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Additive manufacturing applications in the medical industry

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Abstract

Additive manufacturing techniques have been introduced in the medical field and can be considered the field of biofabrication or bioprinting. Some applications of additive techniques have included the enhancement of medical imaging techniques, drug delivery, and replacement and regeneration of skin, bone, and other tissues. Imaging techniques can be evaluated with 3D printed models whereas drug delivery systems can be conducted with 3D printed tablets. Additionally, different scaffolds of various material compositions can be used for the replacement and regeneration of skin, bone, and other tissue. Overall, the application of additive manufacturing to the medical industry has increased in prevalence and has shown positive outcomes for bioprinting and biofabrication's usage in drug delivery and the replacement and regeneration of skin, bone, and other tissue.

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1. Introduction

Additive manufacturing (AM) defines many different 3D printing processes which allow for customizability of parts by material usage and design of complex geometries. Interest in AM application has been growing in many industries for its specific control on the properties of a finished part. Similarly, the introduction of AM techniques in the biological field has allowed for customizability specific to each patient. Additionally, with an aging and increase in population, there are greater needs for the medical care. AM processes can help to accelerate the recovery and care by 3D printing protheses, fabricating patient-specific prescriptions, and patient-specific regeneration and replacement of organs. The bioprinting and biofabrication fields have been developed to address these applications. Bioprinting and biofabrication can be the opportunity to provide accurate, targeted, and completely personalized medical care.

Bioprinting is considered the layer by layer positioning of biological materials, biochemicals, and living cells with precise spatial control of placement of these functional components to fabricate 3D structures. The field of bioprinting and biofabrication has evolved from 2D cell cultures to cells on biodegradable scaffolds, planar structures. Scaffolds, provide a microenvironment for the incorporation of cells or growth factors to regenerate damaged tissues or organs since they are highly porous and can have interconnected networks while maintaining structural integrity and certain mechanical properties [1]. From further research, cells have become embedded in hydrogels, marking a transition into 3D structures, and pushing closer to the development of cell aggregates which become self-sustaining and functional organoids and tissues. While there is a need for further research in its applications, the bioprinting or biofabrication field has applied additive techniques to enhance imaging techniques, drug delivery, and the replacement and regeneration of skin, bone, and other tissues.

2. Medical Imaging Techniques

Computed tomography (CT) is one of the most common imaging techniques used in the medical field, however the quality of the image can be easily affected by patients' breathing and other noise. Thus, CT image quality must be assessed and is typically evaluated using geometric phantoms that have different test objects embedded in a uniform background [2]. Images are evaluated on the detection of objects, amount of noise, amount of contrast, and spatial

resolution. Phantoms are used since they have non-linear qualities and can more realistically reflect the anatomical texture of tissues, patient shape, and anatomical detailing. A 3D printed phantom organ using FDM was developed to assess image quality of a CT scan and the dose characteristics of the print [2]. Details of the lung were mimicked with the 3D model, and the printed lung was compared to a commercial lung and five patients. The final images obtained concluded the 3D printed lung was more similar to patient images than the commercial phantom since the printed phantom had higher attenuation, less noise, and higher visibility of nodules in comparison with patient images [2].

3D printed phantoms were also used for the evaluation of dose amounts for the youth who undergo cone-beam computer tomography scans. CBCT is cone-beam computer tomography used in orthodontics since it provides a visual representation of mineralized tissues in high resolution so that irregularities or other issues may be identified [3]. However, CBCT has a higher dosage of radiation which can become an issue for the younger populations who undergo this treatment [3]. Therefore, CT number and kerma rates were evaluated since it helps to separate materials based on dosimetric performance. A high CT number would represent high resolution of material like bone. Whereas kerma rates are the kinetic energy released in material, thus representing absorbed dose of x-ray radiation. A cylindrical 3D model was printed to emulate tissue with PLA, PLA with water, ABS, ABS with water, and PLA with metallic charge. CBCT was run on the samples and their equivalence to human tissues by CT number and kerma rates were determined. The kerma rates and CT numbers of the studied materials were compared to PMMA, tissue material equivalent to the human body. While PMMA has the highest kerma rates for three applied voltage used in CBCT, the other materials had very similar kerma rates at the different voltages of 100 kV, 120 kV, and 150 kV. However, the materials varied immensely with CT number. The CT number range of PLA was 98-269 which most emulated the PMMA CT number range of 100-218 [3]. Hence, PLA with water was determined to be the best material since its had average dosimetry performance characterized by kerma rate, but also a CT number which showed compatibility with soft tissue structures [3].

3. Drug Delivery Systems

Additive manufacturing can be applied to pharmaceutical usage to control drug dosage and release mechanics. A controlled drug-release tablet was developed with FDM to prolong metronidazole's gastric residence time and increase drug concentrations at target sites [4]. The tablets were monitored for its drug release rate to the proper site of drug release to determine its applicability as a drug delivery system. Polyvinyl alcohol (PVA) and acrylonitrile butadiene styrene (ABS) were used to print the housing of the tablet. Different shapes of the tablet were examined; floating mechanisms, thickness, diameters, weights, pore diameter, and hardness of the floating tablet housings were determined. Buoyancy studies and kinetics of drug release were also evaluated. Although the ABS tablet housings were harder than the PVA, both had adequate buoyancy, and dynamic and static release rates. Therefore, the proposed PVA and ABS tablets can both be used for drug delivery to the stomach with low risk of interaction of release in the small intestine [4].

4. Skin Regeneration and Replacement

Bioprinting involves the fabrication of 2-dimensional and 3-dimensional structures for biological applications. The scaffold is the 2D structure and a basis for cellular growth and production. The applicability of flexible poly(lactide-co-glycolide) (PLGA) scaffold was determined for rapid production with solvent exchange deposition modeling (SEDM) [5]. The PLGA scaffold was evaluated for its potential use in the facilitation of wound healing as a skin substitute. PLGA was synthesized and used to print homogeneous linear fibers. The scaffolds were printed by SEDM, FDM, and SEDM/E (SEDM and electrospun nanofibers) additive manufacturing processes. However, it was discovered that the FDM process produced scaffolds which shrank after the deposition of the bioink.

Various printing processes resulted in different surface structures and mechanical properties were also compared. Additionally, the binding ability of cells, expression of growth factors, and cell proliferation were also evaluated. The microstructure of the different additive manufacturing processes showed different surface finish, pore size, and cross-section [5]. SEDM printed scaffolds did not shrink, had higher toughness and tensile strength than the FDM samples [5]. Nanostructure further enhanced cell proliferation and other properties such as tensile strength, thus a bilayer scaffold was constructed with SEDM scaffolds with the use of electrospinning; the tensile strength of the added electrospun nanofibers was 3.80 MPa which was higher than 1.65MPa of the SEDM sample [5]. The bilayer scaffold with nano and microstructure prepared by SEDM and electrospinning effectively promoted wound healing since its mechanical properties, surface, and porosity, promoted protein absorption and cellular growth [5].

5. Bone Regeneration and Replacement

The development replacement and regeneration scaffolds used in bone applications can be the next step to medical care of the world's aging population. Various methodologies have been developed to conduct further research on bone applications. While some research has focused on the microstructure of the additively manufacturing scaffolds, others focus on the produced extracellular matrix, mechanical properties, cell proliferation, or stem cell differentiation.

A purposed methodology was to fabricate artificial scaffolds which mimic the natural extracellular matrix (ECM) of cells [6]. PLA models were created FDM to form random distributions of varying pore sizes in the models. CT scans were used to assess morphological properties and mechanical evaluations were also conducted. Ultimately, the PLA models with the largest pore size, 600 μm, had the most appropriate pore variability, mechanical properties, and biocompatibility that could be considered in real-world application [6].

To produce possible bone-application scaffolds, the combination of hydroxyapatite (HA) and PLA as a polymer was evaluated with an emphasis on similarity of mechanical properties [7]. The HA/PLA composites were formed and used to print models of bones. The models were evaluated for tensile strength, elastic moduli, elongation rates, and other mechanical properties. The HA/PLA composite of 10:90 weight ratio was more comparable in mechanical properties to human bone and could also be easily printed using FDM [7].

Further developments using HA and the addition of glycerin were evaluated for their mechanical properties as another bone scaffold replacement [1]. Slurries of Bovine HA (BHA) were formed and mixed with glycerin as a BHA binder to create the FDM printed scaffold. Porosity, compressive strength, hardness, and density were evaluated for different BHA/glycerin ratios. The 45/55 wt% of BHA/glycerin had well developed interconnection between small pores and the most similar mechanical properties to commercial products and human bone [1].

Silk fibroin, gelatin, hyaluronic acid, and tricalcium phosphate with a treatment of platelet-rich plasma was also developed for application in bone tissue engineering in order to promote osteogenic differentiation of adult stem cells [8]. A mixture of silk fibroin, gelatin, hyaluronic acid, and tricalcium phosphate was developed and used to print a model scaffold pattern which was subjected for evaluation of mechanical properties and cross linkage [8]. Platelet-rich plasma was isolated and used to treat the mixture scaffolds [8]. Osteogenic cells were then cultured on the mixture scaffolds and cell viability and proliferation were evaluated [8]. The post-printing treatment with the platelet-rich plasma was found to promote the growth, proliferation, and gene expression necessary for osteogenic differentiation [8].

6. Tissue Regeneration and Replacement

With growing medical concerns, tissue regeneration and replacement research has been conducted to evaluate different bio-inks which can be 3D printed as scaffolds for different tissue areas to promote healing. The bio-ink scaffolds were evaluated for mechanical strength, porosity, morphology, and printability.

PLA was further enhanced using an epoxy chain extension reaction and a chemical foaming agent to form a PLA foam which could be used in medical applications [9]. The printed scaffolds of different ratios from the composite blend were evaluated for molecular weight, dispersion of polymer chains, morphology, pore size, and microstructure of the surfaces and cross-section [9]. Cell viability was also determined. Overall, the blended PLA scaffold was nontoxic, biocompatible, had enhanced rheology, mechanics, and molecular weight, demonstrating applicability as a medical scaffold for tissues [9].

A hybrid of alginate, carboxymethyl cellulose, and montmorillonite clay was also developed as a potential tissue scaffold with a specific focus on printability, shape fidelity, and cell viability within the material [10]. Shear thinning behavior and effect of air pressure were used to determine printability whereas shape fidelity was determined with swelling tests [10]. Cytotoxicity, pore morphology, and cell viability were also examined since cells were deposited and laden into the filament during the deposition process [10]. The scaffold with ratios of 4% w/v alginate, 2% w/v carboxy methyl cellulose, and 4% w/v montmorillonite clay maintained reproducible printability, shape fidelity, cell viability of above 70%, and cytocompatibility [10].

The deposition of photoreceptor cells (PR) on printed retinal pigment epithelium (RPE) was also evaluated for its application in retinal tissue engineering [11]. RPE was used as a base for photoreceptor cell inkjet dispersion in micropatterns. The developed scaffolds were used to cultivate cells and cell viability was evaluated by cellular growth, cell density, and gene expression of growth factors and functional factors [11]. Images indicated mixtures of cellular population density and shapes, similar to natural cells, of RPE and photoreceptor scaffolds [11]. Overall, the PRE and photoreceptor scaffolds demonstrated protein expression, biological function, and microstructure which resembled native retina [11].

7. Conclusions

Additive manufacturing techniques has created the field of bioprinting and biofabrication in the medical industry. In many cases, 3D modeling and the additive techniques have helped to further develop medical techniques, imaging technology, and materials used to advance the replacement and regeneration of tissues. The mechanical properties and cell viability of different bio-ink compositions have shown a promising future for different composites in the regeneration and replacement of tissues. However, effects on the living system of animals and biodegradation must be further evaluated before application in humans.

Conflict of Interest

The author has no conflict of interest.

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