

REVIEW

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Recent advances in 3D and 4D printing in pharmaceutical technology: applications, challenges, and future perspectives

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Abstract

Background The conventional drug delivery devices always present a “one-size-fits-all” approach which limits their application in pharmaceutical industry, because of their inability to adapt to individual pharmacokinetic features. Three-dimensional (3D) printing is the most economical substitutes for transferring from the “one-size-fits-all” approach (*i.e.*, mass production) to fabricate small individualized batches.

Main text 3D printing, advanced by the additive manufacturing technology, has gained growing demanding and popularity to develop pharmaceutical dosage forms and medical devices; and offered much more preferences over the traditional fabrication technologies. This advanced technology presents the ability of fabricating customizable design, 3D structures with sophisticated architecture, intended for personalized treatment. As a further advancement, the emergence of four-dimensional (4D) printing extensively contributed to the advancement of personalized medication by combining the benefits of smart multiple functional materials with the 3D printing technology. In spite of all of the offered notable progresses in both techniques, some regulatory issues, scalability, and production cost present key obstruction.

Conclusions In the present article, an overview on the latest research articles demonstrating some step forward accomplishments for exploiting 3D and 4D printing technologies in developing advanced pharmaceutical dosage forms, medical devices, and tissue engineering as well as presenting the foremost challenges and future perspectives.

Keywords 3D printing, 4D printing, Artificial intelligence, Machine learning, Pharmaceutical dosage forms, Tissue engineering

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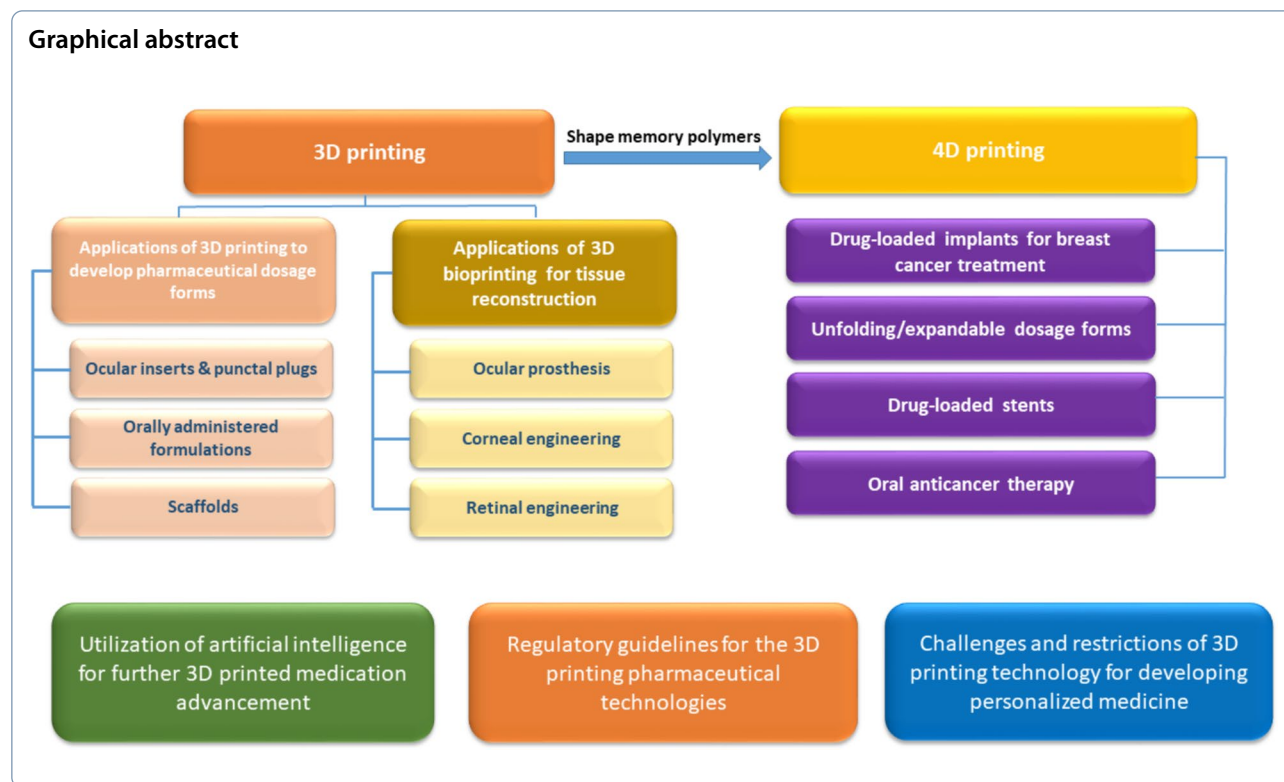
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Introduction

There is always a continuous demand for developing advanced drug delivery systems (DDS) to boost the therapeutic effect of pharmaceutically active ingredients, including large biomolecules (e.g., peptides and proteins) suffering from poor bioavailability, hydrophobicity, or narrow therapeutic window. Conventional DDS demonstrate a restricted ability for adapting to patient-to-patient pharmacokinetic behaviors variations [1, 2]. Additionally, conventional DDS are more likely to cause undesirable side effects resulting from over- or under-dosing [3]. Failure of precisely dose controlling based on individual patient differences can lead to patient non-compliance, mainly for pediatrics and geriatrics [4, 5]. More specifically, the use of implantable DDS may rise some safety concerns related to the unfavorable foreign body reactions [6]. Additionally, the presence of different formulations for a certain drug varying the dosage and physical form may affect its *in vivo* performance [7]. Also, the limitations in size and design of conventional DDS restrict the highest incorporated dosage in a single device, which, in turn, affects the ability and durability for long-term delivery. Accordingly, the need for dosage controlled DDS has attracted the attention of scientists for the last years [8].

Since the research in the drug delivery field constantly attempts to meet new challenges and hard-to-reach

therapeutic objectives, such as enhancing the pharmacokinetic profiles, and improving patient compliance, this attitude entailed to manufacture unusual approaches for advanced fabrication techniques [9]. Additive manufacturing has been developed as a highly auspicious procedure for personalized medicine in the pharmaceutical technology field, to resolve the problems related to current DDS [8].

Additive manufacturing, also known as 3D printing technology, utilizes a 3D model as a base to superimpose printing materials layer by layer with computer-aided control into a 3D object using a printer [10]. Additive manufacturing offers greater flexibility levels for the creation of sophisticated 3D structures directly based on design requirements. Compared to conventional manufacturing techniques since 1980s, and till now, emerging 3D printing technologies have been developed and applied [11, 12]. Because of its extremely automated, high efficiency, extraordinary precision, and low cost, this advancing technology plays a significant role in the fields of construction, automotive industry, electrochemical energy storage, aerospace, flexible sensing as well as medical devices [12].

On the other hand, the more advanced four-dimensional (4D) printing, the smart materials are 3D printed to produce items that alter their shape after production, in a programmed manner over time, when exposed to a

certain external stimuli. 4D-printed dosage forms differ from 3D ones in that time is considered as the 4th dimension during their performance. The term “4D printing” describes smart materials manufactured by the additive technique to produce easily achieved, complex-shaped, nonstatic objects that are more advanced than 3D objects. 4D-printed objects can be manufactured with 3D printers [9].

Moreover, 3D printing can be exploited in the biomedical research fields represented in regenerative medication, tissue engineering, cancer research, and drug screening. The term “Bioprinting” describes this emerging, potent, and multipurpose biofabrication technique which demonstrated promising applications in this field. In bioprinting process, depositing solutions or hydrogels of cell-laden polymer on a podium constructed using a computer-aided design (CAD) model is performed [8, 13, 14]. Various merits are offered by bioprinting process over other conventional biofabrication techniques, such as the accurate modeling of cells and biologics, permitting coprinting of numerous cells and biomaterials, and assisting the construction process for a tissue or an organ by imitating three-dimensional (3D) model [15, 16].

Commonly adopted bioprinting methods comprise inkjet-based bioprinting, laser-assisted bioprinting, and extrusion-based bioprinting. The former lies bioink picoliter droplets, via a noncontact process, on a substrate. On the other hand, laser-assisted bioprinting utilizes a laser source to deposit biomaterials onto a substrate. [17, 18]. While in extrusion-based bioprinting technique, layer-by-layer bioink deposition creates pre-designed 3D constructs. Such technique offers an advantage of printing highly viscous ink and high cell density over the other techniques, and thus, it is the mostly adopted bioprinting technique [17]. This technique was adopted by Joung et al. to fabricate a spinal cord scaffold aiming to construct an *in vitro* tissue model of complex central nervous system [19], to fabricate 3D scaffolds intended for bone regeneration by Roque et al. [20], and also employed by Gospodinova et al. to develop hydroxyethylcellulose-based bioink implanted with Hela cells to bioprint a model for cervical tumor [21]. Extrusion-based bioprinting can be further differentiated, based on ink dispensing systems, into the following categories: screw-driven dispensing, piston-driven dispensing, and pneumatic dispensing [22].

Some complications are needed to be overcome upon applying the bioprinting technology. The most challenging one is to simultaneously adjust the bioink printability and keep cell functionality and viability throughout the bioprinting process. Bioink printability considers the ability to form a reliable, integral, and good shaped pre-designed 3D constructs [23–26]. Printability significantly

influences the biological function and mechanical properties of printed scaffolds, and is controlled by intrinsic and extrinsic factors [24, 27]. Intrinsic factors are related to bioink properties represented in its concentration, composition, and ratio of the composing components. In contrast, extrinsic factors comprise nozzle characteristics, cross-linking conditions, printing parameters and temperature. An equilibrium between printability and cell viability must be considered, as for example, increasing bioink concentration over a certain level may restrict cell proliferation and spreading [28], while decreasing bioink concentration inversely affects the printability and mechanical properties [29]. Moreover, extreme printing speed and pressure induce excessive shear stress which could ruin cell viability [30], and also, diminish the surface tension and viscosity of the used ink, bringing about poor printability [31]. Consequently, to guarantee both the mechanical characteristics of bioprinted structures and the biological functionality, careful monitoring of the bioprinting-related factors should be kept in consideration.

The current article provides an in-depth demonstration on the latest applications of 3D and 4D printing technologies for developing drug delivery carriers and medical devices, major technical contests and regulatory issues, as well as the future perspective.

Three-dimensional printing

3D printing technology can be defined as a process to construct subjects having a 3D structure applying a computer-aided design (CAD) model. This is performed via layer-by-layer deposition on a built platform [32]. 3D printing was invented based on a stereolithography procedure four decades ago and was primarily used in industrial process optimization and prototyping [33]. 3D printing has proved a pronounced potential in interdisciplinary biomedical research field, including pharmaceutical technology and bioengineering [13, 34]. Additionally, 3D printing technology is a required substitute for the traditionally fabricated DDS as it facilitates the efficient and cost-effective preparation of sophisticated customizable creations. Furthermore, polypills fabricated by additive manufacturing technology include multiple pharmaceutically active ingredients and excipients compositions, and demonstrate distinctive drug pharmacokinetics, prompting the pharmaceutical industry revolution [35, 36]. 3D-printed DDS also enable drug controlled release for different compounds exerting specific functions in human body.

Types of 3D printers

The 3D printers used in the pharmaceutical field comprise inkjet-based 3D printers, selective laser sintering,

stereolithography, pressure-assisted microsyringe, and fused-deposition modeling.

Inkjet-based 3D printers

Inkjet-based 3D printers spray the liquid in droplets form. This type is classified as drop-on-demand and continuous jet printers. The former type, being more economic, produces an accurate ink amount as demanded for the printing process. The droplets stream is controlled by piezoelectric nozzle vibration or vapor bubble induction by a thermal nozzle. Whereas, in continuous jet printers, a continuous ink droplets stream is produced from a pressure pump [37]. In 2015, Spritam[®], fast-disintegrating levetiracetam tablet was introduced in the market manufactured by the inkjet-based 3D printer solving the problem of swallowing difficulty associated with high drug dose conventional tablets [38].

Selective laser sintering 3D printers

Selective laser sintering 3D printers point a beam of laser on a powder bed surface containing a mixture of the polymer and drug, the beam raises the powder bed temperature resulting in sudden powder sintering. Performing this process repeatedly lays new powder layers over the sintered ones, with the aid of a roller till the construction of the intended 3D object [39]. This type of printers utilizes the powder form of the polymer and drug excluding the use of solvents and without any extrusion process [40, 41]. The use of this type is limited due to the liability of drug decomposition by the elevated heat; however, this could be overcome by speeding up the laser scanning [41].

Stereolithography 3D printers

The principle of stereolithography (SLA) 3D printers is based on exposing a liquid dispersing a mixture of a photosensitive polymer with the drug to ultraviolet light, as a high source of energy, till solidification [42]. The source of ultraviolet light in SLA printers is the laser beam whereas in digital light processing printers, digital light is the source [43]. Briefly, upon exposing photosensitive polymers to the high energy of light, they act as a cross-linker initiating liquid solidification into the intended 3D objects. SLA 3D printers are able to produce high-resolution 3D designs with smooth surfaces. Conversely, the main disadvantage arises from the toxicity endorsed from the photosensitive cross-linkers [44].

Pressure-assisted microsyringe 3D printers

One type of nozzle-based printers is the pressure-assisted microsyringe 3D printers. A paste, formed from the drug and excipients, is deposited by the pressure force of the piston of the syringe's nozzle to form the designed 3D

object. This process is suitable for thermolabile drugs; however, the produced objects might shrink or get destructed in the post-printing drying step [45].

Fused-deposition modeling 3D printers

On the other hand, in the commonly used fused-deposition modeling printers, a hot-melt extruder is used to form filaments from the polymer and drug, which are rolled in a spool to be ready for the printing process. Then, the printer pulls the filament from the spool to move across a preheated nozzle, to deposit the designed 3D object on the printing platform. Fused-deposition modeling printers are rapid and cheap in printing, this merit aided in their widespread use; however, they demonstrate a limited use with thermosensitive drugs owing to the exposure to high temperature [46]. Also, a step of surface smoothing is required to obtain objects with acceptable shape [47]. In this article, demonstration of the applications of 3D printing to develop pharmaceutical dosage forms as well as 3D bioprinting for tissue reconstruction that were recently published is presented.

Applications of 3D printing to develop pharmaceutical dosage forms

Described below are the different applications of 3D printing to develop pharmaceutical dosage forms. These comprise developing drug-loaded ocular inserts and punctal plugs, formulations intended for the oral administration, as well as scaffolds for tissue regeneration. Table 1 summarizes applications of 3D printing to develop pharmaceutical dosage forms that are explained in details below.

3D printing for fabricating drug-loaded ocular inserts and punctal plugs

The production of patient-centered, tailored, and complex-shaped ciprofloxacin HCl-loaded ocular insert was facilitated by combining fused-deposition modeling and hot-melt extrusion 3D printing. The biodegradable, biocompatible, and bioadhesive Klucel[™] hydroxypropyl cellulose was the polymer of choice for the 3D printing process with the aid of an experimental design approach to attain the intended tailored drug release profile. The authors performed a thorough investigations regarding drug-excipient compatibility, thermal characteristics, drug content, topography, in vitro drug release, antibacterial efficacy, ex vivo transcorneal penetration, as well as a stability study for the prepared ocular inserts. The optimum design revealed the presence of the drug in an amorphous form and attained an extended drug release profile for 24 h. The optimum formulation also possessed smooth surfaces, good mucoadhesive strength, and absence of chemical or physical incompatibility.

Table 1 Applications of 3D printing to develop pharmaceutical dosage forms

Aim	Dosage form	Adopted technique	Drug	Impact of the study
1. Designing advanced ocular preparations	Ocular inserts	Combining fused-deposition modeling and hot-melt extrusion 3D printing [48]	Ciprofloxacin HCl	The optimum formulation attained an extended drug release profile for 24 h, and possessed smooth surfaces, good mucoadhesive strength, with no chemical or physical incompatibility
2. Enhancing the performance of orally administered formulations	Punctal plugs	Ultrafluidic nanovesicles and 3D printing [49]	Ganciclovir	The proposed ocusert offered a noninvasive prolonged-release dosage form for ganciclovir for the treatment of cytomegalovirus retinitis
	Immediate-release tablets	Digital light processing 3D printing technique [50] Melting solidification printing process technique [53]	Dexamethasone Albendazole	Cell compatibility study proved the complete safety for unloaded plugs The inclusion of albendazole nanocrystals in the developed printlets improved the drug dissolution in HCl 0.1 N compared to the free form, with maintained crystallinity, particle size, and chemical stability of the nanocrystals during 6 months-storage
		Fused-deposition modeling 3D printing [54]	Hydrocortisone	Careful adjustment of printing temperature and drug concentration were recommended
		3D printing dose titration [55]	Caffeine	Smooth and consistent filament extrusion was obtained with predictable fast-release dose-independent profiles of caffeine within an hour
		Single-step 3D printing direct powder extrusion technique [56]	Camabidiol	Direct powder extrusion technique successfully produced amorphous solid dispersions with suitable quality and immediate-release property
	Colon-targeted tablets	A combinatorial approach of pH-responsive drug release and 3D printing techniques [57] Pill-in-pill 3D configuration [58]	N-acetylglucosamine Budesonide	The presented formulation demonstrated superior processability, printability, safety as well as desirable drug release kinetics Enhanced budesonide delivery to the targeted colon region through a simple, controllable, and effective approach was achieved
	Floating device	Fused-deposition modeling [61]	Domperidone	The prepared devices were of identical shapes and narrow standard deviation values for their weights. Cumulative drug release study revealed a precise release rate, with complete drug release within 24 h following the zero-order release kinetics

Table 1 (continued)

Aim	Dosage form	Adopted technique	Drug	Impact of the study
3. Augmenting the tissue regeneration of scaffolds	Skin restoration scaffolds	3D printing and electrospinning technologies [64]	Mupirocin	Excellent antibacterial activity, highest cell adhesion rate and viability, and great angiogenic potential were recorded with significant wound healing acceleration
		Hot-melt extrusion technique [65]	Ciprofloxacin hydrochloride	Designed scaffolds revealed an early burst drug release followed by a sustained release pattern, which was beneficial for effective controlling of the bacterial load and enhanced promoted wound curing effect
		3D bioprinting [66]	Tacrolimus	The in vivo evaluation of the tested scaffolds revealed that medicated scaffolds resulted in significantly faster closure rate than the used positive control
		3D printing and electrospay techniques [67]	Tetracycline	Polycaprolactone scaffolds containing tetracycline-loaded polyvinylpyrrolidone nanoparticles demonstrated an extended, controlled drug release profile owing to tetracycline encapsulation into the interlayer
	Scaffolds for treating bone diseases	3D solvent-casting technique [68]	Doxorubicin	The matrices underwent a slow hydrolytic decomposition proving their durability, permitting a prolonged doxorubicin delivery for potential bone regeneration
	Bone tissue engineering scaffolds	Fused filament fabrication 3D printing technique [69]	Inulin	The prepared scaffolds were compatible with human fibroblasts, human adipose-derived mesenchymal stem cells, and hemocompatible. Remarkable osteogenic activity was proved via significantly up-regulating alkaline phosphatase
4. Developing vaginal formulations	Intravaginal scaffolds	Pressure-assisted microsyringe 3D printing [70]	Metronidazole	Scaffolds showed a localized sustained metronidazole release profile for 14 days with insignificant cytotoxicity

Moreover, it inhibited the bacterial growth and enhanced the transcorneal ciprofloxacin HCl for an extended period of time compared to immediate-release inserts and commercial eye drops. Stability of the prepared inserts was assured over three months, at room temperature. The designed inserts could lessen frequency of administration to once-daily dosing. This could be considered an auspicious topical delivery platform for the treatment of ocular bacterial infections with prolonged, and superior therapeutic activity [48].

The combination of the merits of ultrafluidic nanovesicles and 3D printing was exploited to fabricate a non-invasive ocusert for the treatment of cytomegalovirus retinitis. The disease is a vision-threatening and affects immunosuppressed patients. Ganciclovir was loaded in glycosomes, which preparation and optimization were performed with the aid of Design-Expert® software. Optimum formulation was further incorporated in polylactic acid-based 3D-printed ocusert, manufactured using a computer-aided design, to prolong drug release. The prepared formulation proved its superior penetration capability through the rabbit's cornea using confocal laser scanning microscopy. Histopathological assessment of the rabbits' eyes following the ocular application of the ocusert laden with the optimum glycosomes evidenced their safety. Additionally, a pharmacokinetic study, conducted in the rabbit's aqueous humor, confirmed the prolonged ganciclovir release from the designed ocusert over 5 days. Thus, the proposed ocusert formulation could be considered a noninvasive prolonged-release dosage form for ganciclovir for the treatment of cytomegalovirus retinitis [49].

Dexamethasone-loaded punctal plugs were developed by Xu et al. using digital light processing 3D printing technique [50]. Punctal plugs are tiny biomedical tools placed in the tear ducts to increase the tear film production and enhance ocular hydration. Cautious selection for the plug size and monitoring should be carried out to guarantee the treatment's success [51, 52]. In the study performed by Xu et al., dexamethasone-loaded plugs were prepared utilizing polyethylene glycol 400 and polyethylene glycol diacrylate to create semi-interpenetrating networks (Fig. 1). Physical characterization for possible drug-polymer interactions, in vitro dexamethasone release profile, as well as cell compatibility of the prepared plugs were thoroughly investigated. To evaluate the plugs' in vitro drug release kinetics, an internal flow rig model simulating the subconjunctival region was applied. The analysis indicated that increasing polyethylene glycol diacrylate content in the punctal plugs from 80 to 100%w/w extended the drug release for more than 21 days. Cell compatibility analysis executed by direct contact using a BALB/3T3 fibroblast cell line,

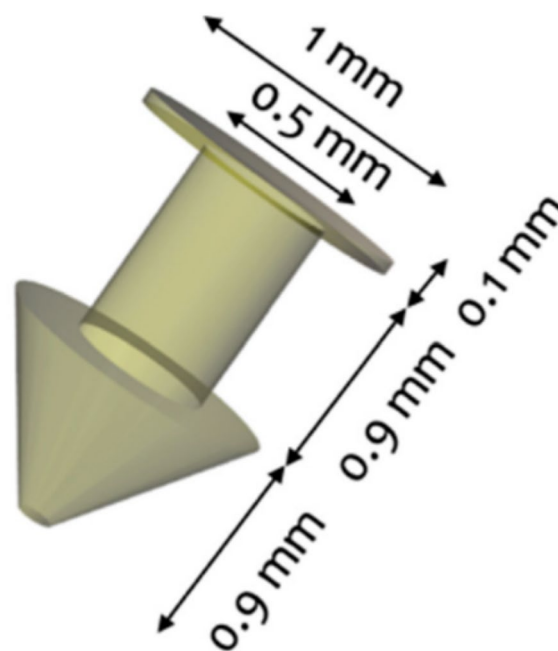


Fig. 1 3D design of the punctal plug as obtained from Xu et al. [50], under the CC BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/>)

demonstrated 100% cell viability after 24 h incubation for unloaded plugs, and 50% cell viability for drug-loaded plugs post 24 h incubation. These results indicated that extra post-curing and post-washing procedures should be performed to improve the biocompatibility of punctal plugs [50].

Application of 3D printing to develop formulations intended for the oral administration

Formulation of immediate-release tablets Lopez-Vidal firstly reported the inclusion of nanocrystals within 3D-printed tablets (printlets) adopting the melting solidification printing process technique. By applying this technique, albendazole nanocrystals was successfully incorporated in high concentration (50% w/w) which was never reached in conventional tablets. Polyethylene glycol 1500/propylene glycol was used as a carrier ink in which albendazole nanocrystals were included. No physicochemical interactions or loss of crystallinity was recorded after this inclusion. The inclusion of albendazole nanocrystals in the developed printlets improved the drug dissolution in HCl 0.1 N compared to the free form. Moreover, the designed formulation maintained the crystallinity, particle size, and chemical stability of the nanocrystals during 6-month storage. The obtained findings reveal the pharmaceutical potential for developing fast-release, stable, solid dosage forms for hydrophobic drugs by merging the nanocrystals and 3D printing techniques. Furthermore, this technique

is useful for printing objects incorporating nanocrystals in low melting temperature polymers [53].

Fused-deposition modeling 3D printing was utilized to produce instant-release, cost-effective for delivering hydrocortisone in personalized doses for the management of children suffering from congenital adrenal hyperplasia. The drug content in the formulated tablets was investigated as a critical quality attribute utilizing a compact, cheap near-infrared spectroscopy as an analytical assessment method. The printing temperature as well as hydrocortisone concentration were critical factors to ensure the pharmacopeia limiting parameters for drug contents. Although elevating hydrocortisone concentration favored drug retrieval, extra-drug loading produced incompatible filaments, which might be related to the plasticizing effect of hydrocortisone. Additionally, a validated near-infrared spectroscopy model detected hydrocortisone in relatively low drug contents. The results could provide a necessary preclinical background to manufacture immediate-release hydrocortisone tablets for pediatrics use [54].

Dose titration is one of the many options to customize the personalized medicine that could be achieved through continuous medication delivery at dose intervals smaller than the commercially available ones. Hence, caffeine was selected for a 3D printing dose titration application, owing to its well-known dose-dependent adverse effects. Filaments base was composed of polyvinyl alcohol, starch, and glycerol, coupling the hot-melt extrusion and fused-deposition 3D printing. Tablets with different caffeine loadings (25, 50, and 100 mg) were printed successfully. The drug contents of the prepared tablets lied within the acceptable range for pharmaceutical manufacturing (90–110%). Interestingly, results showed that the fabricated tablets could be splitted easier than the commercially available ones. As thoroughly investigated, smooth and consistent filament extrusion was obtained with no evidence for caffeine degradation. A predictable fast-release dose-independent profiles were obtained within an hour. This study spot the lights of the beneficial merits of dose titration offered by 3D printing over the traditional medications. The authors suggest that with continued research, 3D printing could revolutionize drug dosing for medications with critical titration-dependent adverse effects by delivering finely-tuned, and patient-specific dosages for individual patients, achieving improved efficacy and safety [55].

Although fused-deposition modeling is the commonly utilized 3D printing technique in the pharmaceutical technology research, it is tedious as it requires the initial preparation of filaments with appropriate mechanical properties by hot-melt extrusion. Thus, the single-step 3D printing direct powder extrusion technique has emerged,

permitting direct printing of powder blends. Cylindrical-shaped tablets containing cannabidiol having an immediate release were developed by printing blends of Polyox[®] WSR N10/Eudragit[®] E100 and Polyox[®] WSR N10/Soluplus[®], containing cannabidiol (10%). Produced tablets were examined according to the European Pharmacopoeia specifications for uncoated tablets regarding mass variation and uniformity as well as tablet friability. Formulations containing Eudragit[®] E100 succeeded to enhance the aqueous solubility and dissolution rate of cannabidiol, whereas those containing Soluplus[®] formed a gel upon contacting the dissolution medium and retarded drug release. This pointed out the importance of polymer screening. The obtained results confirmed the ability of direct powder extrusion technique producing and shaping amorphous solid dispersions with suitable quality and immediate-release property. This could be considered promising for on-demand manufacturing of small-scale batches by community pharmacies, hospitals and upon conducting clinical trials, as time and process waste is greatly diminished compared to conventional manufacturing methods [56].

Formulation of colon-targeted tablets A combinatorial approach of pH-responsive drug release and 3D printing techniques were applied for colon-specific oral administration of N-acetylglucosamine to overcome the limitations of current treatments. One-step 3D printing technique was adopted for the production of pH-responsive polymeric structure entrapping the medication. Tablet shells were fabricated from Eudragit[®] FS100 and polylactic acid while the core consisted of methyl cellulose hydrogel containing N-acetylglucosamine. Upon assessing formulation variables, methyl cellulose concentration and the influence of polymer blending ratios on physical, thermal, and material characteristics as well as the in vitro drug release kinetics, a promising formulation was obtained containing 30 mg/ml of the drug in 3% w/v MC, with 8:2 w/w ratio of Eudragit[®] FS100 to polylactic acid. The presented formulation demonstrated superior processability, printability, safety as well as desirable drug release kinetics. Application of this approach would enhance the shifting of the traditional “one-size-fits-all” concept to the personalized medicine by effectively delivering various combinations with different dosages to the inflammation site. As recommend by the authors, continuing future studies could exploit the use of inkjet printing to automate the deposition of drug-loaded hydrogel during preparation. This could permit accurate, layer-by-layer placement of drug-excipient mixtures (the ink) as microdroplets onto the targeted surface. This approach could boost scalability while preserving a high degree of customization. Applying further studies aiming to evaluate the effect of drug

release from the hydrogel should be performed, to study if it affects diseases pathology, both in vitro and in vivo, whether used alone or along with other medications [57].

Novel 3D-printed colonic targeting dosage form with adjustable and controllable budesonide release was developed for the treatment of inflammatory bowel disease with reduced off-targeting adverse effects. The ability of the designed tablets for targeted delivery of budesonide was investigated using an in vitro gastrointestinal simulated system (GISS) model. The designed tablet having pill-in-pill configurations were fabricated and demonstrated superior dose accuracy and quality over commercial tablets. Also, the correlation between the 3D-printed design and the resulting dissolution profiles was recorded. Results proved the enhanced budesonide delivery to the targeted colon region through a simple, controllable, and effective approach. This offers a persuasive substitute to the currently prescribed therapy of rectally administered suppositories or enemas, which are highly invasive, uncomfortable, and commonly associated with poor patient adherence [58].

Enhancing drug's bioavailability and stability Johansson et al. studied the crucial quality control aspects for developing lipid tablets containing the hydrophobic drug: fenofibrate from emulsion gels, using the semi-solid extrusion 3D printing. Quality control aspects for the printable emulsion gel as well as the printed tablets were investigated. A printable emulsion gel was produced having unchanged precise dose for 30 days of storing at 4 °C. The 3D-printed tablets fulfilled the requirements of the European Pharmacopoeia for mass and drug content uniformity. Short-term storage study demonstrated that fenofibrate was maintained in an amorphous form with unchanged release profile. The obtained results highlight the prospective of semi-solid extrusion 3D printing of a lipid-based formulation approach for personalized dosing after considering the quality control attributes [59].

3D-printed tablets were produced from a binary mixture of hydroxypropyl methylcellulose and prednisolone. Three HPMC grades of varied molecular weights suitable for hot-melt extrusion method (90, 180, and 500 Da) were investigated. Hot-melt extrusion was used to fabricate filaments (the feedstock material) at the lowest possible temperature. Filaments of hydroxypropyl methylcellulose were prepared to contain different loads of prednisolone (2.5, 5, 10, and 20%w/w). Prednisolone was kept in an amorphous form, for at least 6 months of storage, except for those filaments prepared with 10% load and low molecular weight hydroxypropyl methylcellulose. Afterward, fused-deposition modeling was exploited to print honeycomb-shaped tablets from hydroxypropyl methylcellulose filaments. 3D-printed tablets fabricated from low molecular weight hydroxypropyl methylcellulose demonstrated greater structural similarity with the virtually designed model compared to those prepared using high molecular weight hydroxypropyl methylcellulose. From the above results, it could be concluded that the polymer's molecular weight and the drug concentrations play a crucial rule for determining the microstructure and structural properties of 3D-printed tablets [60].

3D tablet-shaped floating device prepared using the fused-deposition modeling was exploited to control domperidone release. The cap part was composed of polylactic acid and polyvinyl alcohol filaments aiming to decrease total floating time. The internal architecture contained polyvinyl alcohol permitting for water-diffusion pathway, thus providing a predictable total floating time. After complete dissolution of polyvinyl alcohol, the air chamber was detached intentionally to allow the device to sink and be excreted from the body (Fig. 2). Adjustment of the total floating time to an optimum value of 24 h was carried out by varying the water-diffusion pathway represented by the polyvinyl alcohol filaments length from 1.5 to 4.5 mm. The device contained a hole which diameter was varied to control the

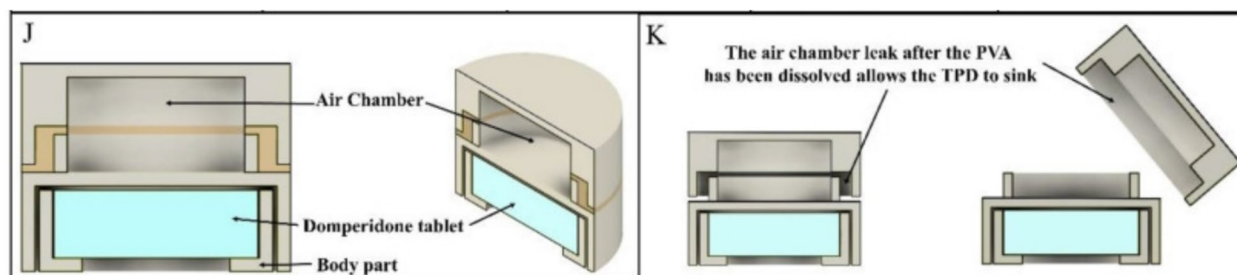


Fig. 2 (J) Cross-sectional view of the assembled floating tablet, showing the domperidone-loaded core and integrated air chamber for buoyancy, and (K) Intended structural failure after PVA dissolution, showing cap separation and the subsequent leakage of the air chamber leading to buoyancy loss, as adapted from Fig. 1 (Panels J & K) by Charoenying et al. [61], with permission from Elsevier. RightsLink copyrights license number: 6071410450739 for republishing

drug release. The prepared devices showed nearly identical shapes and narrow standard deviation values for their weights proving the success and accuracy of the adopted 3D printing technology. Cumulative drug release study revealed a precise release rate, where devices with a PVA filaments length of 4.1 mm and a hole diameter of 4.5 mm released the drug completely within 24 h following the zero-order release kinetics. The suggested design is a proof-of-concept formulation that can be applied for gastric delivery of drugs [61].

Exploiting 3d printing for enhancing the pharmaceutical technology research field A recent study by Seoane-Viaño et al. was performed in order to investigate the intestinal behavior 3D-printed formulations in humans, seeking a complete translation of the clinical practice of these formulations by utilizing magnetic resonance imaging for evaluating the real in vivo disintegration profiles. In their study, selective laser sintering technology was used to prepare placebo 3D tablets applying variable laser scanning speeds. The in vitro disintegration was calculated by two different tests: a standard USP disintegration apparatus, and an alternative method using a petri dish-based setup as an example for the use of low-volume media with minimal agitation. The produced tablets were administered by human volunteers and tested for the in vivo disintegration time using magnetic resonance imaging. Two laser scanning speeds for the process of 3D printing (90 mm/s and 130 mm/s) (Fig. 3) and the obtained in vitro disintegration time were (7.2 ± 1 and 2.8 ± 0.8 min, respectively) when measured using the USP method and (25.5 ± 4.1 and 18.8 ± 1.9 min, respectively) when measured using the alternative method. On the other hand, the in vivo disintegration time was 17.3 ± 7.2 and 12.7 ± 6.8 min, respec-

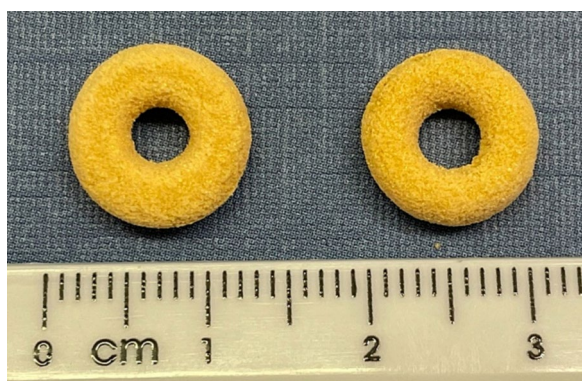


Fig. 3 Image of two torus printlets, printed at different laser speeds (90 mm/s (left) and 130 mm/s (right), obtained from Seoane-Viaño et al. [62], under the CC BY 4.0 license. (<https://s100.copyright.com/AppDispatchServlet?publisherName=ELS&contentID=50168365923007393&orderBeanReset=true>)

tively. Although closer resemblance between the in vivo data and that obtained from the alternative in vitro disintegration method was observed, absence of direct correlation between the in vivo and in vitro disintegration times highlights the necessity to develop and advanced in vitro disintegration technique to evaluate the behavior of 3D-printed formulations [62].

The translation and validation of the advanced powder bed-based 3D printing from the small laboratory to the commercial use scales were conducted through a study performed by Van den Heuvel et al. under good manufacturing practice constrains. Formulations based on lactose and starch containing acetaminophen as a model drug in two different loadings were scaled up to a scalable Aprexia GMP printer. After investigating wettability and flowability for the powder blends as the critical material aspects for small-scale printing, preparations were prepared using both the “R&D” and “GMP” equipment to investigate the influence of the printing device change on the critical quality aspects of the produced tablet (dimensions, tensile strength, mass, and acetaminophen release). Both equipment produced tablets with the desired mechanical and dissolution characteristics as the compositions for the powder blends kept the same. However, print settings were modified from the “R&D” to the “GMP” printer where the printing ink composition was set to fit the nozzle criteria of the “GMP” printer. This modification brought about an altered balance between the tensile strength and dissolution of some formulations. The obtained data proved that the successful scaling up 3D printing process. Even though the alteration in print settings produced slight change in product characteristics, tablets produced from both printers showed acceptable dissolution characteristics and tensile strengths—values [63].

Application of 3D printing to develop scaffolds

Fabrication of drug-loaded scaffolds for wound healing, burn injuries treatment and skin restoration The hierarchical structure similarity between multilayered scaffolds and the skin was exploited by Mirhaj et al. aiming to hasten wound healing process, and shield the wound from infection and contamination. Augmenting 3D printing and electrospinning technologies was performed to manufacture three-layered scaffolds. The top layer was composed of polyurethane nanofibrous coating, fabricated by electrospinning, for preventing microorganism penetration, whereas the central layer was functionalized as porous, absorbent, and antibacterial layer that was created by 3D printing of Pluronic F127-quaternized chitosan-silver nitrate nanoparticles. The bottom layer was placed over the middle layer and intended to enable anti-

bacterial activity and enhance tissue regeneration. The bottom layer had a core–shell nanofibrous construction of Pluronic F127-mupirocin/pectin-keratin. The antibacterial efficacy of the dressings was investigated against *E. coli* and *S. aureus*, where excellent antibacterial activity was attained. Highest cell adhesion rate and viability, as well as great angiogenic potential were recorded to the designed three-layered scaffold. Additionally, significant wound healing acceleration was recorded. The obtained results of this study advocate the utility of three-layered scaffold as an appropriate skin emulator regarding the hierarchical structure; this is specifically beneficial for full-thickness wounds repair. The authors recommended that upon applying more technological advancements with amended 3D printer resolution, customized scaffolds would replace traditional wound dressings. These personalized scaffolds can be promptly fabricated in specialized centers, allowing the incorporation of autologous repair-enhancing products such as platelet-rich fibrin. However, the elevated cost of raw materials and the fabrication process complexity comprise a significant limitation. Additional preclinical studies, adopting good laboratory practice conditions, in wound healing models are necessary prior to moving ahead to clinical trials [64].

Sagare et al. presented an organized scheme to produce a continuous flow procedure of personalized dosage form intended for the treatment of burn injuries. Ciprofloxacin hydrochloride-coated polyvinyl alcohol pellets and ciprofloxacin hydrochloride-loaded doped halloysite nanotubes coated polyvinyl alcohol pellets were subjected to hot-melt extrusion technique to prepare filaments with adjustable printing potentials. Afterward, designed filaments were printed into 3D scaffolds using fused deposit modeling printing technique. The authors assessed the mechanical characteristics and drug release profiles from the fabricated scaffolds, and the results were promising for wound healing applications. Designed scaffolds revealed an early burst drug release followed by a sustained release pattern. The achieved drug release profile was considered beneficial for effective controlling of the bacterial load and enhanced promoted wound curing effect. A stability study was conducted and proved the stability of the fabricated scaffolds at room temperature. Therefore, the proposed study focused on the capability of 3D printing techniques for the production of personalized dosage forms for wound healing [65].

In another study by Al-Hashmi et al., 3D-printed tacrolimus-loaded carboxymethyl chitosan scaffold was prepared and evaluated as a prospective bioactive multi-functional dressing for prolonged wound healing (Fig. 4). The structural, physical properties of designed formulations as well as the tacrolimus release profile were investigated. Both medicated and unmedicated scaffolds were

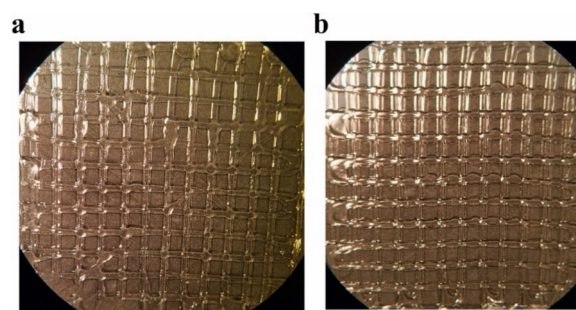


Fig. 4 Light microscope images showing the topography of CMC and TAC-CMC printed constructs (a, b, respectively), as adapted from Fig. 1 (Panels a & b) by Al-Hashmi et al. [66], with permission from Elsevier. RightsLink copyrights license number: 6071231153402 for republishing

biocompatible; however, medicated scaffolds increased the vascular endothelial growth factor secretion from fibroblasts. Pronounced antibacterial activity of medicated scaffolds was proved upon carrying out the disk diffusion test against both *S. aureus* and *E. Coli* as Gram positive and negative bacteria, respectively. The in vivo evaluation of the tested scaffolds revealed that medicated scaffolds resulted in significantly faster closure rate than the used positive control. Finally, histopathological assessment proved the efficacy of medicated scaffolds for wound healing by improving epidermal regeneration, angiogenesis, inflammatory responses, and fibroblasts proliferation [66].

Polycaprolactone 3D scaffolds including free and tetracycline-loaded polyvinylpyrrolidone nanoparticles were manufactured. The drug delivery system prepared utilizing the additive manufacturing, strived for a settlement to a stable drug delivery carrier. Tetracycline was electrospayed inside polyvinylpyrrolidone nanoparticles on various layers of the fabricated polycaprolactone 3D-printed scaffolds. This will form a porous, layered scaffold and drug-loaded nanoparticles in an easy way. Polycaprolactone scaffolds containing tetracycline-loaded polyvinylpyrrolidone nanoparticles demonstrated an extended, controlled drug release profile owing to tetracycline encapsulation into the interlayer. The designed scaffolds were safe and biocompatible. Morphology assessment confirmed that polyvinylpyrrolidone nanoparticles were homogeneously distributed between the layers of the scaffolds with a complete cover of the layers they were sprayed onto. This design comprising hydrophobic polycaprolactone scaffolds containing the hydrophilic drug, tetracycline, within polyvinylpyrrolidone nanoparticles manufactured using 3D printing and electro-spray technologies offer a prospective strategy for the development of a new functional scaffolds [67].

Fabrication of scaffolds for treating bone diseases 3D polymeric platforms for targeting doxorubicin to solid cancer tissues would comprise a promising strategy to prolong device retention at the target site, triggering the redox-responsive release of the loaded anticancer drug, and promote normal bone regeneration by prohibiting local cancer recurrence in the resection sites after operations. Variety of polyurethane urea derivatives composed of soft segments of *tri-block* polycaprolactone-polyethylene glycol-polycaprolactone and hard segments based on 1,4-diisocyanatobutane and glutathione were synthesized and characterized to assess the effect of polyethylene glycol/polycaprolactone chain lengths on physicochemical properties. One optimum synthesized polyurethane derivative displayed a suitable hydrophobicity degree to be dispersed in dichloromethane for next 3D printing step. The optimum formulation was loaded with the drug and further examined with and without the incorporation of hydroxyapatite nanoparticles. The obtained data suggested that the examined formulation permitted a slow doxorubicin release by positively responding to the reducing and acidic environments that were simulated in vitro. Moreover, the matrices underwent a slow hydrolytic decomposition proving their durability, assisting for a prolonged doxorubicin delivery for potential bone regeneration. The delivery of drug directly to the resection site is expected to avoid metastasis and recurrence while concurrently motivating bone regeneration by the presence of loaded osteoinductive hydroxyapatite nanoparticles [68].

The approach of bone repair and tissue engineering needs unique biomaterials to fabricate scaffolds with vital biological and structural features along with enhanced performances compared to those currently available. Hybrid biomaterials composed of a blend of the aliphatic polyester poly(ϵ -caprolactone) with the amphiphilic graft copolymer Inulin-g-poly(D,L)lactide were synthesized adopting the fused filament fabrication 3D printing technique to produce macroporous scaffolds. Poly(ϵ -caprolactone) and Inulin-g-poly(D,L)lactide were firstly blended in the form of thin films by the solvent-casting method. Subsequently, they were extruded to form filaments by the hot-melt extrusion ready for processing by fused filament fabrication 3D printing technique. The physicochemical characterization of the developed structures revealed excellent homogeneity, amended surface wettability/hydrophilicity in comparison with poly(ϵ -caprolactone) alone, and accurate thermal properties for fused filament fabrication technique. Very close resemblance was detected between the 3D-printed scaffolds with those of the digital model regarding the structural and dimensional parameters. Moreover, they exhibited mechanical performances well-matched with the human trabecular bone. Besides, in hybrid scaffolds

demonstrated enhanced surface properties, in vitro biodegradation rate and swelling ability compared to poly(ϵ -caprolactone) alone. The prepared scaffolds were both compatible with human fibroblasts, human adipose-derived mesenchymal stem cells, and hemocompatible, as well. Remarkably, the constructs proved an osteogenic activity via significantly up-regulating alkaline phosphatase. The authors suggest that the presented hybrid biomaterial produced by fused filament fabrication 3D printing technique could be thought about as a promising treatment for bone repair and tissue-engineering applications [69].

Fabrication of scaffolds for treating intravaginal infections Topical antibiotic treatments of the highly recurrent bacterial vaginosis are challenging, as it is controlled by the drug solubilization in the vaginal fluid, absence of patient's daily-based adherence and convenience. In order to overcome this challenge, antibiotic-loaded 3D-printed scaffolds were developed by Kyser et al. to offer a targeted sustained delivery. In their study, metronidazole-loaded 3D-printed silicone scaffolds were formulated and characterized, silicone vehicles were selected in order to offer biocompatibility, structural stability, and flexibility. Scaffolds were characterized for their swelling, degradation, and drug release in simulated vaginal fluid. Results showed that they retained high structural integrity, minimal swelling and mass loss, compared with the initial post-cure measurements. Moreover, scaffolds showed a localized sustained metronidazole release profile for 14 days. Insignificant cytotoxicity was detected in treated keratinocytes compared to untreated cells. The presented article intended to propose an approach by which extrusion-based 3D-printed structures were developed for sustained, local intravaginal delivery of metronidazole for bacterial vaginosis treatment [70].

Applications of 3D bioprinting for tissue reconstruction

These include 3D bioprinting for constructing ocular prosthesis, corneal, and retinal engineering.

3D bioprinting for constructing ocular prosthesis

3D printing technology was exploited to produce high-quality, personalized dosage forms after being designed from a digital file on a computer using various biomaterials by layering printed materials over each other [71]. 3D bioprinting was established to create sophisticated ocular models for therapeutic application. To grow a bioprinted tissue, a sequence of steps must be carried out. This comprises production of a series of printed directions, precise selection of target cells and appropriate bioinks, controlling the bioprinter setup, then, the final step of printing and the quality control assessment [72]. A tailored

polymeric implant in the form of an ocular prosthesis was prepared by 3D printing technology and sublimation, to be located in the eye socket, aiming to retain the normal look for patients who lost their eyes. After conducting the required cytotoxic activities, intradermal response, systemic toxicity, and topical sensitization analysis, a case study was performed using three patients in whom the 3D-printed prosthesis was applied at least 8 h/day for a month. Safety assessments were accomplished for the subjects to record any allergic response or conjunctival irritation using slit-lamp assessment. The physical, chemical, and pharmacological safety inspections proved absence of cytotoxic effect, systemic toxicity, and transcutaneous sensitivity for the 3D bioprinted ocular prostheses. Also, the designed ocular prosthesis did not generate any adverse effects in the conjunctival sac and demonstrated identical observations for iris color, sclera, and vascular patterns. The formulated prostheses were acceptable regarding their appearance and function, physiochemically and physiologically safe [73].

3D bioprinting for corneal engineering

The absence of balance between the demand and supply of donor corneal grafts, their cost, and the rejection probability paved the way for the pharmaceutical technology sector to construct 3D-printed corneas [74, 75]. *In vitro* models were applied for analyzing tissue interaction and testing the drug [76, 77]. Printing of corneas was performed with the aid of scaffolds with injected cells, collagen, or gelatin [78]. Corneal image of 3D design was developed using optical coherence tomography or ultrasound. The printing bioink should be transparent, permeable to nutrient and oxygen diffusion, biodegradable, with adequate mechanical strength to withstand the extrusion-generated shear stress through the nozzle [79, 80].

3D-printed corneal structures imitating the human corneal stroma were constructed using bioink composed of sodium alginate and methacrylate type I collagen, in addition to corneal keratocytes isolated from a healthy cornea. Following, corneal stromal equivalents were printed using a dual extruder 3D bioprinter. The structure was printed inside out; then, the cross-linking of the corneal configuration was performed in calcium chloride solution. Positive results of the evaluated parameters shed the light on the feasibility of the conducted method for corneal tissue-engineering applications [79].

In another study, 3D bioprinted synthetic corneas were prepared utilizing chitosan and polyvinyl alcohol composites as the bioink. After fabricating corneal support structure as a template, development of the corneal model was conducted using G-code, for the printing process of the designed cornea. The exact morphology of the

cornea was obtained by a Tribot 3D printing device, after careful control of the printing speed, temperature, and dimensions of the extruder. Cell viability and distribution studies proved the efficiency of the established corneal structure. The results were promising in the field of corneal tissue engineering [81].

3D bioprinting for retinal engineering

Retinal degeneration and irreversible vision loss could be resulted from retinal pigment epithelium and photoreceptors malfunction [82]. The existing medication only postpone disease's progression and do not restore complete function. Besides, diagnosing retinal diseases, in old-ages, at its primary phases is difficult being asymptomatic. Thus, exploitation of 3D bioprinting technology could comprise a great physiological relevance in retinal restoring [83].

In a recent study, 3D bioprinting technology was utilized to construct a hybrid retina, where ARPE-19 cell monolayer, polycaprolactone ultrathin film, and Y79 cell-packed alginate/pluronic bioink were the constructing materials. Drop-by-drop transfer pattern of Y79 cell-laden bioink and ARPE-19 cells were carried out for 3D bioprinting technology. Then, Y79 cell seeding was packed above the ARPE-19 cell layer, by two different seeding ways, to yield even ARPE-19 cell seeding. The bioprinted cells were observed for two weeks by inversion and laser scanning microscopy. While the Y79 cells in the alginate/pluronic bioink were carefully checked for one week after bioprinting process, where their morphology and survival capacity were tested using a live/dead assay and scanning electron microscope. Results demonstrated migration and dispersion of the ARPE-19 cells that were primarily attached to the surface, all over the membrane. After two weeks of rapid multiplication, cells were structured in the form of a monolayer on the ultrathin membrane. Moreover, the established structure revealed good cytocompatibility with a structure simulating the human native retina. Therefore, 3D bioprinting possibly can play an important role for the treatment of retina-related disorders [83].

Four-dimensional printing

Four-dimensional (4D) printing is an evolving technique in which smart materials are 3D printed to produce items that alter their shape after production, in a programmed manner over time, upon exposure to certain external stimuli (electric or magnetic fields, temperature, moisture, pH, UV, or ion composition). 4D-printed dosage forms differ from 3D ones in that time is considered as the 4th dimension during their performance. The term "4D printing" describes smart materials manufactured by the additive technique to produce

easily achieved, complex-shaped, nonstatic objects that are more advanced than 3D objects. 4D-printed objects can be manufactured with 3D printers [9]. 4D printing technologies yield high-resolution biostructures in a more advanced manner than the 3D printing biofabrication methods do [84]. The transformation potential of 4D-printed substances has the ability to fabricate either dynamic and controlled structures or unique, hollow structures as well. It also gives the ability of the transformation from 2D patterns to 3D patterns via self-folding abilities [85].

Shape memory materials are smart materials that gained much interest in different research fields [86–88]. They dynamically react to an externally applied environmental stimulus, and adapt themselves to perform the required function according to the endured change [89–91]. The ability of shape memory materials to control the undertaken modification is behind their description as smart materials. By applying an excess stress, a temporary shape is attained from a permanent one. The process can be referred to as a “shape memory creation process” or “programming step.” After stress removal, the temporary shape is maintained till the substance is subjected to a specific unmechanical stimulus to recover its original shape. Thus, they are able to temporarily preserve the applied mechanical stress during the programming step and undergo the predefined mechanical actuation. Remarkably, the restoring happening throughout the recovery alters the mechanical distortion causing the acquired temporary shape [92].

Employment of the shape recovery behavior has many reasons and applications. It may be employed to enable a sustained in situ retention with minimal invasive administration, or to ensure removal from the target site. In addition, it can trigger drug release after reaching drug delivery site [92].

Types of shape memory materials

Shape memory materials are generally categorized as shape memory polymers, shape memory hydrogels, shape memory ceramics, and shape memory alloys. The first two types being the most important for the pharmaceutical technology field.

Shape memory polymers

Shape memory polymers possess two shapes. Shape “A,” created from a mechanical distortion, is a temporary architecture and can be transformed to the permanent structure; shape “B.” The transformation from the temporary to the permanent forms depends on the molecular structures, which are not essential to be positioned within the chemical structure and that get the mechanical properties through repeated units, in a manner that

precise molecular parameters can be adjusted [93, 94]. In this type of polymers, the net points are linked through chain fragments, which creates the permanent form. Physical interaction takes place in the polymeric units, the morphological framework of which involve amorphous and crystalline phases. The efficient shape transformation requires the net points to be deformed, to elongate the chains and increase chains flexibility. Hence, the permanent form is achieved via recoiling of the chain structures. Shape fixation is completed via extra temporary cross-links, which could be either chemical cross-links or physical interactions [84].

The specific use of shape memory polymers to ensure retention and targeted action is specifically useful to enhance the bioavailability of the delivered cargo, cure local diseases, offer a controlled drug release with diminished dose frequency required [95–98]. Also, these polymers have been used to develop medical devices, for instance: embolization plugs, self-expandable biodegradable stents, self-tightening sutures, and thrombectomy devices [91, 99–104]. Polyvinyl alcohol is a good example of shape memory polymers and thus has many applications in the pharmaceutical and cosmetic fields. A previous study manufactured a capsule from PVA, responding to body temperature variations. It possessed a three-dimensional S-shape with a temporal paper-clip shape. A thermoviscoelastic constitutive model was applied, and the thermomechanical influence was assessed. Following their proposed strategy, Inverardi et al. suggested its exploitation for designing various shape memory polymers-based drug delivery systems [105].

Shape memory hydrogels

Hydrogels can also respond to pH, light, or temperature resulting in programmable temporary shape memory hydrogels. The amendment of shape memory polymers arises from changing the network morphology in the polymeric backbone as a consequence of functional chains responding to an effect as temperature or polarity. The first introduction of shape memory hydrogels was performed by copolymerizing acrylic acid and stearyl acrylate with the aid of a cross-linking agent (methylenebisacrylamide) creating a thermosensitive shape memory hydrogel [106]. Molecular switches permit polymer reshaping, by combining with water molecules resulting in architecture alteration [107, 108]. Whereas the temperature-responsive influence of shape memory hydrogels is affected by a thermal stimulation to the cross-linking groups, the breakdown of the weak physical cross-links produces a temporary structure. Consequently, structure is deformed and the materials is softened. When cooled, shattered physical bonds reformed and positional deformation is retained [109].

Shape memory hydrogel was also effectively exploited for chronic wounds treatment; by responding to a specific temperature, geometrical change of the polymer would result in terminating the need of repeated wound dressing application, resulting in better patient compliance [110]. In another study by Yasin et al., a shape memory hydrogel was developed using the host–guest approach. A crystalline domain resulted from cross-linking α -cyclodextrins and hydrophobic chains of the polymers with the aid of N,N' -methylenebisacrylamide. The produced crystalline domain can be delineated to temporary forms in response to temperature variation and complete regaining of the deformed shape [111].

Shape memory polymer composites

Shape memory composites involve numerous constituents that enhance the matrix material performance or function, together. They are intended to improve the mechanical characteristics and to consolidate more stimulus techniques [112, 113]. Lin et al. designed a composite for photothermal therapy, biomedical use, and tissue engineering. In their study, 3D filaments of polylactic acid and polylactic acid/polybutylene succinate were manufactured by a high-quality fused-deposition modeling printer. The shape memory behavior, tensile strength as well as surface morphology of the produced filaments were examined. Then, the honeycomb-structured carbon compound, graphene oxide that possesses an outstanding photothermal property was functionalized on the prepared filament. This unique design was intended to function as a vascular, tracheal, or intestinal stent. Endoluminal and starfish stents were prepared using the polylactic acid/polybutylene succinate filaments. To assess their shape recovery performance, temporary shapes were placed in a hot water bath, where the starfish-shaped stents exhibited a changed recovery time relative to the endoluminal structure. This might be related to the dense wall of starfish stent, taking more time to transfer heat and restore its shape. Furthermore, 4D-printed scaffolds of near-infrared-triggered (graphene oxide/polylactic acid/polybutylene succinate) composite were applied for bone regeneration. The scaffold had a porous structure, and their transformation was remotely and dynamically controlled by the near-infrared laser. As a conclusion, the prepared polylactic acid/polybutylene succinate scaffolds could be functionalized as various structures based on the required disease to be treated [114].

Applications of 4D printing

4D printing for developing drug-loaded implants for breast cancer treatment, unfolding/expandable dosage forms, drug-loaded stents as well as tablets loaded with

anticancer drugs. The applications described below are summarized in Table 2.

4D printing for developing drug-loaded implants for breast cancer treatment

Although breast-conserving surgery is performed as a primary approach to treat breast cancer in its early-stage, the chance of recurrence and body image alteration adversely influence patient by the emotional distress. It is advised also to complete the treatment with either radiotherapy or systemic therapies to increase the patient's survival chance, and also to avoid possible recurrence. This leads to longer treatments durations, and undesirable systemic adverse effects. A patient-centered approach is essential to eradicate the heterogeneity between tumors and individuals. To achieve this aim, a multipurpose 4D-printed doxorubicin-loaded implant was developed by Moroni et al. by blending carboxymethyl cellulose sodium salt and cellulose nanocrystals. Full rheological investigation was performed in order to expect the printability accomplishment. Herein, by swelling, the designed smart device was programmed to change size for exact fitting in the intended tissue cavity. This fitting is highly desirable for personalization of treatments and improves the esthetic results. The effect of the printing as well as formulation parameters on shape conversion was tested by conducting a swelling test, to prove the possibility of programming a 4D shape. The assessment of the anticancer efficacy was performed *in vitro* using MDA-MB-231 cells, where the designed 4D-printed implant displayed an excellent anticancer efficacy. The results of the *in vitro* studies as well as the morpho-transformation suggested the potential of the designed implants as a promising treatment approach for breast cancer after resection, by filling the surgery-left void and providing an anticancer influence to prevent recurrence, as well. The authors suggested performing comprehensive investigations for the technical aspects for the fruitful translation of 4D printing technology into biomedical applications. This necessitates proficiency regarding material selection, including their availability and smart properties, as well as a thorough understanding of how printing parameters and design could influence responsiveness to specific stimuli. Moreover, exploring other trigger stimuli that could increase other potential applications of 4D printing. However, in spite of these prospects, lack of clear regulatory guidelines for additive manufacturing technologies, and inadequate focus on scalability, hinders further progression from research to clinical use. Therefore, foregrounding regulatory strategies for large-scale production is fundamental [115].

Table 2 Examples of applications of 4D printing technology in the pharmaceutical field

Application	Specific aim	Outcome
Developing drug-loaded implants for breast cancer treatment	Multipurpose 4D-printed doxorubicin-loaded implant [115]	The designed smart device was programmed, by swelling, to change size for exact fitting in the intended tissue cavity
Developing unfolding/expandable dosage forms	Designing gastroretentive devices containing allopurinol [117]	Various shapes of allopurinol-containing prototypes were fitted within commercial hard gelatin capsules. The prototypes regained the original shape and attained the required spatial encumbrance in short time in the gastric fluid
Developing drug-loaded stents	Designing a controlled drug release device into hollow muscular organ, as the bladder [118]	The proposed systems effectively restored the required original shape from the temporary one, upon contacting the aqueous fluids at the physiological temperature
Developing drug-loaded stents	Designing biodegradable high-resolution shape memory stents [119]	The stents conserved their folded shape at room temperature, while restored their shapes effectively at body temperature. Materials were cytocompatible. Tunable release kinetics when the devices were loaded with levofloxacin or nintedanib
Developing anticancer drug-loaded tablets	Preparation of drug-loaded printed tablets adopting the drop-on-demand technique [120]	The performed study emphasized the impact of drop-on-demand technology in distributing drugs uniformly on the surface of tablets

4D printing for developing unfolding/expandable dosage forms

Thermoplastic, flexible, and elastic polyurethanes are widely used in the field of medical and pharmaceutical research as implants, dosage forms, or components of medical devices. Various shaped and foldable objects can be obtained using the 3D printing technique from polyurethane filaments, to be applied in expanding (unfolding) dosage forms. Exploitation of the shape memory behavior was performed to fold and package the designed dosage forms in hydrophilic hard gelatin capsules. Time for unfolding as well as dimensional recovery of prepared objects was considered as critical factors that were correlated with the material properties and shape. This could be useful for designing flexible dosage forms which can acquire an unfolded size fitting for gastroretentive purposes. However, careful consideration should be taken into account regarding the stability of the designed shapes after storage regarding dimensional recovery and expansion time. The proposed perception of the hybrid shape memory effect could be convertible to develop innovative medical devices or sustained release dosage forms which require to possess flexible and elastic behavior [116].

Expandable gastroretentive system was designed based on the shape memory behavior of poly(vinyl alcohol). The designed device would be administered in a collapsed form suitable for swallowing, then get into a larger size in situ, allowing longer residence time in the stomach, hindering escape from the pylorus. Prototypes containing allopurinol, with various original shapes, were successfully fabricated by 4D fused-deposition modeling printing or manually by processing of extruded rods. The attained size was fitted within commercial hard gelatin capsules. Shape modifications of the extruded samples were evaluated by a quantitative method over time in a static acidic environment at body temperature. Results revealed the ability of the prototypes to regain the original shape, attaining the required spatial encumbrance in short time. Release of the drug had no correlation with the shape of the systems, yet it was decelerated by coating with Eudragit[®] RS/RL [117].

4D printing also was exploited to develop coated expandable drug delivery systems with extended retention and controlled drug release into hollow muscular organ, as the bladder. The shape memory behavior of poly(vinyl alcohol) was used to attain prototypes able to be programmed in a temporary configuration suitable for administration, which recover into the original intended shape and retain at the targeted site. Coating of the 4D-printed prototypes was carried out using the insoluble, yet, permeable Eudragit[®] NE despite their shapes (elongated or folded). The coating process turned out to

be reproducible, yielded samples with good physical and technological features, regarding the reproducible thickness, release performance and capability to effectively restore the required original shape from the temporary one, upon contacting the aqueous fluids at the physiological temperature. The shape memory effect was independent on the coatings. The promising results, obtained for the reservoir-like expandable prototypes intended for intravesical applications, encouraged the industrial scaling up. The potentiality of the suggested technique was verified by inspecting the coated prototypes regarding their physical–technological characteristics, shape memory restoring, and release performance in urine simulated fluids. The obtained results were promising encouraging taking out the challenge of processing and scaling up for more advanced prototypes [118].

4D printing for developing drug-loaded stents

As another advanced application for 4D printing, soft robotics and medical devices could be manufactured, in high resolution and with tailorable functionalities, coupling novel shape memory photopolymer and digital light processing [119]. The major challenge being faced during the preparation of 4D objects is the type of materials used; nondegradable ones have limited clinical applications. Alternatively, using biodegradable elastomers is challenging, specifically if the transition points are in good match with the physiological temperature. Thus, shape fixation under ambient conditions is attained. Paunović et al. reported the 4D printing processing of biodegradable shape memory elastomers using poly(D,L-lactide-*co*-trimethylene carbonate) methacrylates at different feed ratios of monomer. High-resolution digital light processing printed stents conserved their folded shape at room temperature, while restored their shapes effectively at body temperature (Fig. 5). The materials were degradable under physiological conditions and cytocompatible. Tunable release kinetics when the devices were loaded with levofloxacin or nintedanib. This study shed the light for the potentiality of 4D printing in developing a new generation of medical devices [119].

4D-printed tablets loaded with anticancer drugs

Drug-loaded binder jet printed tablets could be prepared adopting the drop-on-demand technique, where drugs are dissolved in either ethanol or water. The porosity in the tablets would arise from solvent evaporation and can be manipulated by controlling the percentage of ethanol and water. Rhodamine 6G was chosen as an example of a hydrophilic drug to be loaded in the designed tablet, as it could be assayed easily being fluorescent and the potential therapeutic anticancer effects. The ink solutions were printed on blank 3D-printed tablets, containing calcium

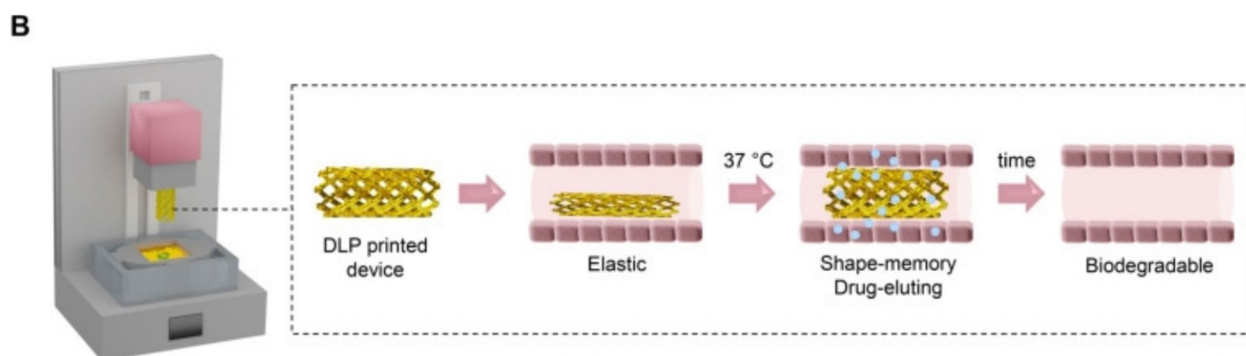


Fig. 5 Diagrammatic representations of a 4D-printed elastic and biodegradable drug-eluting device activated by transition at physiological temperature, as adapted from Fig. 1 (Panel B) by Paunović et al. [119], under the CC BY 4.0 license. (<https://s100.copyright.com/AppDispatchServlet?publisherName=ELS&contentID=50168365923004777&orderBeanReset=true>)

sulfate hemihydrate utilizing the drop-on-demand technique. Then, tablets were characterized, after drying at room temperature. Results showed that increasing the water ratio in the ink solutions resulted in greater interaction with the bulk material, resulting in thicker tablets with heavier weights, while higher ethanol ratios showed faster tablet penetration. Investigation by SEM–EDX and fluorescent microscope revealed uniform drug distribution. In vitro drug release study indicated the reverse relation between water content and release rate. The performed study emphasized the impact of drop-on-demand technology in distributing drugs uniformly on the surface of tablet, and the significant influence of the ratio of water to ethanol on drug release from the fabricated tablets [120].

Utilization of artificial intelligence for further 3D-printed medication advancement

Artificial intelligence would accelerate the introduction of 3D-printed pharmaceutical and medical formulations and devices to the healthcare community and spread the idea of a personalized medication [121]. Artificial intelligence could be integrated with interconnected hardware networks, or the so called "Internet of Things" (IoT), which is the up-to-date use of technology. Devices having distinctive properties are coupled with the "IoT" to perform integrated processes [122]. IoT is an expanding field, which is hoped to participate in developing more products based on the 3D printing technique [123]. Augmenting artificial intelligence and IoT results in numerous intelligently automated operations.

Genetic algorithms and artificial neural networks were used to adjust the 3D printing process computationally regarding selection of the material to obtain the highest tensile force of a hand exoskeleton constituent. The designed component was 3D printed aided by Cura

0.1.5 software and fused filament fabrication technology. Samples were tested using INSTRON 5966 universal testing equipment to examine the highest obtained value of tensile strength for the exoskeleton's [124].

A balanced dataset is crucial for machine learning models for optimum performance of prediction. In-house and literature-mined data on hot-melt extrusion and fused filament fabrication 3D-printed formulations were integrated to generate a more illustrative dataset of more than one thousand formulations. The formulation development process could be accelerated by the web program, which paved the way for numerous advanced pharmaceutical 3D print-based research output. This could be replicated by workflow replication to produce fused filament fabricated pharmaceutical items [125].

The artificial intelligence and machine learning models utilizing literature data to expect the in vitro dissolution quality and the important formulation 3D printing process ingredients. The machine learning algorithms were capable of learning and offering high accuracy values for the hot-melt extrusion process. Furthermore, machine learning was capable to predict the drug release from 3D-printed preparations by correlating data obtained from the composition of formulations with other input variables [126].

Being in the early stages of integrating artificial intelligence, the interactive interface between the typical user and the 3D printing robot is missing. The printing task understood by artificial intelligence should be shared and controlled by collaborative human professionals [127]. Consideration should be given to prevail over the currently confronted obstacle facing the integration between pharmaceutical 3D printing and artificial intelligence of lacking the sufficient artificial intelligence experience [121].

Regulatory guidelines for the 3D printing pharmaceutical technologies

Until recently, the absence of definite guidelines or concepts for regulating the production of 3D pharmaceutical objects comprises a major issue to be considered. Some of the investors of the industrial sectors lack the sufficient awareness needed to fulfill the regulatory bodies' vague requirements. Till now, Spritam[®] is the most recognized 3D pharmaceutically manufactured formulation in the market. The Food and Drug Administration published the "Technical Considerations for Additive Manufacturing of Medical Devices" in 2017, to address essential regulatory strategies required to give the approval for manufacturing 3D biomedical devices and pharmaceutical formulations [128]. Although, these regulatory guidelines waved the path to the US markets, in addition to all of the available techniques and advances, the number of 3D pharmaceutical formulations in the market is still so limited [121].

An Emerging Technology Team was constituted by the US pharmaceutical industry, under the Food and Drug Administration, to apply the fundamental standards, to be responsible for evolving 3D models prototypes to pharmaceutical industry [121]. Currently, FDA is giving guidelines consideration for polypills loading multiple drugs to obtain the efficacy and safety data for clinical studies. The major obstacle being faced is the necessity of standardizing the mixtures of polymers and excipients and the difficulty of handling several drugs. Also, another important factor is to select the suitable preparation method eligible for the polymers and loaded drug involved in the modeling [129]. Regulatory moderators constructed regulations for developing 3D-printed models. The most significant elements to be considered for the personalized designs are the physical structure and layout assessment of the finished products, sterilization, or post-printing requirements, as well as human compliance [130]. Consequently, it is a must to follow the standards and guidelines for any future advancement and implementation of 3D printing techniques.

The quality by design approach should be adopted to eliminate any possible factors that could affect the final product appearance and qualifications. This is especially important because of the variation between the available commercial printers producing drugs and medical devices. This could influence the final product standards and appearance, and should be taken into consideration [131–133].

Challenges and restrictions of 3D printing technology for developing personalized medicine

As mentioned in the previous section, sophisticated regulations were set limiting the modeling methodology and variables for setting up the printers, filaments, and appropriate standards. All of these issues should be considered

prior to design and optimize a 3D model. The fabricating materials, mainly the used polymers, should follow some regulations. Thus, specific safe and biocompatible materials are desirable and employed for the fabrication processes to ensure safety and efficacy throughout the shelf-life [134, 135].

Each technique possesses welfares and limitations. The mechanical properties of the employed components may be considerably influenced based on the method. Laser-based 3D printing technique could degrade some thermolabile drugs or polymers during the fabrication process. Another problem is encountered with nozzle-based techniques that arise from clogging during fabrication resulting in improper thickness values of the produced objects [136, 137].

Adjusting the morphology presents a challenge in 3D printing processes to design an appropriate shape that meets all specific requirements based on individual variations. The interior and exterior designs of the model should be involved in the design space. The optimizing step significantly affects the manufacture process in a way that may result in reduced resources, manufacturing labor, ecological expenses, and, saving energy, bringing about affordable expenses [138, 139].

In most cases, models demand the production of several elements simultaneously. The adopted technologies should be consistent with the homogenous components or parts. While a heterogeneous hard model has several ingredients within the element, the manifold compounds' parts can be dealt with as distinct zones with sharp boundaries [140]. Substantial challenges are faced upon designing and dealing with numerous interconnected constituents utilizing limited approaches. Considering compliance of polymers with active ingredients as well as the material sciences contributes extensively to process success [141]. Additional substantial challenge facing the 3D bioprinting is the cell source selection criteria. Based on theoretical bases, cells used to build tissues such as heart valves may be acquired from people or animals. Cells from animal sources include allogeneic ingredients, proposing a threat of disease xenotransmission, nevertheless, are able to proliferate into tissue for surgical application. Conversely, cells from man source are biocompatible and customizable, yet their application is limited due to stricter regulation, higher prices, and longer production time. The biological part of implants makes interactions and integration more nonpredictable after implanting into hosts, as compared to presently utilized stents, artificial joints, and pacemakers [142]. The actual success of the implantation of an engineered tissue process is the creation of microvessels, patterning, and maturation. Still, current procedures cannot incorporate a full network of blood vessels into the implanted printed

tissues [143]. It is also important to determine the cost, regulations, quality, and the timeliness for delivering an implant for developing a medical device. The amended efficacy of the additive manufacturing over subtractive manufacturing, with the merit of saving raw materials and inventory costs, may partially counterbalance the elevated costs as every customized device needs a special design input because of the small production volumes [144].

Conclusions and future perspective

The presented article demonstrates the merits achieved upon utilizing the 3D printing technique in the pharmaceutical field. Knowing that this technique is still in the initial stages, but in retrospect, it will enable the manufacture of personalized or customized medications with favorite features that cannot be achieved by the traditional manufacturing technologies. Although, as stated in the above sections, some challenges are facing their large-scale manufacturing, 3D-printed pharmaceuticals will overcome such challenges sooner or later.

In the upcoming future, 3D printing technique will be exploited to develop organ transplantation and tissue repair remedies. On-demand 3D pharmaceutical and medical devices manufacture will be more economical and affordable. Also, the opportunity of manufacturing 3D-printed tablet with multiple drugs “a polypill” will be globalized, enhancing the patient compliance and promoting patient adherence to given medications. 3D printing will be applied to prepare customized drugs, organs as well as nutritional products, after solving the obstacle of integrating 3D printing with tissue engineering.

The incorporation of complicated drug delivery systems within smart dosage forms via the 3D printing technology will enable successful personalized release profiles and targeting, which in turn, enhances the therapeutic outcomes. Also in the future, developing portable compact 3D printers that can be utilized at hospitals or pharmacies. This will enhance the speedy manufacture of personalized treatments, and improve patient access to customized medications. Furthermore, 3D printing can be integrated with other digital health technologies, such as patient monitoring systems and electronic health records to facilitate adaptive dosing based on individual patient requirements, continuous data transfer, and real-time monitoring of patient response to the administered therapy.

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Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used ChatGPT and DeepSeek to improve the manuscript readability and language. After using these services, the author reviewed and edited the content as needed.

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