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Medical, pharmaceutical, and nutritional applications of 3D-printing technology in diabetes

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ABSTRACT

Aims: Despite numerous studies covering the various features of three-dimensional printing (3D printing) technology, and its applications in food science and disease treatment, no study has yet been conducted to investigate applying 3D printing in diabetes. Therefore, the present study centers on the utilization and impact of 3D printing technology in relation to the nutritional, pharmaceutical, and medicinal facets of diabetes management. It highlights the latest advancements, and challenges in this field.

Methods: In this review, the articles focusing on the application and effect of 3D printing technology on medical, pharmaceutical, and nutritional aspects of diabetes management were collected from different databases.

Result: High precision of 3D printing in the placement of cells led to accurate anatomic control, and the possibility of bio-printing pancreas and β-cells. Transdermal drug delivery via 3D-printed microneedle (MN) patches was beneficial for the management of diabetes disease. 3D printing supported personalized medicine for Diabetes Mellitus (DM). For instance, it made it possible for pharmaceutical companies to manufacture unique doses of medications for every diabetic patient. Moreover, 3D printing allowed the food industry to produce high-fiber and sugar-free products for the individuals with DM.

Conclusions: In summary, applying 3D printing technology for diabetes management is in its early stages, and needs to be matured and developed to be safely used for humans. However, its rapid progress in recent years showed a bright future for the treatment of diabetes.

1. Introduction

Since the development of 3D printing in 1980s, many fields in science developed and changed significantly, including medicine, food, aerospace, and engineering. Additive manufacturing technology is another name for 3D printing technology [1]. It is now feasible to move a step farther toward integrating the virtual and actual worlds because of technology. 3D printing is a set of processes that allows the conversion of 3D models created on a computer into physical objects. This work is done in layers, whereby three-dimensional objects are formed by

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successively placing layers on top of each other [1]. This technology aims to design and produce objects by reducing the production waste while achieving the desired geometric accuracy [2]. Rapid prototyping (RP) and additive manufacturing (AM) are alternative names for this process [3]. Numerous novel 3D printing technologies have emerged in succession as a result of continued research and development [4]. Several advantages were identified for 3D printing, including the ability to produce various shapes and sizes, the capability to make complex shapes and forms, and its low-cost manufacturing process. Despite many developments in 3D printing technology, some significant challenges remain; for example, the lack of universal standardization, reproducibility of 3D-printed objects, and regulation challenges [5,3].

3D printing is considered a disruptive modern technology in healthcare and medicine. It is applied to produce small batches of a specific drug-loaded medical device for the clinical purposes, and other medications based on market demand [4]. When contrasting technologies, it becomes evident that 3D printing has the capability to produce intricate and precise spatial structures for individuals, which hold significant potential for use in the biomedical domain [6]. 3D printing application in medicine allows a move toward more personalized medicine. Creating 3D-printed objects for medical applications includes several steps: finding the anatomical models, producing initial 3D models based on the anatomical images, editing the initial designs for 3D printing purposes, and selecting the best method and materials to print the final models [7]. By repairing shattered bones and limbs, a variety of medical gadgets and implants are being made using a 3D printer to help patients live better lives and address impairments. Some advanced and contemporary applications of 3D printers in medical science are listed as producing knee or hip prosthetics, porous trabecular bones, tissue engineering, artificial stents, and surgical designs [6,8,9].

3D printing was beneficial in pharmaceutical sciences compared to the conventional manufacturing of drugs. This advanced technology allows customized drug products with superior resiliency by selecting the shape and size of dosage for patient's needs [10].

3D printing technology allows for producing the customizable drug tablets, which can be used as medication for various diseases, such as diabetes (Fig. 1) [11]. Furthermore, it is a significantly more efficient process than conventional manufacturing because it is time-efficient and requires fewer resources. Moreover, the progression of pharmaceutical science toward personalized drug therapy is aided by this emergent technology [12]. In pharmacogenetics, 3D printer is used to personalize medicine to create suitable 3D dosage forms, and deliver them to the organs using the microneedles (MNs) mechanism or transdermal drug delivery system [3,13,14].

Furthermore, 3D printer technology is applied to produce biocompatible materials embedded in the drugs in various dosages, and it helps deliver specialized drugs to organ or tissues in the form of living tissue without interfering with any contamination. 3D printing technology positively affected nutrition and food science using digitalized and personalized nutrition and helping to customize food designs [12]. These developments facilitate the estimation of energy consumption in accordance with an individual's specific nutritional needs and physical state, with the aim of averting or controlling ailments such as diabetes and obesity. Diabetes mellitus (DM) is a chronic disease categorized by hyperglycemia caused by improper glucose metabolism, which results in the macrovascular and microvascular difficulties like retinopathy, neuropathy, nephropathy, cardiovascular disease, and vasculopathy [15,16]. The current average cost of care for a diabetic person is $16,752 annually, which will continue to rise due to the growing occurrence of diabetes, and the increase in the cost per diabetic person [17]. The global prevalence of DM was estimated to impact over 220 million individuals in 2013, with projections indicating that this number will more than double by 2030 [18]. The current method for treating patients with Type 1 Diabetes Mellitus (T1DM) consists of insulin therapy via daily insulin injections or pumps and simultaneous monitoring of blood glucose levels [16]. Studies suggest that these treatments are

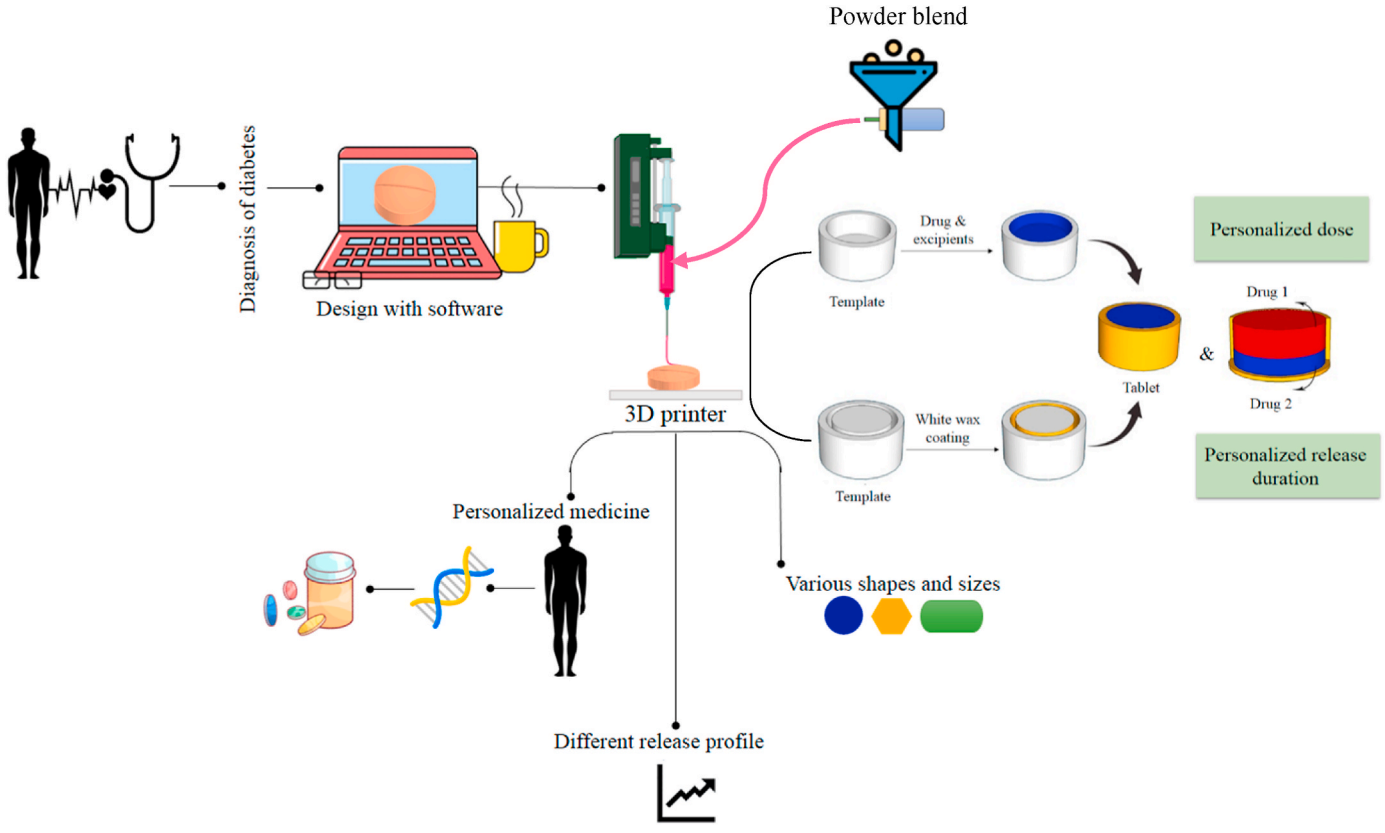

Fig. 1. Fabrication of customizable drug tablets via 3D printing.

successful in delaying secondary diabetic complications, such as nephropathy and retinopathy, but they will not prevent them [16,19]. Alternative approaches to β-cell function replacement encompass islet cell transplantation and whole pancreas transplantation, both of which will be elaborated upon in subsequent sections. In the past decade, several studies were conducted to cover different properties of 3D printing technology, and its applications in food science and disease treatment incremented. However, no study was performed to review the application of 3D printing in diabetes. Therefore, the current literature review centers on the utilization of 3D printing technology in the context of diabetes disease management. This paper discussed the role of using 3D printing to produce bio-printing of artificial pancreas and β-cells, as well as the fabrication of microneedle patches for glucose control using 3D printing. We also reviewed recent advances in the pharmaceutical and nutritional application of 3D printing in diabetes. Fig. 2 shows different applications of 3D printers in the prevention and treatment of diabetes diseases. This is the only article that specifically deals using 3D printing in the treatment of diabetes.

2. Medical application of 3D printing in diabetes

2.1. Bioprinting an artificial pancreas and β-cell replacement

Pancreas transplantation is undertaken in individuals who rely on insulin in terms of the factors, such as Type 1 Diabetes (T1DM), complete removal of the pancreas, and Type 2 Diabetes (T2D) mellitus [18]. Pancreas transplantations can be classified into three categories: 1) simultaneous kidney, and pancreas transplants, conducted in uremic patients, 2) pancreas transplantation after kidney transplant in post-uremic patients and 3) pancreas transplantation alone, conducted in nonuremic individuals. Furthermore, it should consider surgical perils associated with this procedure, including intraabdominal bleeding, thrombosis of the transplanted pancreas graft, wound infections, and graft-related pancreatitis, in addition to the lifelong requirement for immunosuppressive therapy [16,18,20]. Medical applications of 3D printers in diabetes disease are presented in Table 1.

Concerning clinical complications of a whole pancreas transplant, scientists concluded that the ideal approach is only to transplant destroyed cells, and endocrine parts of the pancreas [16,19]. Islet transplantation is a minimally invasive procedure that begins with the isolation and purification of islet cells. Islet cells are subjected to considerable trauma and duress during the isolation procedure [43,44,45]. Therefore, next step is the pretransplant culturing of islets to provide oxygen and required nutrients, and inhibit further islet loss [19,46]. Ultimately, the pancreatic islets are infused into the recipient's liver via the portal vein through a percutaneous transhepatic approach [16,19,43,47,48]. This procedure is less invasive in comparison with a pancreas transplant, because major surgery is not performed and, therefore, is more acceptable for patients, physicians, and endocrinologists [16,18]. However, several barriers limit the prevalent clinical applications of islet cell transplantation as the primary cure of T1DM [16,19]; Clinical success and long-term results of this procedure are yet less than whole pancreas transplantation so based on the reports of some single-center studies, insulin independence rate five years after islet transplant is 50 % and complete insulin independence has not been achieved yet [16,18,44,45]. Moreover, a single donor pancreas is not adequate for islet cell transplantation, and each patient requires multiple islet infusions for better outcomes [18,45]. Islet transplantation has certain clinical problems with pancreas transplantation, including bleeding, hepatic infarction, portal vein thrombosis, and an acute blood-mediated inflammatory response that results in islet cell function loss [43,49,26]. These factors together limit the availability, and successful outcomes of islet transplantation.

Three-dimensional printing (3DP), and its application in science and bioengineering have grown rapidly in recent years [50]. 3D bioprinting can create cells, tissues, organs, and biomaterials in a layer-by-layer manner [24,50,51]. This technology provides exact control for spatial distance and placement of cells, drugs, and biological components, which leads to better tissue and organ generation [24,23]. Hence, the restoration of pancreatic islets via 3DP technology is possible due to accurate anatomic control, as well as great potential in regenerating the multicellular environment and morphology of the pancreas [24].

The present diversities of 3D bioprinting methods are inkjet printing, extrusion printing, laser-assisted bioprinting, and stereolithography bioprinting [25]. Extrusion bioprinting is the most widely assessed to generate artificial tissue constructs like cartilage [52], liver [49], and

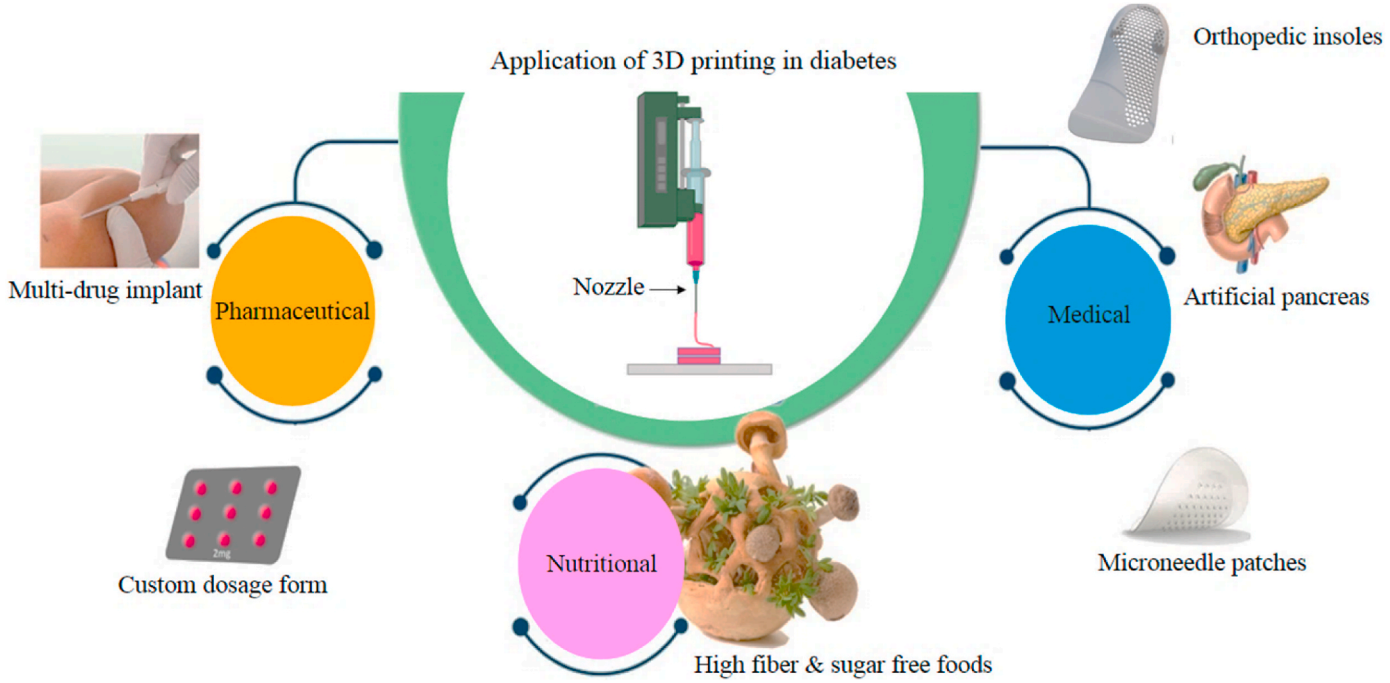

Fig. 2. Different applications of 3D printers in diabetes.

Table 1
Medical applications of 3D printers in people with diabetes.

References	Field of application	Moot point	Purposes
[21]	Bioprinting	Artificial Pancreas	3D bioprinting of islets for the generation of an artificial pancreas
[22]	3D Printing	Customized pharmaceutics, and medical	Achievements and challenges of additive manufacturing in the field of pharmaceutical, and biomedical research
[23]	Bioprinting	Scale-up tissue and organ constructs for transplantation	Bioprinting scale-up of functional tissue and organ constructs for transplantation, and provide the reader with alternative approaches
[24]	Bioprinting and Cellular Therapies	Type 1 Diabetes	Generate β cells and how this can be coupled with bioprinting technologies to fabricate pancreas tissues, which hold great potential for type 1 diabetes
[25]	Bioprinting	Islet cell transplantation	Create new structures for more effective islet cell transplantation
[26]	3D bioprinting	Human neural tissue	Functional 3D Neural Mini-Tissues from Printed Gel-Based Bioink and Human Neural Stem Cells
[27]	3D bioprinting	Biomedical devices and tissue engineering	3D bioprinting application in medical sciences and the high-performance bi-oinks
[28]	Bioprinting	Soft tissue engineering	Applications of the new hydrogel scaffolds including especially its potential for tissue engineering
[29]	Three-dimensional bioplotted	Islet cell transplantation	Fabrication of three-dimensional bioplotted hydrogel scaffolds for islets of Langerhans transplantation
[30]	Hydrogel-based 3D bioprinting	Cell-laden hydrogels, bioink formulations	3D printable hydrogels where cells can be encapsulated without significant reduction in the cell viability
[31,32]	Tissue engineering	Degradability in tissue engineering	Hydrogels exhibit tunable degradation rates and provide a powerful material system for tissue engineering
[33]	3D printing	Drug delivery	Extrusion-based 3D printing and post-stretching to fabricate a microneedle patch system for diabetes treatment
[34]	3D printing	Microneedles	3D printed microneedle arrays were fabricated using a biocompatible resin through stereolithography
[35]	Microneedles	Insulin delivery	The functionality of microneedles for the delivery of insulin
[36]	Microneedles	Drug and vaccine delivery	Microneedle in enhancing both transdermal and intradermal drug delivery
[37]	Microneedles	Transdermal protein delivery	Using the polymeric MNs for transdermal protein delivery
[38]	Microneedles	T2D therapy	Smart exendin-4 (Ex4) delivery device based on microneedle (MN)-array patches integrated with dual mineralized particles separately containing Ex4 and glucose oxidase
[39]	Microneedles	Glucose-responsive drug delivery	A designed glucose-responsive drug delivery system has a potential application in diabetes treatment
[40]	3D-printing	Orthopedic Insoles	Development of 3D-printed insoles using two polymers, thermoplastic polyether-polyurethane, and thermoplastic polyurethane polyester-based polymer, and the evaluation of plantar pressure distribution
[41]	3D-printing	Auxetic heel pads	A novel pressure relieving heel pad based on a circular auxetic re-entrant honeycomb structure by using three-dimensional 3D printing technology is proposed to minimize the pressure on the heel, thus reducing the occurrence of foot ulcers
[2]	3D-printing technology + artificial intelligence	Acute diabetic wound	Functional 3D-printing inks comprising DNA from salmon sperm and DNA-induced biosilica inspired by marine sponges, are developed for the machine learning-based 3D-printing of wound dressings.
[1]	3D printing	Diabetic wounds	Design and prepare a novel cerium-based Metal-organic frameworks (MOFs) nanozyme hydrogel via 3D printing technology to provide a personalized hydrogel wound dressing
[42]	3D printing	Diabetic wound	Double-cross-linked angiogenic 3D-bio-printed patches were developed for diabetic wound healing by the photo covalent crosslinking of vascular endothelial growth factor (VEGF) using ultraviolet (UV) irradiation.

neural tissues [26], with its capability to fabricate different biomaterials with higher cell densities [27].

3D bioprinting based on extrusion, can produce scaffolds with determined macro-porous clinically related cell size, and incorporate them properly [53]. Because of their macroporous nature, 3D plotted structures are projected to boost nutrition transport and significantly increase oxygen penetration to islets. Plotting embedded islets is already possible without impairing survival; however, to the best of our

knowledge, it is impossible with no impairing function [29].

Extrusion bioprinting is used to generate artificial pancreatic. To successfully print rat β-cell line, human, and mouse islets into a predetermined 3D scaffold, alginate-based bioinks were used. It was found that consequent cell morphology and viability were unaffected [29]. Moreover, an alginate/methylcellulose bio-ink was utilized to print rat islets into macro-porous 3D constructs. The function, viability, and morphology of these printed rat islets were retained for over seven days in culture [54].

Novel alginate-based bioinks were established in another study to create cell-laden grid-shaped hydrogel constructs with immunomodulation capacity, and constant integrity [55]. Printability and integrity were enhanced by including the *co-block*-polymer Pluronic F127 in alginate solution. The addition of pectin with a lower amount of methylation decreased inflammatory responses, as did tests for suppression of Toll-Like Receptor 2/1 (TLR2/1) activation and dimerization, as well as tissue reactions on the mice's skin. The pectin incorporation did not affect the viscoelastic features of alginate-Pluronic constructs. The printed insulin-producing MIN6 cells were protected by examined pectin from inflammatory stress. This is represented by many surviving cells within the pectin-comprising construct after exposure to a cocktail of the pro-inflammatory cytokines: IL-1β, TNF-α, and IFN-γ. The findings revealed that the responses of tissues were reduced by the cell-laden construct bio-printed with pectin-alginate-Pluronic bioink through inhibition of TLR2/1. Moreover, it can be seen that the response of support insulin-generating β-cell survival under inflammatory tension was reduced. They provided a possible novel approach to enhance the survival of pancreatic islet graft for the long period of curing Type 1 Diabetes (T1D).

Three-dimensional bioprinting for T1D treatment can still be considered in an early development phase. As a result, it is challenging to choose the best choice of biomaterials to suit the biocompatibility standards while also considering material and characteristics. As a result, cell activity and survival are ensured by meeting the stringent requirements for optimum printing, such as post-printing stability, extrudability, and viscosity [56]. A favorable microenvironment is provided by natural polymers like pectin and alginate, supporting cell proliferation and viability [57]. Moreover, such natural polymers present constructs simply carrying and releasing molecules to encapsulate cell survival [58]. Nevertheless, compared to synthetic polymers, producing the polymers in a reproducible way is more difficult since they may have less stability over the longer term [30]. The possible durability issues can be overcome by designing and studying an internal scaffold reinforcement of gradually degrading coatings. Considering natural biomaterials, using these materials as *bioinks* will be supported by modified biomaterials gradually degrading with optimum biocompatibility features [59,31].

2.2. 3D printing of microneedle patches for glucose control

To date, subcutaneous multiple daily insulin injections or pump therapy were developed as the conventional methods for treating insulin-dependent patients [33,60,61]. Subcutaneous needle injection, on the other hand, is an agonizing procedure that may result in skin thickening due to the need for repeated injections and needle phobia [62–64]. Furthermore, inaccurate insulin injection dosage may be highly associated with significant side effects, including hypoglycemia [33,56,65]. Hypoglycemia is determined as a "blood glucose level less than 70 mg/dl", which can lead to adverse effects on the brain, coma, and even death [33,56]. Moreover, postprandial blood glucose level control via the percutaneous insulin injection is difficult to achieve [33, 65]. To address these problems, transdermal drug delivery systems (TDD) involving the application of microneedles and glucose-responsive materials were developed [66–68].

Microneedles are small three-dimensional with diameters of less than 300 μm and a length of 50–900 μm which have attracted remarkable attention in recent years as a replacement to traditional drug delivery systems [33,68,35]. The utilization of microneedle patches for transdermal drug delivery enables the direct administration of various proteins, medications, and vaccines into the cutaneous circulation [62, 69–72]. Microneedle administration is effortless, harmless, non-invasive, and requires little instruction [35,64,72–74]. Considering these advantages, the microneedle systems were used for treating different diseases such as cancer, influenza, and diabetes [62,63,75,76]. For example, Yu, Zhang [62] developed a melanin-mediated cancer immunotherapy approach using a transdermal microneedle patch. Melanin in the patch mediated the heat generation, which enhanced tumor-antigen uptake by dendritic cells, and highly improved antitumor vaccination. They established a novel device for glucose-responsive insulin delivery taking advantage of a pain-free noninvasive microneedle-array patch holding glucose-responsive vehicles. In a mouse model of T1DM, this intelligent insulin patch effectively improved glucose regulation in the bloodstream; if implemented in humans, it could be a potentially effective means for preventing hyperglycemia and hypoglycemia in diabetics. However, in these studies, microneedle patches were fabricated via a template molding procedure which involves multiple complexes, and time-consuming steps [33,62, 63].

Zhu, Zhang [64] investigated treating diabetes in mice. They prepared lixisenatide-loaded bilayer (MNs) utilizing polyvinylpyrrolidone K29/32 (PVP K29/32) as matrix materials via a two-stage molding method to prevent therapeutic wastes in the main shell. They obtained MNs with adequate mechanical strength and suitable shapes. After being inserted into the rat skin, the MNs needles were completely dissolved in $<$3 min for releasing the therapeutic payloads. Based on the *in vivo* pharmacodynamic study, the Lix was successfully delivered by MNs, and the blood glucose levels were downregulated. In general, a unique transdermal delivery system is provided by the PVP K29/32-based bilayer fast-dissolving MNs to explore various biological therapeutics further.

Wang, Cheng [77] designed a glucose-responsive system to deliver drugs by integration of glucose-responsive poly (3-acrylamidophenylboronic acid) (PAPBA) functionalized hollow mesoporous silica nanoparticles (HMSNs) with transcutaneous (MNs). A gatekeeper was provided by grafted PAPBA to inhibit drug release from HMSNs at the normoglycemic level. Nevertheless, at a typical hyperglycemic level, PAPBA's hydrophilicity is altered, resulting in a more rapid release of the drug. An operative hypoglycemic effect is obtained by transdermal administration to diabetic rats, compared to subcutaneous injection. Such observations reveal a potential application of designed system for glucose-responsive drug delivery for diabetes treatment.

In another study by Economidou, Pere [34], biocompatible resin was used via stereolithography (SLA) to make 3D-printed microneedle arrays, for transdermal insulin delivery. To create microneedles, the polymerization of the consecutive layers of photopolymer resin has been used. Hence, thin layers of disaccharide carriers or insulin and sugar alcohol were coated over the needle surface via inkjet printing. Optimizing the printing method improved the skin penetration capability of 3D printed microneedles compared to metal arrays, with minimal altering applied pressures in the 2–5 N range. Micro-CT analysis represented stronger adhesion of covered films over the microneedle surface, even followed by penetrating to the skin. The fast insulin action was shown by *in vivo* animal trials along with superb hypoglycemia control and fewer glucose levels obtained within 60 min, integrated with steady-state plasma glucose over 4 h in comparison with subcutaneous injections.

Wu, Zhang [33] provided a novel technique to make a microneedle patch system. For the treatment of diabetes, they utilized post-stretching and extrusion-based 3D printing to fabricate microneedle patch systems that deliver insulin in a minimally invasive and glucose-responsive manner. The prepared microneedle patch contained 6 × 6 microneedles, and only microneedles performed glucose-responsive release of

insulin. The fabricated microneedles showed adequate mechanical strength for penetrating the mice's skin and responsively released insulin according to the glucose levels both in glucose solution and in type 1 diabetic mice. When the transdermal application was performed merely on the mice's skin, blood glucose levels of diabetic mice were regulated by the microneedle patches in normoglycemic ranges for more than 40 h and alleviated the mice's diabetic signs. Wu, Zhang [33] study proposed a method for the fabrication of microneedle patch systems, which can be potentially used for transdermal drug delivery.

2.3. Development of 3D-Printed orthopedic insoles for patients with diabetes

Diabetic neuropathy may be accompanied by clinical complications, including leg amputations and ulceration. In order to control diabetes, redistribute plantar pressure, prevent ulceration, or promote ulcer recovery, orthopedic insoles are essential. Handmade insoles have been used before, but these traditional techniques have limitations for customization. An emerging technology for insole manufacturing is 3D printing, and numerous studies in developed countries have demonstrated its potential benefits for individual therapy [40].

Report on the development of 3D printed insoles using two polymers, thermoplastic polyether polyurethane and thermoplastic polyurethane polyester-based polymer. The distribution of plantar pressure during walking assessments was then assessed in their research utilizing a low-cost electronic system and a clinical protocol. The two 3D-printed insoles functioned like a standard insole. In middle-income countries, digital manufacturing workflows for customized insoles can be implemented. 3D-printed insoles have the potential for diabetes management and further material evaluation is needed before they can be used in health facilities.

As mentioned, 3D printing technology seems to be useful to minimize pressure on the heel and thus reducing the incidence of foot ulcers. In the study [41], a novel pressure relieving heel pad based on a circular auxetic re-entrant honeycomb structure using three-dimensional 3D printing technology is proposed to minimize the pressure on the heel, thus reducing the occurrence of foot ulcers. The findings of their research indicate that the circular auxetic structure not only offers novel perspectives on diabetic foot protection but also facilitates the development and design of a wide range of impact-resistant products. **3. Pharmaceutical use of 3D printing in diabetes**.

3D printing technology also can be beneficial in pharmacotherapy to alleviate the symptoms of diabetes patients. This includes making multiple active pharmaceutical ingredients (APIs) and complex geometries in a single dose unit. Moreover, these devices are recognized as multi-drug or polypill tools that can deliver various drugs at pre-defined release rates [69]. 3D printed multi-drug implant is an auspicious method to obtain a programmed release in treating several chronic diseases like diabetes [70,71]. 3D printing has another advantage, enabling the formation of customized dosage forms with individualized dosage strengths [72]. It is crucial to customize the dosage according to the patient's weight, sex, disease severity, and age in order to reduce adverse effects and improve adherence. Moreover, 3D printing allows information from interdisciplinary fields like clinical medicine, polymer chemistry, and pharmaceutical sciences to achieve various appropriate features [73]. Besides, 3D-printed dosage forms can be distributed because they can be made on-site in the pharmacy [74]. Such a method is advantageous highly to producing drugs with restricted shelf lives. Though 3D printing is greatly promising, various regulatory and technical challenges exist for using this technology in the practical applications. For example, there is no clear regulation for 3D printed dosage forms, and difficulties obtaining approval from the Food and Drug Administration (FDA). An additional drawback pertains to the potential reduction in patient compliance caused by certain 3D printing techniques, which arise from the inconvenience associated with the oral administration of irregular and sizable capsules or tablets [78]. The lower production rate is another restriction of 3D printing compared to conventional manufacturing [79]. Pharmaceutical applications of 3D printers in diabetes disease are presented in Table 2.

Some studies assessed using 3D printing technology in the pharmacotherapy of diabetes. For instance, a bilayer dosage form comprising two anti-diabetic drugs with various daily dosage regimens was made i.e., glimepiride (GMD), and metformin via Fused Deposition Modeling (FDM) 3D printing. It was assessed utilizing various methods and characterized in vitro [80]. Glimepiride and metformin were embedded in the polyvinyl alcohol (PVA) layer and Eudragit® RL sustained release layer, respectively. It is preferable to include more than one API in the formulation since it improves medicine-patient compliance while lowering the cost of cure and treatment. This is particularly true when

Table 2
Pharmaceutical applications of 3D printers in diabetes disease.

References	Field of application	Moot point	Purposes
[80]	Pharmaceutics	Drug delivery	A bilayer dosage form containing two anti-diabetic drugs with different daily dosage regimens; i.e. metformin and glimepiride
[81]	Pharmaceutical	High drug loaded	TPU-based FDM feedstock material offers a lot of formulation freedom for the development of personalized dosage forms
[69]	3D Printing	Drug delivery	3D printing technologies being utilized for the fabrication of drug delivery system
[72]	Pharmaceutical	Personalized dosing	The technical and clinical aspects of ink-jet printing
[73]	Pharmaceutics	Customized drug delivery	Pragmatic tools, which can be used for designing customized drug delivery systems using 3D printing
[79]	3D printing	Multi-active tablets	Extrusion-based printing as a medicine manufacturing technique for the production of multi-active tablets
[82]	3D Printing	Metformin HCl PVA Tablets	AM of ML-PVA tablets by fused deposition modeling
[83]	Pharmaceutical	Controlled-release glipizide	Combining FDM 3D printing technology with HME to fabricate a novel controlled-release drug delivery device
[84]	3D Printing	Polypills & drug delivery	Develop a Curcuma oil-based SNEDDS 3D-printed polypills containing GMD and RSV for the treatment of dyslipidemia in patients with diabetes as a model for MS
[85]	3D Printing	SNEDDS	develop a 3D printing tablet containing GLMP and/or RSV for treatment of dyslipidemia in patients with diabetes
[86]	3D Printing	Ocular drug delivery carrier for diabetic retinopathy (DR)	Avastin-loaded PHEMA hydrogel lens as a topical implan fabricated by 3D printing
[87]	3D Printing	Diabetic foot ulcer (DFU)	Using electrospinning 3D printing and FDM techniques, different designs have been fabricated for the delivery of an antibiotic (levoflocixin) to DFU.

adjusting different dosages of APIs individually in situ to satisfy the specific requirements of each patient, a proficiency presented by 3D printing. Numerous preparation methods were tested, including various extruders and plasticizers, on making Eudragit® RL drug-loaded filaments to print the sustained release layer. The created filaments' features were evaluated through physicochemical, and mechanical characterization methods. Moreover, the filaments were utilized for printing with optimal features. Printing accuracy was revealed by Microfocus computed tomography (μCT) imaging-based actual/nominal comparison analysis within the range of −100, +200 μm. However, X-ray (XRD) diffractograms represented the integration of the initially crystalline APIs (with the amorphous structure) dispersed into polymer matrices.

Dissolution examinations revealed adequate drug release for both drugs in preferred time frames (metformin and glimepiride require 480 min and 75 min to release, respectively). Gioumouxouzis, Baklavaridis [80] used the potentiality of 3D printing technology for tailor-made solid dosage forms for integrated pharmacotherapy in diabetes while employing API's with various desired release profiles. Such bilayer tablets might provide the flexibility to change dosage form, dose, and release kinetics. Thus, on-demand fabrication is possible. These pharmacological combinations in poly-pills are quite effective in controlling diabetes mellitus.

Verstraete, Samaro [81] developed higher drug-loaded (less than 30 %, w/w) dosage forms based on thermoplastic polyurethane (TPU), via fused deposition modeling (FDM) 3D printing. Model drugs with various aqueous solubility, and particle sizes were pre-processed in integration with various TPU grades through hot-melt extrusion (HME) into filaments in 1.75 ± 0.05 mm diameter. Consequently, TPU-based filaments with suitable characteristics (smooth surface morphology, good mechanical features, and consistent filament diameter) were printed into tablets. In vitro, an examination was performed to check the potential capability of persisting release 3D printed dosage forms. Furthermore, the effects of printing parameters on drug release were investigated in vitro. TPU-based filaments may be loaded with 60 % (w/w) fine medication powders without affecting filament diameter or causing significant shark skinning. Within testing 3D printers, HME filaments oriented by hard TPU grades were converted into personalized dosage forms comprising a higher crystalline drug concentration (more than 60 %, w/w). In vitro conditions, the release kinetics were impacted by the tablet infill degree and matrix composition. Thus, Verstraete, Samaro [81] revealed that TPU-based FDM feedstock material presents a considerable deal of formulation versatility based on the patient's genomic information, weight, age, and sex.

In another study by Ibrahim, Barnes [88], metformin HCl–loaded PVA (ML-PVA) tablets were 3D-printed by fused deposition modeling. For loading metformin HCl onto PVA, a modified aqueous solvent diffusion method was used. A solvent mixture of ethanol-water (9:1) significantly increased and accelerated metformin loading compared with absolute ethanol. The presence of a low water content in the solvent combination affected the crystallinity of PVA in the ML-PVA filament. The tweaking of the 3D printer parameters enabled the successful printing of the ML-PVA filament into several tablet designs. Studies showed that the introduction of one or more hollow channels with different diameters increased the area/volume ratios of the tablets, but their area/mass ratios were comparable to the solid ones. In Ibrahim, Barnes [88] study, the release of metformin from the ML-PVA tablets was mainly influenced by their area/mass ratio. Therefore, the design, the printing pattern, and the infill percentages of the 3D-printed tablets should be considered to achieve the desired area/mass ratio to enhance the dissolution rate of the 3D-printed tablets.

Besides, glipizide, another anti-diabetic medication, was used via a 3D printing approach. Using the hot-melt technique, two filaments of PVA integrating glipizide were produced (2.2 and 4.8 %) successfully with proper features for use in FDM 3D printing [83]. It is feasible to create oral drug delivery instruments with complex interior structures (such as the DuoTablet) using modeling and simulation, demonstrating the promise of 3D printing as an advanced pharmaceutics technology. Based on the testing of drug release, a controlled-release profile within 5 h is based on the device's structure; the drug release profile fits Korsmeyer–Peppas release kinetic (R^2 = 0.982). In different layers, drug release rate was moderated by the ratio of drug successfully. By releasing the glipizide integrated into the outer shell, the release performance of the glipizide combined in the internal layer appeared, followed by a lag time based on the outer layer's features. Li, Wen [83] revealed that the FDM 3D printing method was an encouraging method for manufacturing a controlled-release drug delivery system. It has the advantages of versatility and simplification compared to the conventional technique. They also proposed that this promising method be strengthened by future modifications and advances in water-soluble printing materials as a viable technique in the commercial process. The aim of the study [84] was to develop a Curcuma oil-based self-nano emulsifying drug delivery system (SNEDDS) 3D-printed polypills containing GMD and rosuvastatin (RSV) for the treatment of dyslipidemia in the patients with diabetes as a model for metabolic syndrome (MS). Compartmentalized 3D-printed polypills were prepared and studied in streptozotocin/poloxamer-induced diabetic/dyslipidemia rats. The pharmacokinetic parameters of GMD and RSV in the prepared polypills were evaluated. Blood glucose level, lipid profile, antioxidant, and biochemical markers activities were investigated. In addition, the liver and pancreas were histopathologically examined. The atherosclerosis index, islet of Langerhans area, and liver steatosis lesion scores were all computed. The developed SNEDDS-loaded GMD/RSV polypills showed acceptable quality control characteristics with a high relative bioavailability of 217.16 % and 224.28 % for GMD and RSV, respectively, when compared with corresponding non-SNEDDS pills. In response to Poloxamer 407 intoxication, prepared polypills showed a significant reduction in blood glucose levels and notable improvements in lipid profile and hepatic serum biomarkers. Furthermore, there was a significant drop in serum antioxidants linked with these effects. The produced polypills also reduced the risk of atherosclerosis and cardiovascular disease by increasing the amount of high-density lipoprotein while decreasing triglyceride and low-density lipoprotein. Upon microscopic examination, hepatocytes displayed minimal steatosis and exhibited normal hepatic sinusoids, indicating a high level of protection. Normal-sized pancreatic islets with apparently normal exocrine acini and pancreatic duct were noticed. This formulation strategy clearly shows the potential of developed polypills in personalized medicine for the treatment of patients with MS.

3. Nutritional application of 3D printing for diabetes patients

3D food printing integrates 3D printing technology, and food manufacturing. Fig. 3 depicts the steps involved in 3D food printing process. It utilizes edible materials like vegetable and fruit powder and juice, meat, starch, chocolate, and algae as printing materials [89]. To the best of our knowledge, the most critical advantage or feature of this new technology is the formation and manufacturing of complicated 3D structures. However, in the food industry, the potential of personalized food choices and nutrition may cause the fast advancement of this technology. With 3D food printing technology, the preparation and fabrication of food can satisfy the needs of a variety of people with different tastes, dietary requirements, and health conditions like diabetes [90]. To improve health and prevent sickness, some elements are included in customized meals by adding certain nutrients and functional substances, or by eliminating or replacing them within the formulation [36]. 3D food printing technology can be used for people with diabetes. It can transfer blood glucose information to a cloud-based platform, where subsequently, the computer determines a nutritionally balanced recipe for utilized meal as an internal program. The customized meal is then produced by the 3D food printer. This process can therefore prevent a non-customized diet and unhealthy food consumption. Nutritional

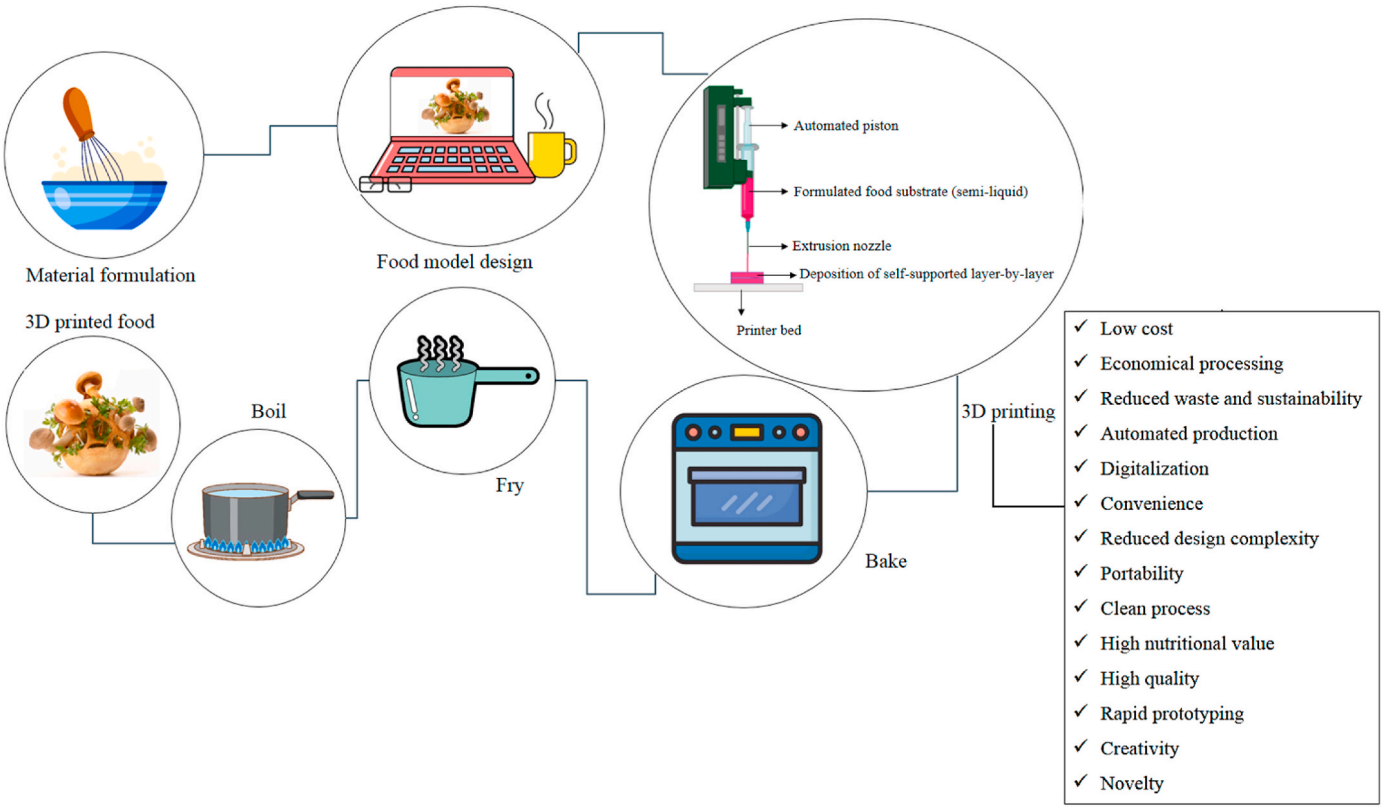

Fig. 3. Schematic of the 3D food printing process.

applications of 3D printers in diabetes disease are presented in Table 3.

3D printing technology can replace sugar substitutions to fabricate sugar-free foods such as sugar-free chocolate. For instance, substituting sucrose with maltitol or xylitol in chocolate decreases its calorie density and diminishes the likelihood of obesity [37]. Maltitol and xylitol are often used by individuals with diabetes as sugar replacements. Therefore, the production of chocolate-based 3D printed foods with these artificial sweeteners in the complex combination with functional polysaccharides seems interesting. The polysaccharides formula includes extracts of *Ganoderma fungus*, *goji*, and *liriope*. Regulation of the immune system, tumor inhibition, antioxidant activity, and anti-aging properties are among the benefits of these substances. Besides, the production of 3D-printed samples of healthy sugar-free chocolate with acceptable texture characteristics was done, which makes this product a good alternative for patients with diabetes [92,96,97]. Different carbohydrates can also be added to foods using 3D printers. For example, pectin was utilized as a thickening and gelling agent. Pectin preserves have the ability to form polymers or thicken solutions in the gastrointestinal tract; as a result, they have numerous positive effects on the human body, including the prevention and control of obesity and diabetes, increase in cholesterol, and improvement of lipid metabolism [37]. 3D printing design may be used for functional properties, including specific types of slow-absorbing carbohydrates that can be useful for glucose control in patients with diabetes [97].

Whole grains, fruits, and vegetables (such as wheat bran, oat, cereal, whole wheat flour, and brown rice) are the main sources of dietary fiber recognized as 17th nutrient in the nutrition field. They have a crucial role in the promotion of gastrointestinal peristalsis, accelerating the food passage through the gastrointestinal tract, modulation of nutrient absorption, and inhibiting and curing constipation [98]. Food and Drug Administration's (FDA) recommendations on the advantages of dietary fiber indicate that a diet containing whole grains, higher amounts of vegetables and fruits, as well as lower saturated fat, and cholesterol can decrease the risk of diabetes [93] and coronary heart disease [78]. Thus, considering product development and health-promoting functions, it is essential to utilize dietary fibers for 3D printing. Cellulose, the fundamental component of plant cell walls, is the most abundant polymer on earth and one of the most vital intractable fibers; however, the human body lacks the necessary enzymes to break it down. Finely milled (such as ball-milled) cellulose fiber was successfully used by Tuck, Holland, Tuck [99] to create 3D-printed structures. Xanthan gum and glucomannan were utilized as printing aids to facilitate the printing process. Therefore, using the cellulose-base formulation produced low-calorie 3D-printed foods.

Huang, Zhang [100] interestingly found the printability of brown rice and the effects of the three variables including infill densities (15 %, 45 %, and 75 %), nozzle size (0.84, 1.20, and 1.56 mm), and perimeters (3, 5, and 7), on the quality characteristics of printed samples. Using the dimensional features, diameter, and height, they evaluated the texture features and the printing precision as thickness and hardness. Their findings revealed that the 3D-printed specimens were nearly identical to the designed specimens; however, for the three variables listed above, there were some discrepancies in size and dimension between the prepared samples and the 3D-printed specimens. The nozzle size and perimeters both affect the dimension of features of 3D printed specimens, while the infill density imposes no impact. By reducing the nozzle size from 1.56 to 0.84 mm, the diameter and height of printed specimens are likely to match the dimension of designed samples. This demonstrates that the 3D printer with a smaller nozzle can create a satisfactory performance on the dimensional features of 3D printed specimens. The texture features (gumminess and hardness) were intensely associated with infill density, after nozzle size and perimeters. However, the nozzle size changed the void rate and the number of deposited layers, which indirectly affected the texture features. The printing time can also be highly reduced by decreasing the void rate, indicating an excellent method to enhance the effectiveness of printing and decrease the hardness by creating the internal structure. The brown rice has six times the dietary fiber content compared to white rice.

Table 3
Nutritional applications of 3D printers in diabetes disease.

References	Field of application	Moot point	Purposes
[89]	Food printing 3D	Characteristics of raw materials or additives used during 3D printing	Estimating and improving printing performance and self-supporting ability in extrusion-based AM
[90]	Food engineering	Printable edible inks	The impact of printing parameters on accurate printing
[91]	Customized Nutrition	Improve the quality and the content of proteins	The production of 3D printed wheat-based snacks enriched with insect powder
[92]	Functional 3D printing of foods	Functional ingredients	The functions of internal structures used or developed during 3D printing and their effects on texture properties of 3D printed food
[93]	Dietary fiber	Effects of dietary fiber and its	Concepts and potential mechanisms that might contribute to the further understanding of the involved processes
[78]	Dietary fiber	Metabolic health	Data concerning dietary fiber, and its effects on metabolic health
[94]	3D food Printing	The printability of brown rice	Assess the printability of brown rice, and evaluate the effects of the three variables: nozzle size, perimeters, and infill densities
[95]	3D food Printing	Protein and fiber-rich food materials	The applicability of extrusion-based 3D printing technology for food pastes made of protein, starch, and fiber-rich materials

Moreover, brown rice-based 3D printed foods can be created, which is appropriate for diabetic people who need slower digestion of starch [98]. Another proper food was made by the 3D printer for diabetic people, which was rich in fiber and protein with lower fat and sugar [95]. Lille and Nurmela [91] investigated the application of 3D printers, which utilize printing-extrusion technology, to produce customized, nutritious sustenance items from fiber-rich materials, specifically food pastes composed of carbohydrate and protein. The printability of cellulose nanofiber-, starch-, milk powder, fava bean protein, and oat-based materials and their mixtures was assessed by evaluating the uniformity and ease of extrusion, and the stability and precision of the printed pattern. The best shape stability and printing precision was attained with a semi-skimmed milk powder-based paste. Based on rheological measurements, there was a link between shape stability after printing and the paste's yield stress. At higher initial solids contents (less than 50 %) of printed specimens, post-processing by oven drying was the most effective. Extrusion-based 3D printing is a promising instrument to produce structured and healthy foods; however, further studies are required to optimize the printed materials' mechanical features.

Over the decades, research in the medical sector has achieved some wondrous results by utilizing a whole host of novel technologies. Diabetes treatments haven't really progressed all that much when compared to other areas in the field of medicine. For this reason, it is critical that innovative technologies such as 3D printing be utilized effectively. In the battle against diabetes, a disease that causes irregularities in a patient's blood sugar levels, 3D printing is utilized. Recent research has focused on medical, pharmaceutical, and nutritional applications of 3D-printing technology in diabetes. 3D printing opens a world of endless possibilities – for both industrial and medical applications. This technology is considered a new and useful method for treating diabetes. As the number of people with diabetes is increasing every year, 3D printing offers an alternative to current diabetes treatments, which could revolutionize diabetes treatment and improve patient outcomes. 3D printing technology has provided new horizons for managing diabetes disease, including Bioprinting artificial pancreas and β-cell replacement, Supply of insulin using 3D-printed microneedle patches, Deliver an accurate dosage of drugs, Improved sustained release drug delivery, Production of functional foods with high fiber and low calories and with new formulations.

4. Limitations of 3D printed

Although 3D printing has many advantages, it has limitations. For example lack of access to 3D printers, scanners and software for everyone, is the lack of regulatory guidelines from FDA and other regulatory bodies to fabricate 3D printed personalized products in, lack of approved 3D printers and approved polymers that fabricate high quality products, cost affordability for personnel training, a range of printers set up in clinical settings, and lack of GMP guidelines to avoid cross contamination, and batch to batch variability of printed products are considered limitations of 3D printing [101].

5. Conclusion and prospects

3D printing technology has provided new horizons for the management of diabetes disease. Researchers have made efforts to bio-print artificial pancreas, and β-cell replacements, which has led to promising results. On the other hand, the secure application of these methods to humans must surmount numerous obstacles. Utilizing 3D-printed microneedle inserts to deliver insulin to rodents with diabetes has been shown to effectively regulate their blood glucose levels. Development and the fulfilment of this method may relieve people with diabetes from painful subcutaneous needle injections. Recently, studies were performed to take advantage of 3D printing technology for pharmacotherapy in diabetes. It was helpful to deliver an accurate dosage of drugs to patients, such as metformin and glimepiride, as well as improved sustained release drug delivery. Concerning nutrition, 3D printing has been helpful to replace sugars with sugar substitutes, which led to the prevention and control of diabetes. Moreover, this technique was utilized to produce functional foods with beneficial effects on diabetes. Production of functional foods with high fiber and low calories with new formulations has proven to be effective for the prevention and control of diabetes. In summary, the application of 3D printing technology for diabetes management is, in its early stages and needs to be matured and developed to use safely for humans. However, its rapid progress in recent years reveals a bright future for the treatment of this disease.

Ethical approval

This article does not contain any studies with human or animal subjects performed by any of the authors.

Consent for publication

Not applicable.

Declaration of competing interest

The authors declares that there is no conflict of interest. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Chen Z, et al. 3D printing MOF nanozyme hydrogel with dual enzymatic activities and visualized glucose monitoring for diabetic wound healing. Chem Eng J 2023; 471:144649.
[2] Kim N, et al. 3D-Printed functional hydrogel by DNA-induced Biomineralization for accelerated diabetic wound healing. Adv Sci 2023:2300816.
[3] Bg PK, et al. 3D printing in personalized medicines: a focus on applications of the technology. Mater Today Commun 2023:105875.
[4] Xu X, et al. Vat photopolymerization 3D printing for advanced drug delivery and medical device applications. J Contr Release 2021;329:743–57.
[5] Pugliese R, et al. Polymeric biomaterials for 3D printing in medicine: an overview. Annals of 3D Printed Medicine 2021:100011.
[6] Cakmak AM, et al. 3D printed polycaprolactone/gelatin/BacterialCellulose/ hydroxyapatite composite scaffold for bone tissue engineering. Polymers 2020;12 (9):1962.
[7] Aimar A, Palermo A, Innocenti B. The role of 3D printing in medical applications: a state of the art. Journal of healthcare engineering 2019;2019.
[8] Tserovski S, et al. Advantages and disadvantages of 3D printing for pre-operative planning of revision hip surgery. J Surg Case Rep 2019;2019(7):rjz214.
[9] Sun Z, Jansen S. Personalized 3D printed coronary models in coronary stenting. Quant Imag Med Surg 2019;9(8):1356.
[10] Beg S, et al. 3D printing for drug delivery and biomedical applications. Drug Discov Today 2020;25(9):1668–81.
[11] Tan YJN, et al. Customizable drug tablets with constant release profiles via 3D printing technology. Int J Pharm 2021;598:120370.
[12] Liu Z, et al. 3D printing: printing precision and application in food sector. Trends Food Sci Technol 2017;69:83–94.
[13] Khatri P, Shah MK, Vora N. Formulation strategies for solid oral dosage form using 3D printing technology: a mini-review. J Drug Deliv Sci Technol 2018;46: 148–55.
[14] Parhi R. Recent advances in 3D printed microneedles and their skin delivery application in the treatment of various diseases. J Drug Deliv Sci Technol 2023: 104395.
[15] Gregory JM, Moore DJ, Simmons JH. Type 1 diabetes mellitus. Pediatr Rev 2013; 34(5):203–15.
[16] Kim J, et al. Bioprinting an artificial pancreas for type 1 diabetes. Curr Diabetes Rep 2019;19(8):1–10.
[17] Riddle MC, Herman WH. The cost of diabetes care—an elephant in the room. Diabetes Care 2018;41(5):929–32.
[18] Gruessner RW, Gruessner AC. The current state of pancreas transplantation. Nat Rev Endocrinol 2013;9(9):555.
[19] Agarwal A, Brayman KL. Update on islet cell transplantation for type 1 diabetes. In: Seminars in interventional radiology. Thieme Medical Publishers; 2012.
[20] Troppmann C. Complications after pancreas transplantation. Curr Opin Organ Transplant 2010;15(1):112–8.
[21] Kim J, et al. Bioprinting an artificial pancreas for type 1 diabetes. Curr Diabetes Rep 2019;19:1–10.
[22] Jamróz W, et al. 3D printing in pharmaceutical and medical applications–recent achievements and challenges. Pharmaceut Res 2018;35:1–22.
[23] Ozbolat IT. Bioprinting scale-up tissue and organ constructs for transplantation. Trends Biotechnol 2015;33(7):395–400.
[24] Dino J, Ashley N, Ibrahim T. Bioprinting and cellular therapies for type 1 diabetes. Trends Biotechnol 2017.
[25] Yue Z, et al. Advances in printing biomaterials and living cells: implications for islet cell transplantation. Curr Opin Organ Transplant 2016;21(5):467–75.
[26] Gu Q, et al. Functional 3D neural mini-tissues from printed gel-based bioink and human neural stem cells. Adv Healthcare Mater 2016;5(12):1429–38.
[27] Derakhshanfar S, et al. 3D bioprinting for biomedical devices and tissue engineering: a review of recent trends and advances. Bioact Mater 2018;3(2): 144–56.
[28] Landers R, et al. Rapid prototyping of scaffolds derived from thermoreversible hydrogels and tailored for applications in tissue engineering. Biomaterials 2002; 23(23):4437–47.
[29] Marchioli G, et al. Fabrication of three-dimensional bioplotted hydrogel scaffolds for islets of Langerhans transplantation. Biofabrication 2015;7(2):025009.
[30] Unagolla JM, Jayasuriya AC. Hydrogel-based 3D bioprinting: a comprehensive review on cell-laden hydrogels, bioink formulations, and future perspectives. Appl Mater Today 2020;18:100479.
[31] Boontheekul T, Kong H-J, Mooney DJ. Controlling alginate gel degradation utilizing partial oxidation and bimodal molecular weight distribution. Biomaterials 2005;26(15):2455–65.
[32] Hao Y, et al. A fully degradable and photocrosslinked polysaccharide-polyphosphate hydrogel for tissue engineering. Carbohydr Polym 2019;225: 115257.
[33] Wu M, et al. Assisted 3D printing of microneedle patches for minimally invasive glucose control in diabetes. Mater Sci Eng C 2020;117:111299.
[34] Economidou SN, et al. 3D printed microneedle patches using stereolithography (SLA) for intradermal insulin delivery. Mater Sci Eng C 2019;102:743–55.
[35] Narayan RJ. Transdermal delivery of insulin via microneedles. J Biomed Nanotechnol 2014;10(9):2244–60.
[36] Donnelly RF, Singh TRR. Novel delivery systems for transdermal and intradermal drug delivery. John Wiley & Sons; 2015.
[37] Ye Y, et al. Polymeric microneedles for transdermal protein delivery. Adv Drug Deliv Rev 2018;127:106–18.
[38] Chen W, et al. Microneedle-array patches loaded with dual mineralized protein/ peptide particles for type 2 diabetes therapy. Nat Commun 2017;8(1):1777.
[39] Wang Y, et al. Polymer-grafted hollow mesoporous silica nanoparticles integrated with microneedle patches for glucose-responsive drug delivery. Front Mater Sci 2021;15:98–112.
[40] Zuñiga J, et al. Development of 3D-printed orthopedic insoles for patients with diabetes and evaluation with electronic pressure sensors. Design 2022;6(5):95.
[41] Leung MS-h, et al. 3D printed auxetic heel pads for patients with diabetic mellitus. Comput Biol Med 2022;146:105582.
[42] Liao W, et al. 3D-bioprinted double-crosslinked angiogenic alginate/chondroitin sulfate patch for diabetic wound healing. Int J Biol Macromol 2023;236:123952.
[43] O'Connell P, et al. Multicenter Australian trial of islet transplantation: improving accessibility and outcomes. Am J Transplant 2013;13(7):1850–8.
[44] Bellin MD, et al. Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes. Am J Transplant 2012;12(6):1576–83.
[45] Ryan EA, et al. Five-year follow-up after clinical islet transplantation. Diabetes 2005;54(7):2060–9.
[46] Murdoch T, et al. Methods of human islet culture for transplantation. Cell Transplant 2004;13(6):605–18.
[47] Vardanyan M, et al. Pancreas vs. islet transplantation: a call on the future. Curr Opin Organ Transplant 2010;15(1):124–30.
[48] Robertson RP. Islet transplantation as a treatment for diabetes—a work in progress. N Engl J Med 2004;350(7):694–705.
[49] Lee JW, et al. Development of a 3D cell printed construct considering angiogenesis for liver tissue engineering. Biofabrication 2016;8(1):015007.
[50] Jamróz W, et al. 3D printing in pharmaceutical and medical applications–recent achievements and challenges. Pharmaceut Res 2018;35(9):1–22.
[51] Ozbolat IT, Yu Y. Bioprinting toward organ fabrication: challenges and future trends. IEEE (Inst Electr Electron Eng) Trans Biomed Eng 2013;60(3):691–9.
[52] Kesti M, et al. Bioprinting complex cartilaginous structures with clinically compliant biomaterials. Adv Funct Mater 2015;25(48):7406–17.
[53] Landers R, et al. Fabrication of soft tissue engineering scaffolds by means of rapid prototyping techniques. J Mater Sci 2002;37(15):3107–16.
[54] Duin S, et al. 3D Bioprinting of functional islets of langerhans in an alginate/ methylcellulose hydrogel blend. Adv Healthcare Mater 2019;8(7):1801631.
[55] Hu S, et al. An immune regulatory 3D-printed alginate-pectin construct for immunoisolation of insulin producing β-cells. Mater Sci Eng C 2021:112009.
[56] Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003; 26(6):1902–12.
[57] Chen Y, et al. Three-dimensional bioprinting adipose tissue and mammary Organoids feasible for artificial breast structure regeneration. Mater Des 2021: 109467.
[58] Ashammakhi N, et al. Bioinks and bioprinting technologies to make heterogeneous and biomimetic tissue constructs. Materials Today Bio 2019;1: 100008.
[59] Liu Q, et al. Zwitterionically modified alginates mitigate cellular overgrowth for cell encapsulation. Nat Commun 2019;10(1):1–14.
[60] Daneman D. Type 1 diabetes. Lancet 2006;367(9513):847–58.
[61] Stumvoll M, Goldstein BJ, Van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet 2005;365(9467):1333–46.
[62] Yu J, et al. Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery. Proc Natl Acad Sci USA 2015; 112(27):8260–5.
[63] Chen W, et al. Microneedle-array patches loaded with dual mineralized protein/ peptide particles for type 2 diabetes therapy. Nat Commun 2017;8(1):1–11.
[64] Zhu S, et al. A bilayer microneedle for therapeutic peptide delivery towards the treatment of diabetes in db/db mice. J Drug Deliv Sci Technol 2021;62:102336.
[65] Nathan DM, Group DER. The diabetes control and complications trial/ epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care 2014;37(1):9–16.
[66] Alkilani AZ, McCrudden MT, Donnelly RF. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics 2015;7(4):438–70.
[67] Wang J, et al. Glucose-responsive insulin and delivery systems: innovation and translation. Adv Mater 2020;32(13):1902004.
[68] GhavamiNejad A, Lu B, Wu XY. Transdermal drug delivery via microneedle patches. In: Biomimetic nanoengineered materials for advanced drug delivery. Elsevier; 2019. p. 37–52.
[69] Prasad LK, Smyth H. 3D Printing technologies for drug delivery: a review. Drug Dev Ind Pharm 2016;42(7):1019–31.
[70] Wu W, et al. A programmed release multi-drug implant fabricated by three-dimensional printing technology for bone tuberculosis therapy. Biomed Mater 2009;4(6):065005.
[71] Wang S, et al. A review of 3D printing technology in pharmaceutics: technology and applications, now and future. Pharmaceutics 2023;15(2):416.
[72] Alomari M, et al. Personalised dosing: printing a dose of one's own medicine. Int J Pharm 2015;494(2):568–77.
[73] Goole J, Amighi K. 3D printing in pharmaceutics: a new tool for designing customized drug delivery systems. Int J Pharm 2016;499(1–2):376–94.

[74] Lim SH, et al. Three-dimensional printing of carbamazepine sustained-release scaffold. J Pharmaceut Sci 2016;105(7):2155–63.
[75] Ye Y, et al. A melanin-mediated cancer immunotherapy patch. Science immunology 2017;2(17).
[76] Rouphael NG, et al. The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled, phase 1 trial. Lancet 2017;390 (10095):649–58.
[77] Wang Y, et al. Polymer-grafted hollow mesoporous silica nanoparticles integrated with microneedle patches for glucose-responsive drug delivery. Front Mater Sci 2021:1–15.
[78] Lattimer JM, Haub MD. Effects of dietary fiber and its components on metabolic health. Nutrients 2010;2(12):1266–89.
[79] Khaled SA, et al. 3D printing of tablets containing multiple drugs with defined release profiles. Int J Pharm 2015;494(2):643–50.
[80] Gioumouxouzis CI, et al. A 3D printed bilayer oral solid dosage form combining metformin for prolonged and glimepiride for immediate drug delivery. Eur J Pharmaceut Sci 2018;120:40–52.
[81] Verstraete G, et al. 3D printing of high drug loaded dosage forms using thermoplastic polyurethanes. Int J Pharm 2018;536(1):318–25.
[82] Ibrahim M, et al. 3D printing of metformin HCl PVA tablets by fused deposition modeling: drug loading, tablet design, and dissolution studies. AAPS PharmSciTech 2019;20:1–11.
[83] Li Q, et al. Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing. Int J Pharm 2017;525(1):5–11.
[84] El-Say KM, et al. Pairing 3D-printing with nanotechnology to manage metabolic syndrome. Int J Nanomed 2022:1783–801.
[85] Ahmed TA, et al. Development of multi-compartment 3d-printed tablets loaded with self-nanoemulsified formulations of various drugs: a new strategy for personalized medicine. Pharmaceutics 2021;13(10):1733.
[86] Goswami M, Sadasivam R, Packirisamy G. Viability studies of hydrogel contact lens on a 3D printed platform as ocular drug delivery carrier for diabetic retinopathy. Mater Lett 2023;333:133636.
[87] Glover K, et al. 3D bioprinted scaffolds for diabetic wound-healing applications. Drug delivery and translational research 2023;13(8):2096–109.
[88] Ibrahim M, et al. 3D printing of metformin HCl PVA tablets by fused deposition modeling: drug loading, tablet design, and dissolution studies. AAPS PharmSciTech 2019;20(5):1–11.
[89] Jiang H, et al. 3D food printing: main components selection by considering rheological properties. Crit Rev Food Sci Nutr 2019;59(14):2335–47.
[90] Feng C, Zhang M, Bhandari B. Materials properties of printable edible inks and printing parameters optimization during 3D printing: a review. Crit Rev Food Sci Nutr 2019;59(19):3074–81.
[91] Severini C, Derossi A. Could the 3D printing technology be a useful strategy to obtain customized nutrition? J Clin Gastroenterol 2016;50:S175–8.
[92] Zhao L, et al. Recent advances in functional 3D printing of foods: a review of functions of ingredients and internal structures. Crit Rev Food Sci Nutr 2021;61 (21):3489–503.
[93] Weickert MO, Pfeiffer AF. Metabolic effects of dietary fiber consumption and prevention of diabetes. J Nutr 2008;138(3):439–42.
[94] Huang Ms, Zhang M, Guo Cf. 3D printability of brown rice gel modified by some food hydrocolloids. J Food Process Preserv 2020;44(7):e14502.
[95] Lille M, et al. Applicability of protein and fiber-rich food materials in extrusion-based 3D printing. J Food Eng 2018;220:20–7.
[96] Li P, et al. Intellectual property and 3D printing: a case study on 3D chocolate printing. J Intellect Property Law Pract 2014;9(4):322–32.
[97] Escalante-Aburto A, et al. Advances and prospective applications of 3D food printing for health improvement and personalized nutrition. Compr Rev Food Sci Food Saf 2021;20(6):5722–41.
[98] Zhao L, et al. Recent advances in functional 3D printing of foods: a review of functions of ingredients and internal structures. Crit Rev Food Sci Nutr 2020: 1–15.
[99] Holland S, Tuck C, Foster T. Selective recrystallization of cellulose composite powders and microstructure creation through 3D binder jetting. Carbohydr Polym 2018;200:229–38.
[100] Huang M-s, Zhang M, Bhandari B. Assessing the 3D printing precision and texture properties of brown rice induced by infill levels and printing variables. Food Bioprocess Technol 2019;12(7):1185–96.
[101] Alqahtani AA, et al. 3D printed pharmaceutical systems for personalized treatment in metabolic syndrome. Pharmaceutics 2023;15(4):1152.