanomaterials

Metals not only have superior mechanical strength but also serve as essential frameworks for several bone-forming proteins and enzymes, and as enzyme co-factors to start angiogenesis and the formation of extracellular matrices. In comparison to their bulk counterparts, metallic nanostructures demonstrate an increased ability to boost antimicrobial activity and bioactivity and characteristics, such as fluorescence, plasmonic behaviour, electrical conductivity, and magnetism. The inclusion of metallic nanostructures in 3D printed polymeric tissue constructs brings the multifunctionalities of the engineering applications to the target tissue. Despite the rapidly broadening metal NPs applications in therapeutics, sensors, and medical diagnostics, there are few reports on tissues created by 3DP methods [64]. Silver/graphene oxide homogeneous nanocomposites were applied to 3D printed β-tricalcium phosphate bioceramic scaffolds, resulting in a dual-functional scaffold. Through *in vitro* testing, the scaffold demonstrated both antibacterial and osteogenic properties [65].

Gold NPs (GNPs) have a biocompatible nature and have been the subject of extensive study for bone engineering because they possess the remarkable ability to stimulate osteogenic differentiation and bone formation [64]. The shortcomings of bioactivity and mechanical stability make conventional hydrogels inappropriate for the repair of body tissue. These limitations may be overcome by integrating bioactive GNPs in hydrogel-reinforced PLA using 3DP. The results demonstrated that nanocomposite hydrogel stiffness after reinforcement using 3D-printed microstructures may be adjusted to replicate the stiffness of the human mandibular condyle. Increasing gene expression and better osteogenic differentiation were made possible by employing such a method [66]. In an alternative study, GNPs were produced using an aqueous environment on 3D-printed PCLs having a PDA coating. The GNPs embedding technique with printed scaffolds markedly increased bone matrix deposition both *in vivo* and *in vitro* [67].

3D-printed core-shell capsules exhibiting programmable release were described by Gupta et al. [68]. Those capsules had aqueous cores and PLGA shells loaded with plasmonic gold nanorods which provided selective rupturing of the capsules upon laser irradiation. The capsules were described as a proof of concept of the combination of additive manufacturing and smart materials [69]. Silver NPs (AgNPs) were concurrently grown after embedding them with metal salts, PEGDA oligomer, and photo-initiator, along with radiation exposure, heat treatment, and 3DP of the composite. The AgNPs exerted a positive effect on the thermo-mechanical properties, electrical attributes, and morphology of the 3D-printed nanocomposites [70]. A bionic ear was created in the shape of the anatomical human ear using 3DP with a combination of a cell-seeded hydrogel matrix, silicone, and AgNPs. The cell-seeded hydrogel matrix was used for *in vitro* creation of cartilage tissue, where AgNPs provided electric conductivity to the silicone-based ear antenna coupled to electrodes. The 3D-printed structure exhibited stereophonic ability and auditory detection of radiofrequency signals. Hence, the produced bionic ear has demonstrated both nanoelectronic and biologic characteristics after integration with the 3D printed AgNP composite [71].

The mix of nano-titania (natural oxide of titanium) NPs (32 nm) with PLGA showed potential in drug delivery systems and bone tissue engineering. The adaptable nanocomposite properties show promise in producing dental prosthetics. Moreover, the surfaces of such nanocomposite scaffolds demonstrated uniform dispersion of titanium NPs after 3DP [54]. Implantable magnetic mat systems to tackle hyperthermia during anti-cancer treatment were produced by the introduction of iron NPs (Fe_3O_4) in E-jet 3D printed mats. The magnetic characteristics of PCL/Fe_3O_4 mats provided efficient heating during exposure to alternating magnetic fields [72]. The stability of encapsulated NPs and the retained heating capacity made possible the cyclic heating provided by nanocomposite mats. These mats were positioned near tumours using surgical procedures instead of intravenous injection. 3D printed mats were also recommended for the delivery of iron NPs for inducing hyperthermia for tumour treatment [72].

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The combination of hydrogel with NPs provides the opportunity to develop smart (stimuli-responsive) materials [73].

New avenues in the manufacturing of low-cost and on-demand antimicrobial surgery equipment could be opened by combining 3DP and sonochemistry technology. For example, a surgical retractor was designed from a commercial PLA filament using fused deposition modelling, while a thin layer of Ag NPs was developed via a simple and scalable sonochemical deposition method. The printed retractor exhibited a reduction in *Staphylococcus aureus* (*S. aureus*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Escherichia coli* (*E. coli*) viability in experiments conducted at 30, 60, and 120 min during lab trials. Also, SEM showed homogeneous and full surface coverage of Ag NPs [74]. Furthermore, silver NPs were embedded within PLA filaments; and the 3D-printed objects demonstrated antibacterial activities. The printed objects exhibited antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli,* and *Pseudomonas aeruginosa*. This study showed that incorporating AgNPs (0.01–5% w/w) into PLA does not significantly alter its bulk properties but imparts antibacterial characteristics to the composite [75].

Composite nanomaterials

For tissue engineering, 3DP is making a transition to the creation of complex polymeric structures. Multifunctional 3D constructs can be formed by integrating several monofunctional nanomaterials. PLGA nanospheres (75 ± 17 nm in diameter) and nHA-based (80–100 nm in length) bioinspired nanomaterials were surrounded by chondrogenic transforming growth factors. Nanoink-based stereolithography has been demonstrated to create interconnected three-layer graded osteochondral scaffolds. The results showed that 20% nHA increased the compressive modulus in the scaffold by 29% compared to non-nHA control. Also, *in vitro* experiments using mesenchymal stem cells demonstrated better cellular differentiation and proliferation [62].

Dual nanomaterials were created using carbon nanotubes (CNT) with nHA/PCL composite scaffolds having square pores with a diameter range of 450 to 700 nm. The PCL polymeric phase had well-dispersed CNT and nHA inside the composite having 20 nm mesopores induced by the CNTs present in the scaffold (Figure 2). For composites having variable reinforcement, a 0.75 %w/w CNT caused yield stress to rise by 55% (6.5 MPa, compressive), while 2% CNT caused the electrical conductivity to rise significantly. Hence, electrical stimulations were possible for healing in the trabecular bone. The CNTs demonstrated an improvement in protein adsorption and cell attachment [68]. 3DP was employed to develop a bone clip structure-based internal fixation mechanism. A rat femur bone was scanned using computer-assisted tomography (CAT). PLA and nHA with silk were the construction materials. The PLA-nHA-silk composite demonstrated adequate performance in positioning bony segments with bone fractures in animal studies [76]. PCL and PCL-based CNT composites demonstrated cell proliferation and may potentially have applications in cardiac tissue engineering [77]. Also, PLA/HA composite formulations with 5–15 %w/w HA were used for mimic real human trabecular structure by an FDM printer. However, the HA particle incorporation decreased the printing accuracy, while showing potential for enhancement of the mechanical properties [78].

Pharmaceutical applications

NPs and nanocomposites have been employed in the 3DP of pharmaceutical dosage forms. Examples are given in Table 1 [47, 50, 79–81] and further works are explained in the following.

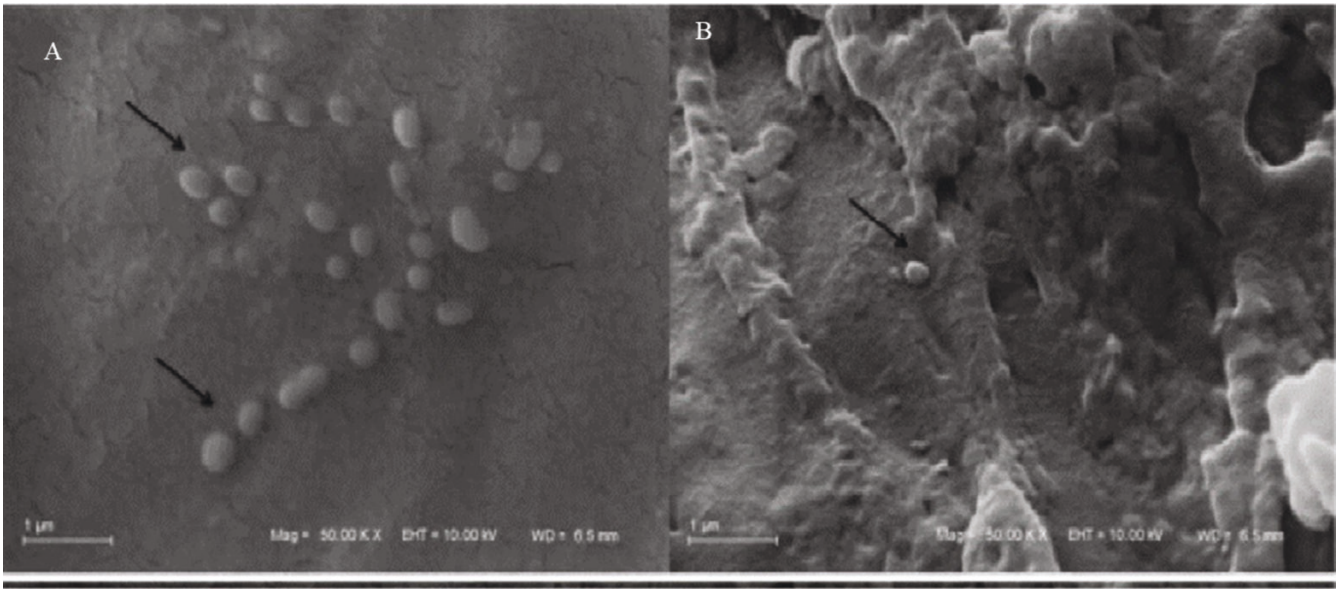

Figure 2. (A) SEM image of the CNT composite scaffold. (B) Higher SEM image magnification of the composite surface. (C) TEM image of the composite (left inset: electron diffraction pattern of HA nanoparticle; right insert: high-resolution image of a HA crystal), demonstrating formation of CNT network in the scaffold at 10% w/w CNT content. Reproduced with permission from reference [68].

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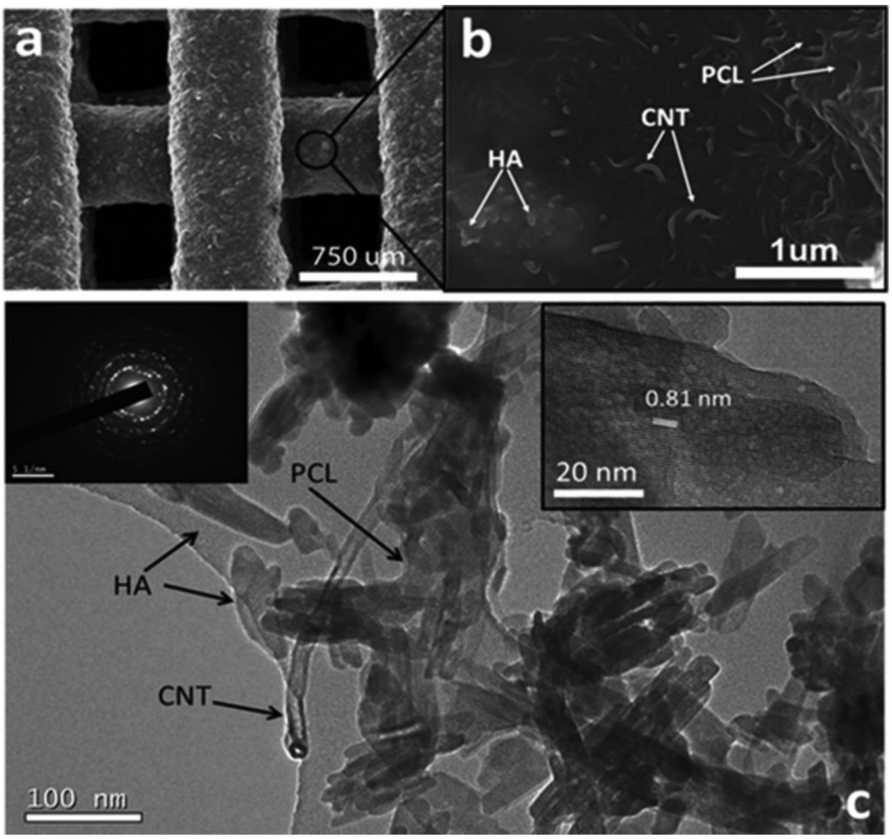

Figure 3. SEM images of (A) surface and (B) cross section of the tablet loaded with nano-capsules. Arrows indicate nanoparticles. Reproduced with permission from reference [35].

Fused deposition modelling

Beck et al. [35] incorporate nanocapsules into 3D printed tablets by soaking the 3D printed devices in the suspension of the nanocapsules, which were detected on the surface (Fig. 3A) and inside (Fig. 3B) of the 3D printed tablets. The researchers utilized FDM to craft drug delivery devices from poly(ε-caprolactone) (PCL) and Eudragit® RL100 (ERL) filaments, with or without a channelling agent (mannitol). PCL was selected due to known biocompatibility and biodegradability. In addition, polymeric nanocapsules have the capability to regulate drug release profiles. These devices were immersed in an aqueous suspension of nanocapsules loaded with deflazacort (with a particle size of 138 nm), resulting in the fabrication of 3D-printed tablets (referred to as printlets), which were observed through scanning electron microscopy (SEM). The presence of the channelling agent (mannitol) enhanced drug loading, with a strong linear relationship observed between soaking time and drug loading. Furthermore, drug release kinetics were influenced by both the polymer composition of the tablets and the inclusion of the channelling agent. Notably, tablets featuring a partially hollow core (50% infill) exhibited higher drug loading (0.27% w/w) and a faster rate of drug release (drug release half-life reduced from 20 min to 10 min by the inclusion of the channelling agent). This study presents an innovative method for converting nanocapsule suspensions into solid dosage forms and demonstrates an efficient 3DP technique for producing novel drug delivery systems, with potential applications in personalized nanomedicine [35].

Hot-melt extrusion method was employed to produce Eudragit® L100-55 filaments containing alginate NPs encapsulating oxaliplatin (OP-NPs). Eudragit L100-55, a pH-sensitive methacrylic acid ethyl acrylate copolymer, was selected due to its widely used excipient in the formulation of the colon-targeted drug delivery systems. The active ingredient was formulated as NPs to improve oxaliplatin antitumor activity, tumour targetability, and safety profile. These OP-NP-loaded filaments were then utilized to produce 3D-printed tablets using an FDM printer. The tablets presented excellent uniformity in drug content and selective release of OP specifically in the colonic environment. To evaluate the antitumor efficacy, CT-26 tumour-bearing mice were treated with the 3D-printed tablets containing OP-NPs, and the results were compared with those of intravenous and oral administrations of OP solution. Additionally, compressed tablets were prepared via a direct compression method with the same formulation containing OP-NPs. The antitumor effects of the 3D-printed tablets containing OP-NPs were found to be remarkable and comparable to those of intravenous OP solutions, while demonstrating a superior safety profile. In contrast, the compressed tablets did not exhibit any significant antitumor effect, possibly due to non-selective drug release in the stomach and upper intestine environments [82]. 3D-printed tablets containing OP-NPs reduced the colon tumour volume in tumour-bearing mice from 150 mm^3 to 50 mm^3 over 14 days [82].

Micro-ribbons/microfibers of chitosan or cellulose were found to alter the mechanical characteristics of filaments

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manufactured through hot melt extrusion. Chitosan and cellulose were selected due to their biocompatibility properties. At elevated concentrations, both chitosan micro-ribbons and cellulose microfibers rendered the filaments unsuitable for high-quality printing. The addition of 1% w/w chitosan micro-ribbons to poly-vinyl alcohol (PVA) powder improved filament mechanical properties in terms of flexibility (from 8.13 kg/mm^2 to 13.09 kg/mm^2) and stiffness (from 7824 g/mm^2 to 8002 g/mm^2) (Fig. 4). Additionally, it enhanced disintegration time of the FDM-printed oral films. Chitosan micro-ribbons may form a network of hydrophilic channels within the film, which facilitates rapid disintegration of the film in aqueous media [34]. Addition of cellulose microfibres (C2000) at 1% w/w increased both film tensile strength and elongation compared to the control formulation (without cellulose microfibre). It was also found that the surface morphology of the filaments became uneven by adding the cellulose microfibre, although this did not affect the quality of the printed films (Fig. 5, unpublished data).

Semisolid extrusion 3DP

The semi-solid extrusion method was utilized to produce fast-dissolving oral polymeric films loaded with indomethacin nanocrystals via 3DP. Hydroxypropyl methyl cellulose (HPMC) served as the film-forming polymer, while glycerol functioned as the plasticizer. HPMC was selected as the film-forming polymer due to its excellent film-forming properties for thin-film formulations and its ability to stabilize supersaturated drug solutions. The aim was to develop an immediate release drug delivery system based on nanocrystals. Optimal mechanical properties were observed in films containing HPMC concentrations of 2.85% (w/w) and 3.5% (w/w), which were selected for further drug-loaded film investigations. Three different drug concentrations

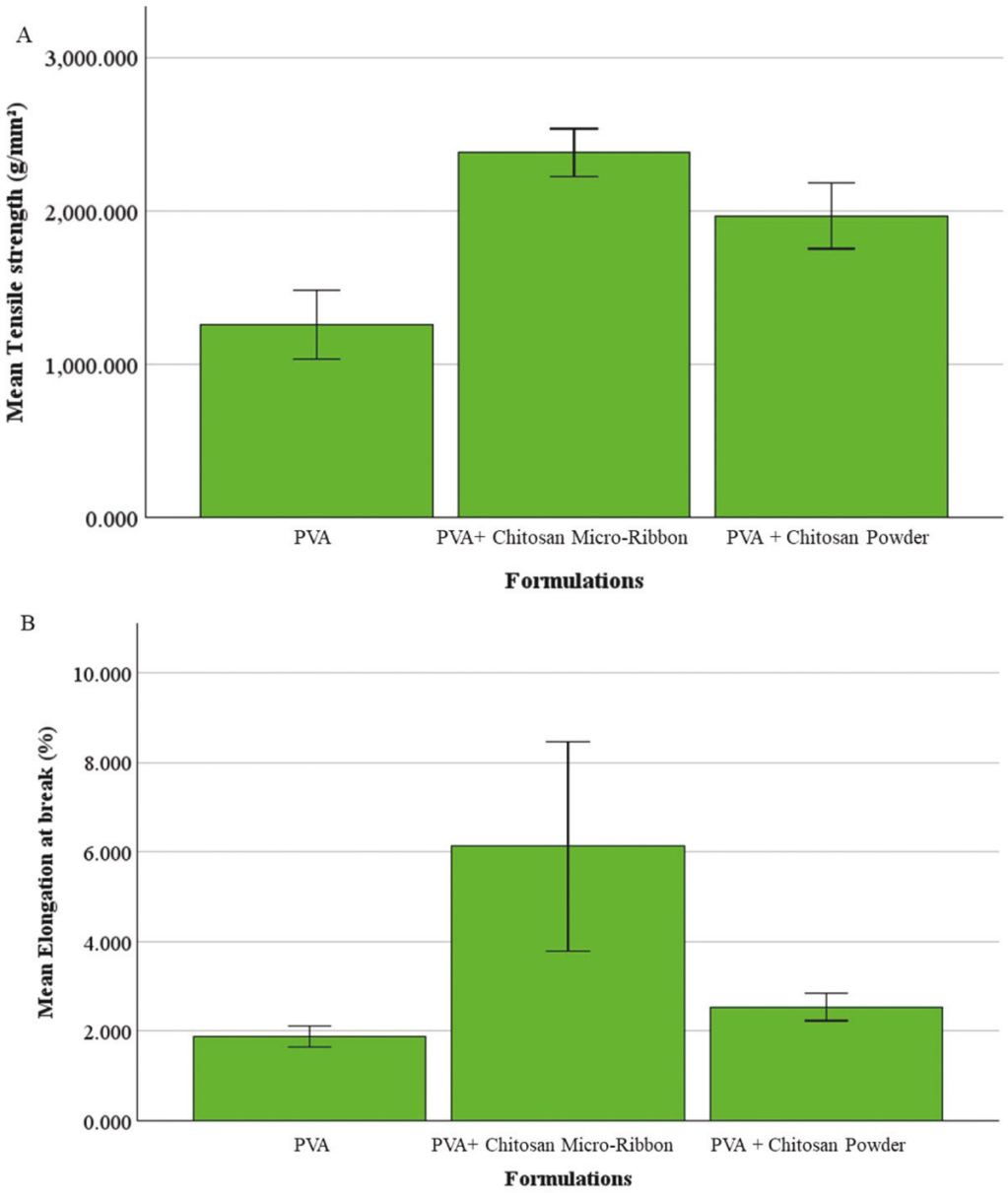

Figure 4. Mechanical properties of formulations contained PVA only, chitosan as micro-ribbon (1% w/w), and chitosan as powder (1% w/w). A: Tensile strength, B: Elongation. Error bars represent standard deviations (n = 3). The data were obtained from a previously published work [34].

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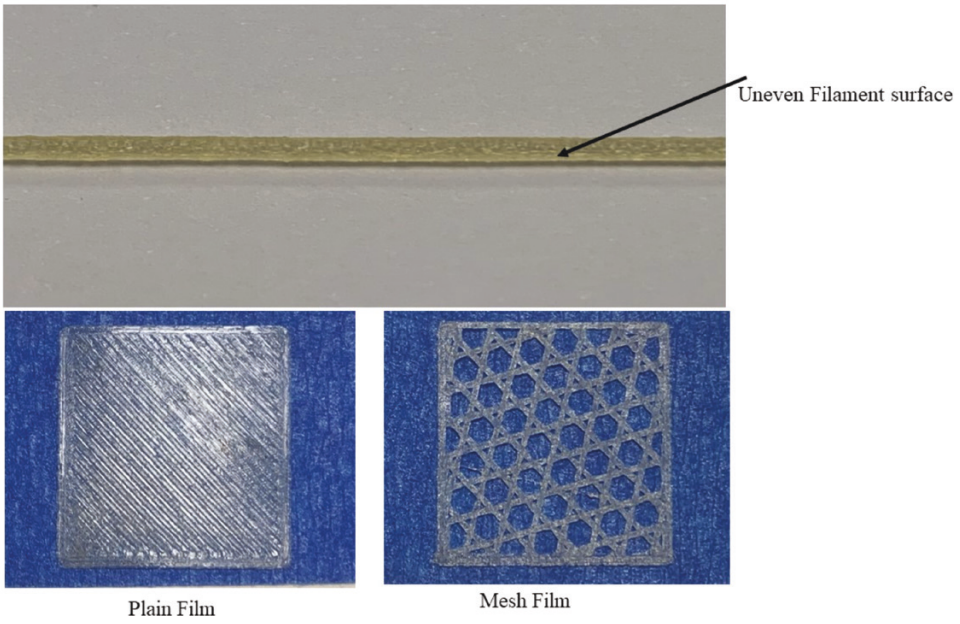

Figure 5. Photographs of a formulation contained polyvinyl alcohol (69%w/w), paracetamol (30% w/w), and 1% w/w cellulose C2000 microfibre. The images demonstrate printing acceptable films, although the surface of the filament was not smooth (Unpublished data).

were examined in the printing studies. At the ideal concentration, the films exhibited flexibility, homogeneity, disintegration within 1 to 2.5 minutes, and drug release within 2 to 3 min. The drug nanocrystals maintained their nano size range (300 to 500 nm) within the polymer films. Comparing the 3D-printed polymer films to conventionally casted ones revealed similar physicochemical behaviour and pharmaceutical performance [79].

Nanogels have been used as a filler of the 3D-printed external construct to modify its physicochemical properties or biocompatibility. Liu et al. incorporated Poloxamer 407 (also known as Pluronic F-127) nanogels carrying simvastatin into the 3D-printed porous titanium alloys for orthopaedic applications. This was to develop materials with desired mechanical properties with an internal porous structure, which provided cavities ideal for filling with the injectable thermosensitive hydrogel. Titanium alloy by itself was poorly compatible with bone ingrowth. Poloxamer 407 nanogels carrying simvastatin-induced osteogenic factors and promoted osteogenesis but were poor in mechanical strength. By combining two composites, a new construct was created. The 3D-printed porous titanium scaffolds filled with nanogels carrying simvastatin achieved both good compatibility with bone ingrowth and mechanical strength. As a result, this construct significantly enhanced vascularization and presented a correlation between the volume of new bone and neovascularization in 4–8 weeks after implantation [83].

3DP can be used to create a mould or a frame for fabricating nanogels. Tao et al. 3D-printed a mould for preparing nanogels using the MRI of a patient's brain tumour cavity. This "customizability" (patient-specific design) is one of the unique benefits that 3DP technology can offer to the indirect production of nanogels in customer-based settings. In this study, customized conformal hydrogel nanocomposites containing paclitaxel were prepared in the shape of the patient's glioma tumour cavity created after surgery. For nanogels, paclitaxel was encapsulated in NPs and then suspended uniformly in macroporous hydrogels. It was observed that NPs slowly released paclitaxel, and the hydrogel matrix further delayed elution of paclitaxel into the external medium *in vitro*. In cell culture settings, slower release of paclitaxel efficiently inhibited the proliferation of glioma tumour cells. This promises an efficient use of hydrogels as a cavity filler after surgical tumour resection to eradicate any residual tumour tissues/cells [84].

Nanogels are promising biocompatible materials that facilitate localized delivery of multiple drugs. Cho et al. [40] demonstrated the precise construction of nanogel discs containing paclitaxel and rapamycin using 3DP technology. These 3D-printed nanogel discs (12 mm in diameter and 1 mm thick) successfully avoided premature gelation during storage and prevented the initial burst release of the drugs in the dissolution medium. *In vivo*, the 3D-printed nanogel discs enabled effective intraperitoneal delivery of paclitaxel and rapamycin in ES-2-luc ovarian-cancer-bearing xenograft mice. Additionally, they proved to be therapeutically effective and capable of preventing postsurgical peritoneal adhesions in the treated xenograft mice [40].

A hydrogel scaffold composed of polyallylamine hydrochloride and pectin, incorporated with mupirocin-loaded quaternized chitosan NPs, was successfully fabricated using 3DP [85]. The 3D scaffold controlled the release of mupirocin via the quaternized chitosan NPs. The mupirocin-loaded quaternized chitosan NPs had an average size of 66.05 nm, while the 3D-printed construct exhibited an average strand diameter of 147.22 ± 5.83 μm and a pore size of 388.44 ± 14.50 μm. Additionally, the scaffolds showed a haemolysis rate below 2%, classifying them as non-haemolytic materials with adequate blood compatibility. The biocompatible scaffold showed a great promise for treating chronic and infected wounds by preventing infections and facilitating faster wound healing. The scaffold demonstrated notable antibacterial activity, improved cell viability in HaCaT cells, sustained mupirocin released up to day 7, and promoted *in vivo* wound healing by stimulating human keratinocytes [85].

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Photopolymerization 3DP

Vat polymerization (photopolymerization) is a technique where a photo-cross linkable resin liquid is converted into a solid upon light irradiation [86, 87]. A study investigated the use of stereolithography (SLA) and vat polymerization to develop 3D-printed nanocomposites for medicinal purposes. Berberine NPs (BBR-NPs) were fabricated and integrated into a biodegradable, biocompatible 3D-printed oral dosage forms [88]. This approach facilitated sustained BBR release, improved gastrointestinal absorption, reduced degradation, and enhanced bioavailability *in vivo* [88]. The findings demonstrated the potential of SLA-assisted 3DP for creating advanced drug delivery systems, including those with multimodal or multi-compartment capabilities. Although NPs were not used in the matrix of 3DP, latticed microneedle array patches (L-MAPs) were manufactured as a platform by the application of photopolymerization. This was done to demonstrate the delivery of small molecules, mRNA lipid NPs, and solid-state ovalbumin protein. The production of programmable L-MAPs was demonstrated with adjustable cargo release profiles, enabling combination of needle geometries on a single patch [89].

The interaction between nanomaterials and formulation components

The successful integration of NPs into the 3DP process necessitates detailed attention to various factors. These include selecting suitable NPs, ensuring their uniform dispersion and distribution within the matrix, and optimizing processing parameters to achieve compatibility and efficient incorporation. Furthermore, a thorough understanding of the interactions between NPs and the matrix polymer is crucial for attaining the desired material properties and enhancing the performance of the final printed parts [90]. A primary advantage of incorporating nanomaterials into material extrusion processes (FDM 3DP) was the substantial improvements in mechanical properties. For example, the inclusion of carbon nanotubes (CNTs) or graphene within the polymer matrix markedly enhanced the tensile strength, modulus, and toughness of the resulting printed components [91]. In addition, printed objects containing PLA-AgNPs exhibited significant antibacterial behaviour against *Staphylococcus aureus, Escherichia coli*, and *Pseudomonas aeruginosa* without chemical changes to the matrix polymer [75]. In the tissue engineering sector, FDM printer was used to print bone scaffold by incorporating gold NPs with PLA. Results showed improvements in cell adhesion and increase stiffness and strength properties [66]. Furthermore, photopolymerization has shown the ability to produce nanocomposites with enhanced mechanical strength and antibacterial properties by integrating cuprous oxide (Cu_2O) NPs into the photopolymerization resin. Incorporating Cu_2O NPs at low concentrations notably improved the materials' mechanical performance by approximately 20% even at low filler loadings and enhanced biocidal efficacy, rendering them highly suitable for diverse engineering and medical applications [92].

Comparative analysis

Among the discussed 3DP methods, FDM is readily available with low prices. There are several suppliers of FDM 3D printers, which makes obtaining one possible within a short period of time. FDMs normally need filaments to generate printed objects. Most of the available filaments do not contain the desired active ingredients or NPs. Therefore, the filaments should be manufactured prior to 3DP. Producing filaments can be challenging, as they should have a uniform diameter and desirable mechanical strength to withstand the mechanical stress from the gearing mechanism at the printer head. The addition of NPs may not create problems during filament manufacturing but may significantly increase the viscosity of the molten filament (unpublished data by the authors). Direct 3DP may eliminate the need for manufacturing filaments. However, again the high viscosity of the molten powder at the printer head may prevent extrusion of the molten formulation. This may require removing excipients from the formulation or limiting the amounts of active ingredient (unpublished data by authors).

There are two types of hydrogel 3D printers: pneumatic gel extruder [93] and mechanical gel extruder [94]. The main advantage of these printers is producing printed objects at low temperatures [93]. However, hydrogel 3D printers are not as widely available as FDM 3D printers. In addition, they cost significantly more than conventional FDM 3D printers, which limits their use in research. Furthermore, precise rheological properties are needed to achieve printing desired objects [93].

SLA 3D printers allow the manufacture of solid objects such as microneedles with fine details [95] or sustained release tablets [96]. Printing at low temperatures and achieving high mechanical strengths of printed objects can be considered advantages of SLA 3DP. In addition, SLA 3D printers are available at relatively low cost from several suppliers. However, SLA 3DP has limitations such as limited variety of suitable polymers. So far, only poly(ethylene glycol) diacrylate has been used for drug delivery. Additionally, long preprocessing and postprocessing are required for SLA 3DP [97].

The inclusion of nanomaterials changed the physicochemical properties of the 3D-printed objects. It was also found that the physicochemical properties of nanomaterials such as the size also affected the properties of the printed objects. For example, increasing the size of SiO_2 nanoparticles (26–847 nm) reduced the printability of 3D-printed objects by direct writing ink method, as well as increasing the nanoparticle size allowed adding more nanoparticle content into the printing ink [98].

Clinical trials, manufacturing, and regulatory aspects

The Food and Drug Administration (FDA) issued guidance about the use of nanotechnology in medicinal products in 2014 [99]. This guidance states that FDA does not categorically judge all products that involve the application of nanotechnology as intrinsically benign or harmful. The FDA considers nanomaterials to be those with the scales falling in the range of 1–100 nm. Another guidance issued in April 2022 about drug products that contain nanomaterials [100]. This guideline states that nanomaterials may modify the bioavailability of the same material if it is not manufactured to be a nanomaterial. However, this refers to the active ingredients. When nanomaterials are used as excipients, it is essential to characterize the properties of nanomaterials and how these impact the safety and efficacy of the final product. In other words, the NPs should be precisely characterized, and any deviations should be carefully considered. The safety of NPs

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should be evaluated. Furthermore, the effects of NPs should be determined on the container closure system and the shelf-life of the product. The guidance indicates that nanomaterials' properties, such as size, size distribution, morphology, and surface charge, may change upon storage or handling (such as hot melt extrusion in 3DP). Therefore, stress stability studies are recommended to elucidate the changes and pathways of those changes. It is a regulatory requirement to ensure the safety and stability of NPs used in 3DP of pharmaceutical dosage forms.

So far, there has been only one clinical trial using NPs in 3DP. The clinical trial aim was to produce complete dental prosthesis for fully edentulous patients by employing stereolithography 3DP, using poly (methyl methacrylate) as the matrix material and titanium oxide NPs (Stereolithographic Technique for Dentures: NCT02911038). The aim of adding titanium oxide NPs was to reinforce the matrix and improve mechanical strength [101]. A total of 35 patients were recruited and the mean values of general satisfaction scores were significantly improved.

The mass production of pharmaceutical dosage forms is desirable, and the 3DP industry heading towards inventing new 3d printers with the ability to print multiple objects at a time. However, personalized medicine is one aspect of pharmaceutical 3DP, but mass production of 3D printed pharmaceutical dosage forms cannot be personalized [102]. On the other hand, a degree of scale-up is required, as patients normally require more than one personalized medicine, which should be produced within a short period of time. Supplying drug-loaded filaments or prefilled-cartridges has been proposed by community pharmacists [103]. The drug-loaded filaments and pre-filled cartridges would be manufactured at large scale by pharmaceutical companies. Currently, Spritam is the only 3D-printed pharmaceutical dosage form produced at large scale. It appears this type of approaches may be feasible.

Current limitations of using nanocomposites in 3DP

Notwithstanding the noteworthy advancements achieved recently in the field of 3DP of nanocomposites, many processing and fabrication obstacles are yet to be overcome. Efficient nanocomposite mixing techniques should be employed to reduce unwanted effects relating to the addition of nanofillers on printing material characteristics, such as transparency, flowability, and viscosity. Material rheology is essential for extrusion-based 3DP techniques; hence, filler content and its dispersion can be adjusted to attain appropriate mixture viscosity and elasticity for the 3DP [104]. Additionally, a higher concentration of nano or micro composites might affect the printing process. As an example, higher concentrations of chitosan micro-ribbons or cellulose micro-fibres were unsuitable for FDM printing of oral films employing PVA or poly-vinyl pyrrolidone (PVP). This perhaps could be due to the alterations in viscosity of molten filaments during printing [34].

Future directions

3DP allows for the manufacture of personalized medicine as well as complex drug delivery systems. Each 3DP method has its own limitations. For example, FDM requires high printing temperatures to reduce the viscosity of the molten polymer to flow through the print-head nozzle. This could lead to the evaporation or degradation of the active ingredient. It was shown that reducing the printing temperature reduced the degradation of the active ingredient [105]. Therefore, novel nanomaterials, different excipients, and the use of direct 3DP should be investigated to reduce the printing temperature and its effects on the incorporated NPs (e.g. decomposition). In addition, the flow properties of hydrogels play an important role in achieving printed objects with desired details [94]. Therefore, a better understanding of the NP effects on the rheological properties should be obtained for 3DP of hydrogels.

Medical 3DP combined with nanotechnology offers the advantages of personalization, customization, and complexity but also poses challenges related to legal liability and ethical considerations. The integration of nanomaterials necessitates thorough toxicity evaluations, studies on degradation behaviour in biological environments, and the establishment of robust evaluation systems such as quantifying marker genes in the soil bacteria using quantitative real-time PCR [106]. Additionally, scaling up the production of nanomaterial-enhanced 3D-printed products remains a significant hurdle. The development of multi-printhead 3D printers could be a future direction. Regulatory frameworks at both institutional and governmental levels need to address the classification of bio-printed products, which may fall under biologics, drugs, or medical devices. 3D-printed personalized medical products must be scientifically validated, and a dedicated regulatory system should be implemented. Group or enterprise standards could help regulating these products, ensuring timely access for patients to cutting-edge technology. Also, advancing medical 3DP requires interdisciplinary collaboration, integrating fields, such as medical imaging, bioengineering, materials science, toxicity studies, pharmacy, and clinical medicine. With continued innovation, medical 3DP may achieve significant breakthroughs and make substantial contributions to healthcare [107].

Ensuring the performance of 3D printed objects such as implants containing NPs could be part of the future investigations when these are sterilized by methods such as gamma irradiation. This method of sterilization may affect the chemical structure of NPs [108]. This will require controlling design parameters, achieving material biocompatibility, and identifying effective sterilization methods. These will become more challenging, when living cells are included in 3D printed objects containing NPs, as nanomaterials may present cytotoxicity towards the incorporated cells. However, the significant benefits offered to patients and the healthcare system justify the extensive research required to establish processes for producing customized products [109].

Future studies should also investigate the environmental impacts of NPs used in 3D printed objects, and perhaps develop novel and environmentally safe nanomaterials. It is suggested the use of environmentally friendly solvents, non-toxic chemicals, and renewable resources in the production of NPs [110]. In addition, NPs may enter the sewage system as faeces/urine following consumption of 3D-printed drug delivery systems containing NPs [111]. These may impose toxic effects on plants or algae [112]. Therefore, future studies should also consider the biodegradability of NPs used in 3D-printed objects in the environment.

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Conclusion

Rapid advancements in nanomaterials and additive manufacturing know-how have transformed the scale of biomedical engineering. Particularly, the alternatives available for producing bespoke biological tissues at cheaper rates and with fewer effort compared to the recent past have significant implications for biomedical as well as tissue engineering. The wide variety of nanomaterials used with compatible biopolymers, which provide nanocomposites having extraordinary characteristics have led to prospects previously unattainable. We have emphasized key nanomaterials, composites, and 3DP techniques, including stereolithography, direct-write techniques based on extrusion, and inkjet-printing methods. Changes achieved using surface functionalization, categories of nanomaterials, and 3DP technology are having a considerable influence on the performance of additive manufacturing and nanocomposites. Though there has been noteworthy progress. On the other hand, many challenges should be addressed specific to composite processing, material availability, fabrication methods, biocompatibility, and personalized constructs to enable further development in this domain. Ultimately, the aim of developing 3D-printed pharmaceutical dosage forms incorporating nanoparticles is to meet the healthcare need in terms of personalized medicines, and this will require the translation of academic research into practice, which would be facilitated by industry. Therefore, initial collaborations and partnerships between academia and industry could speed up the translation process, by using industry experience in the drug development process.

Conflict of interest

None declared.

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