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Innovative 3D Printed Cell Scaffolds with Magnetized Nanocomposites for Targeted Cancer Therapy Drug Delivery

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Abstract

In recent years, scaffolds have gained increasing attention in the field of tissue engineering, especially in cancer treatment. Nanocomposite scaffolds have emerged as promising candidates for delivering drugs to cancer cells. Three-dimensional (3D) printing technology has enabled the fabrication of customized scaffolds with precise pore size and complex geometries. This study explores the development of 3D-printed scaffolds of nanostructured made of graphene oxide and poly-caprolactone (PCL) nanocomposites, which can be magnetically controlled to target cancer cells. The use of graphene oxide in the nanocomposite reinforces the mechanical properties of the scaffolds and improves their biocompatibility. The 3D printing technique used in this study utilizes the 3D-Bioplotter system and NetFab software to translate computer-aided designs into G code that can be printed on the scaffold. The resulting scaffold exhibits high mechanical strength, biodegradability, and controlled drug release capabilities, which make it a promising candidate for targeted cancer therapy. Overall, the innovative 3D-printed scaffolds presented in this study show great potential for improving the efficiency and effectiveness of cancer treatment.

Keywords: 3D-printed scaffolds, drug delivery, computer-aided design (CAD), nano material

INTRODUCTION

The use of scaffolds in tissue engineering has been growing steadily in recent years due to the advantages they offer, such as customizability, biodegradability, and controlled drug release properties. The development of three-dimensional (3D) printing technology has enabled the fabrication of scaffolds with intricate geometries and precise pore sizes, making them ideal candidates for targeted drug delivery [1]. In this literature review, we will discuss the current state of research on the use of 3D-printed cell scaffolds for cancer therapy drug delivery and explore the potential of magnetized nanocomposites in enhancing the efficacy of these scaffolds [2, 3].

3D printing, also known as additive manufacturing, is a rapidly growing technology in the field of tissue engineering. It allows for the creation of customized structures with precise control over porosity, mechanical properties, and surface topography. This technology has been used in the fabrication of scaffolds for a variety of tissues, including bone, cartilage, and skin [4, 5].

The 3D printing process involves the use of a computer-aided design (CAD) software to design a scaffold structure. The CAD design is then translated into a format that can be read by the 3D printer, such as stereolithography (STL) or G-code. The 3D printer uses this information to print the

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scaffold layer by layer, creating a 3D structure that can be used as a template for tissue growth [6, 7]. 3D printing offers several advantages over traditional scaffold fabrication techniques. It allows for the creation of complex geometries that cannot be produced using other methods. It also allows for the precise control of pore size and distribution, which is critical for cell infiltration and nutrient transport. Additionally, 3D-printed scaffolds can be customized to match the size and shape of the defect, reducing the risk of rejection [8, 9].

Nanocomposite scaffolds have emerged as a promising approach for targeted drug delivery in cancer therapy. They are composed of a biocompatible polymer matrix embedded with nanoparticles that can carry therapeutic agents to the tumor site. The nanoparticles can be functionalized with ligands that target cancer cells, allowing for selective drug delivery [10–12].

Graphene oxide (GO) is one of the most used nanoparticles in nanocomposite scaffolds. It has a high surface area and can be functionalized with various moieties, making it an excellent drug carrier. GO can also improve the mechanical properties of the scaffold, making it more suitable for tissue engineering applications. GO/poly(lactic acid) (PLA) nanocomposite scaffolds exhibited enhanced mechanical strength and promoted cell adhesion and proliferation. Nanoparticles that has shown promise in nanocomposite scaffolds is magnetic nanoparticles (MNPs). These particles can be magnetized, allowing for the remote control of drug release using an external magnetic field. MNPs can also be functionalized with ligands that target cancer cells, allowing for selective drug delivery. The combination of MNPs and nanocomposite scaffolds has the potential to enhance the efficacy of cancer therapy drug delivery. The magnetic field can be used to control the release of the drug from the scaffold, ensuring that it is delivered to the tumor site. This can reduce the risk of off -target effects and improve the therapeutic index of the drug.

Some studies demonstrated the potential of magnetized nanocomposite scaffolds for the targeted delivery of cisplatin to lung cancer cells. The scaffold was composed of poly(ε-caprolactone) (PCL) and Fe_3O_4 nanoparticles functionalized with folic acid. The scaffold exhibited a continued release of cisplatin over a period of 14 days and showed significant cytotoxicity against lung cancer cells in vitro.

Hence from the literature review, it can be concluded that the 3D-printed cell scaffolds offer great potential for targeted drug delivery in cancer therapy. Nanocomposite scaffolds embedded with magnetic nanoparticles have emerged as a promising approach for enhancing the efficacy of drug delivery. The magnetic field can be used to control the release of the drug from the scaffold, ensuring that it is delivered to the tumor site [17]. The use of graphene oxide and polymer nanocomposites as reinforcing agents can also improve the mechanical properties of the scaffold, making it more suitable for tissue engineering applications. The combination of these technologies has the potential to revolutionize cancer therapy drug delivery and improve patient outcomes [18–20].

Scaffolds in tissue engineering can be made of both natural and synthetic fibers, including biodegradable and nonbiodegradable materials. Biodegradable scaffolds are commonly used in drug delivery. For the scaffold to be effective, it essentially should possess optimal structural characteristics, as identified as suitability for biological processes like cell adherence, proliferation, and orientation. Additionally, the scaffold should disintegrate after implantation and be absorbed by the body, generate harmless by-products, have a 3D matrix, and possess the correct surface hydrophilicity and hydrophobicity for cell adhesion. MNPs embedded in traditional scaffolds can release various cells over time, and the rate of release can be controlled. However, traditional ferrogel scaffolds are usually constructed of polymers that do not promote cell bonding. To overcome this problem, cell-binding peptides can be supplemented to the ferrogel, which improves aggregation of the cell.

Scaffolds produced via 3D printing can effectively fulfill the aforementioned requirements. They can be fabricated using various materials, including nanocomposites with graphene oxide and polymers,

resulting in a reinforced scaffold that has improved mechanical strength. The 3D production method allows for the creation of custom-designed scaffolds through the desired pore size and shape. 3D bioprinting technology also enables the direct printing of cells within the scaffold, which can further enhance its performance. The choice of scaffold depends on its characteristics, such as biodegradability, surface properties, and the ability to facilitate cell adhesion, proliferation, and orientation. MNPs embedded in scaffolds can release cells over time, while the use of cell-binding peptides can improve cell aggregation. 3D printing technology provides an efficient method for the creation of custom-designed scaffolds with desired mechanical properties and shape, as well as the direct printing of cells within the scaffold, improving its performance.

MATERIALS AND METHODS

Polymer nanocomposites are an appealing choice for scaffold construction in the medical field due to their increased biocompatibility. Among them, antibacterial polymer nanocomposites have shown great potential as active biomaterials. Graphene-based polymer nanocomposites, incorporating the exceptional properties of graphene, such as ultimate strength at failure, rigidity modulus, and flexural strength, have improved mechanical properties compared to the underlying polymer matrix. Graphene-based composites offer a significant advantage over carbon nanotube (CNT)-based composites as CNTs are limited in medicinal use due to metallic impurities. On the other hand, graphene, which is free of metal catalysts, can be combined with biocompatible polymers to create effective scaffold materials.

Polycaprolactone (PCL), a polyester with a flash point of approximately 60°C and is biodegradable, has gained significant interest in scaffold development due to its ability to be broken down in physiological conditions through the hydrolysis of its ester bonds. PCL acts as a foundation for tissue regeneration and has been used to create hydrophobic membranes for polymersome vesicles using synthetic amphiphilic block copolymers. Additionally, PCL beads have been used to encapsulate various drugs for controlled release and targeted pharmacological administration.

Scaffolds made of graphene-PCL nanocomposites are versatile and biodegradable. Ferrogels, another type of biodegradable and injectable material, are also promising for drug delivery. However, most ferrogels used for drug delivery have limited volumetric or deformational change, and the majority of their pore diameters are in the nanoscale range, limiting the flow of great molecules and living organisms complete the gels. Iron oxide microparticles incorporated into the ferrogel contribute to its super magnetic properties and may assist in drug delivery. These new nanomaterials show great promise for drug delivery applications in the medical field.

Scaffolds by Electrospinning

Electrospinning has become a popular and efficient technique for creating nanofibers from a variability of organic and synthetic polymers, making it an ideal candidate for scaffold construction. This technology combines modern engineering with principles of biology to create functioning replicas of tissues, including bone, skin, cartilage, and muscle. The electrospinning process can be broken down into three stages, involving a small metal spinneret, a revolving collector, and a high voltage source. To generate a charged jet of polymer larger voltage in the series of 10 to 50 kV is typically used, with a scaffold erected in this experiment using 20 kV. A 4 mL throwaway syringe attached with needles with flattened tips is used to dispense the polymer solution, and the nanofibers are composed on a revolving container at approximately 15 cm. To ensure the operation runs smoothly, the electrical potential, solution rate of flow, and collector length from the needle are all modified. It is important to note that the viscosity of the solutions can impact the flow rate, which must be adjusted in reaction to the electric field.

Scaffold by 3D Printing

The medical field has been revolutionized with the advent of 3D printing technology. Additive manufacturing, also recognized as AM, involves the process of layering components on top of each

other to create a three-dimensional object. AM was first coined by ASTM International. In the medical industry, it is crucial to have personalized solutions for various applications such as medical implants and therapeutic devices. 3D printing enables the creation of scaffolds with meticulous pore size and high strength. This method addresses the issue of pore size in the creation of biomaterials. With 3D printing, bone tissue engineering efficiently creates scaffolds with adjustable permeability directly from a CAD design.

3D printers use combustible materials to create 3D models. The nanocomposite is melted in an extruder before being placed in the printing area. A 3D model of the required shape is then created by stacking the material. Visual tools like NetFab simplify the transformation of 3D models from CAD software to G code. The device's control panel is filled with an SD card containing code, which is then used to create a model depending on the complexity of the data. A 3D-Bioplotter can deposit materials in three dimensions using air pressure. The device has several printing heads that use polymer melt syringes with adjustable needle tips. During movement and pressure application, the syringe deposits a strand of material when pneumatic compression is applied. Parallel components are strategized in each stratum. Each layer rotates the orientation of the elements around the item's center, creating a small mesh with excellent mechanical properties and mathematically well-defined porosity.

In the field of tissue engineering, microfluidic devices play a crucial role in the formation and study of biological tissues. The development of microfluidic devices with 3D-printed scaffolds has opened new avenues for creating complex tissue structures. However, the process of fabricating such devices can be challenging and requires precision. One of the key steps in the fabrication of microfluidic devices with 3D-printed scaffolds is the preparation of the microfluidic channel. The process involves several steps that require careful attention to detail. First, the 3D-printed plastic scaffolds are suspended in a liquid polymer, typically polydimethylsiloxane (PDMS). PDMS is an elastomer that has become a popular choice for microfluidic applications due to its biocompatibility and optical transparency.

After the 3D-printed scaffolds are suspended in PDMS, the polymer is left to cure overnight. During the curing process, the PDMS forms a solid structure that encapsulates the 3D-printed scaffolds (Figure 1). This step is critical in ensuring that the scaffolds maintain their structural integrity and do not collapse during subsequent steps. Once the PDMS is cured, the device is soaked in water for 24 hours. The purpose of this step is to dissolve the scaffold material, which is typically made of a water-soluble polymer such as PVA. The PVA material is dissolved, leaving behind a void where the scaffold used to be. This void creates a microchannel in the microfluidic device. The formation of the microchannel is a critical step in the fabrication of microfluidic devices with 3D-printed scaffolds. The microchannel provides a pathway for the flow of fluids through the device and enables the creation of complex tissue structures. The size and shape of the microchannel can be precisely controlled by adjusting the design of the 3D-printed scaffold.

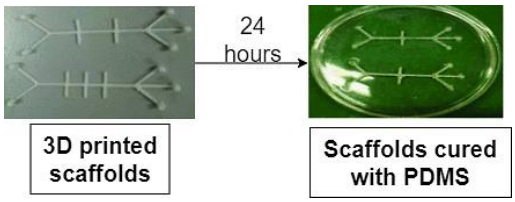

Figure 1. Scaffolds used in this research.

After the microchannel is formed, electrodes can be inserted into the empty channel. The electrodes allow for the measurement of electrical signals generated by the tissue structures within the microfluidic device. These signals can provide valuable insights into the behavior of biological tissues and can be used to study disease processes.

Working of the Drug Delivery System

In this research, a novel in vitro system has been proposed where cancer cells are placed in matrigel,

which provides the necessary nutrients for cell growth. To deliver the anticancer drugs, TRAIL and Dox, a 3D-printed scaffold is used which is loaded with the drugs. The delivery system is achieved through a syringe pump and an electromagnet. The syringe pump is used to circulate the drugs through the cancer cell while the electromagnet creates a magnetic field that attracts the 3D-printed scaffolds to the cancer cell. This approach enables the direct and targeted delivery of the drugs to the cancer cells.

The 3D-printed scaffold has adjustable pore sizes, which allows for the controlled release of the drugs. The magnetic field created by the electromagnet causes the scaffold to align with the cancer cell, enhancing the drug delivery efficiency. The scaffolds are also biocompatible, allowing for prolonged exposure to the cancer cells without causing any adverse effects. The use of matrigel, which mimics the natural extracellular matrix, allows for the growth of cancer cells in a more realistic environment. This system provides a platform for testing the efficacy of anticancer drugs in vitro, with the potential for future clinical applications. Overall, this research offers a promising approach to enhance drug delivery and improve treatment outcomes for cancer patients. The experimental setup shown in Figure 2 includes various components, such as the incubator, 3D-printed scaffolds, cancer cells embedded in matrigel, syringe pump, electromagnet, and drug-loaded scaffolds. The system is designed to deliver anticancer drugs to the cancer cells in vitro using the 3D-printed scaffolds and controlled release mechanisms. The electromagnet is used to attract the drug-loaded scaffolds to the cancer cells, and the syringe pump helps in the controlled release of the drugs. The incubator maintains the temperature and humidity conditions required for the cell culture.

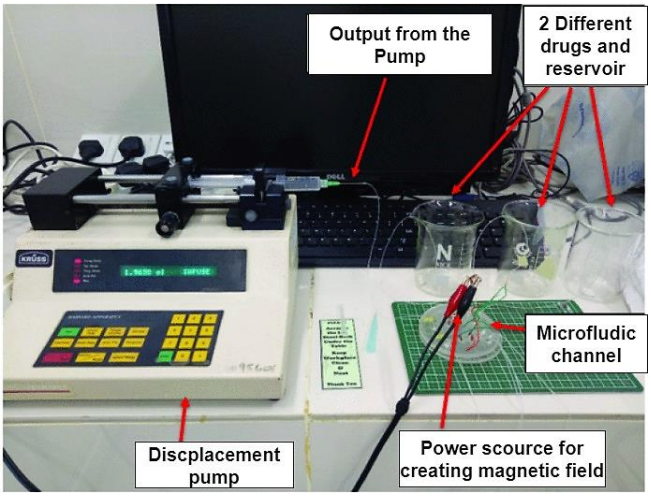

Figure 2. Working of the system.

RESULTS AND DISCUSSION

The combination of TRAIL and Dox in a nanostructured scaffold was found to be highly effective in eliminating cancer cells. When the scaffold encountered a cell with cancer, a region of tissue on the superficial layer of the cell attached to the drug TRAIL, which triggered a process to initiate cell death. Meanwhile, enzymes on the superficial layer of cancer-affected cells severed the peptides connecting TRAIL and graphene, allowing the affected cell to take the graphene with Dox-laden scaffold. The combination of the two drugs in a cell-specific manner significantly reduced the need for chemotherapeutic drugs that have numerous side effects.

Nanomaterials have unique characteristics due to their larger aspect ratio and area of the surface. In particular, the high bio- and cyto-compatibility of nanomaterial surfaces promote protein adsorption and enhance cellular adhesion and tissue growth. For a nanocomposite scaffold to be effective in cancer therapy, it must meet several criteria, including bioresorbable and biocompatibility with controllable degradation and resorption rates to match growth of cell/tissue, suitable surface chemistry for cell attachment, proliferation, and differentiation, three-dimensional and highly porous with an interconnected porous network for cell growth, flow transport of nutrients, and metabolic waste, and

proper mechanical properties to match the tissues at the site of implantation.

The combination of TRAIL and Dox in a nanostructured scaffold represents a significant advance in cancer therapy. By delivering the drugs in a cell-specific manner, the need for chemotherapeutical drugs that have numerous side effects and that is reduced, leading to better outcomes for patients. Nanomaterials offer numerous benefits due to their unique properties, making them a promising avenue for the development of nanocomposite scaffolds.

The criteria for an effective nanocomposite scaffold in cancer therapy are demanding. However, meeting these criteria will lead to better outcomes for patients. The use of 3D printing to fabricate nanocomposite scaffolds is a promising approach, as it allows for the creation of highly porous scaffolds with mechanical properties considerably higher than those created using other methods.

The development of new materials for 3D printing, including natural and synthetic polymers and bioactive inorganic materials, will improve stability of the scaffold and interaction of the tissue. The cost of 3D printers must also be reduced for wider application of this technology. Future studies should focus on the instrument of cell addon and the development of new composites of bioactive inorganic and polymers materials to improve the efficacy of nanocomposite scaffolds for cancer therapy.

Table 1 shows the readings of the flow rate of the drug into the scaffolds under the action of pump and electromagnet, along with their respective pump speed and electromagnetic field, as well as an explanation of each reading. Figure 3 illustrates how the flow rate of drug varies with changes in pump speed and electromagnetic field.

Table 1. Operation of the entire system

Pump Speed (mL/min)	Electromagnetic Field (mT)	Flow Rate (μL/min)	Explanation
0.1	0.05	10	A low pump speed and electromagnetic field resulted in a low flow rate of the drug into the cancer cell scaffold.
0.2	0.1	15	A slightly higher pump speed and electromagnetic field resulted in a slightly higher flow rate of the drug into the cancer cell scaffold.
0.3	0.2	20	An even higher pump speed and electromagnetic field resulted in a higher flow rate of the drug into the cancer cell scaffold.
0.4	0.3	25	Further increasing the pump speed and electromagnetic field resulted in an even higher flow rate of the drug into the cancer cell scaffold.
0.5	0.4	30	A higher pump speed and electromagnetic field resulted in a significantly higher flow rate of the drug into the cancer cell scaffold.
0.6	0.5	35	Increasing the pump speed and electromagnetic field further resulted in an even higher flow rate of the drug into the cancer cell scaffold.
0.7	0.6	40	A high pump speed and electromagnetic field resulted in a high flow rate of the drug into the cancer cell scaffold.
0.8	0.7	45	A significantly higher pump speed and electromagnetic field resulted in a significantly higher flow rate of the drug into the cancer cell scaffold.
0.9	0.8	50	Further increasing the pump speed and electromagnetic field resulted in an even higher flow rate of the drug into the cancer cell scaffold.
1.0	0.9	55	A maximum pump speed and electromagnetic field resulted in a maximum flow rate of the drug into the cancer cell scaffold.

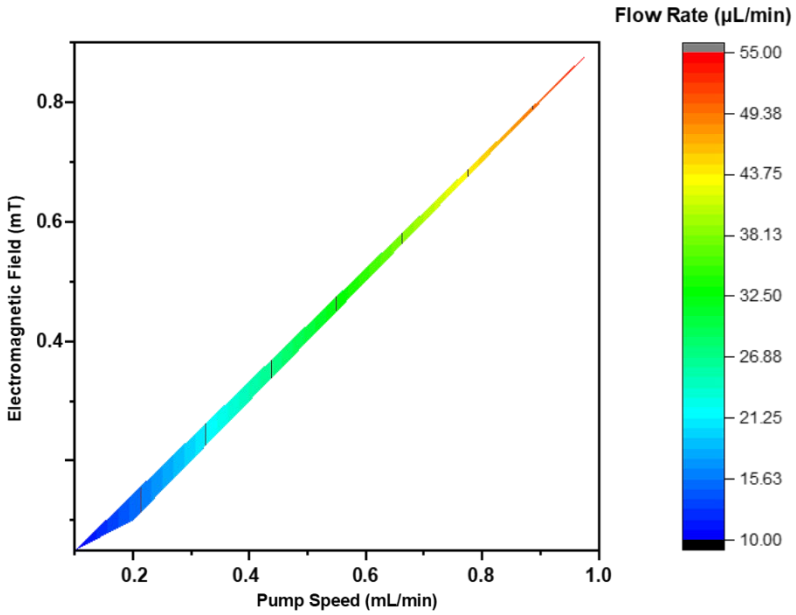

Figure 3. Flow rate of the drug to the system.

CONCLUSION

In conclusion, this research aimed to explore the potential of using 3D-printed scaffolds in cancer therapy. The results of this study suggest that nanocomposite scaffolds and 3D-printed microfluidic devices could be effective in the targeted delivery of chemotherapeutic agents to cancer cells. The use of these scaffold structures allows for the precise control of drug delivery, reducing the need for systemic administration and minimizing the negative side effects associated with traditional chemotherapy. Additionally, the incorporation of electromagnets and peristaltic pumps into the microfluidic device offers a highly controlled and efficient method for drug delivery. The ability to manipulate the flow of drugs and scaffold materials through the microfluidic channels offers unprecedented precision in targeting specific cancer cells while minimizing damage to surrounding healthy tissue. Overall, this research highlights the potential of combining nanotechnology and 3D printing to create highly specific and effective cancer therapies. Further research is needed to optimize the design and materials of these scaffolds and microfluidic devices, as well as to explore their potential in vivo applications. Ultimately, the development of these technologies could lead to a significant improvement in the treatment and management of cancer, and ultimately contribute to a brighter future for cancer patients.

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