3D printing in drug delivery systems

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“Three-dimensional printed drug delivery systems facilitate localized, controlled and sustained release of different active pharmaceutical ingredients”

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Three-dimensional printing can offer potential solutions to everyday problems. 3D printing is a relatively popular rapid prototyping technique, which can accelerate the design and development of unique drug delivery systems. 3D printing, in general, involves the development of a computer-aided design of the desired model that is then digitally sliced into two-dimensional layers which are converted into a machine-readable G-code file where the 3D printer will fabricate the structure. The advancement of 3D printing technology with different 3D printing methods will open new doors to explore novel solutions [1]. The application of this technique is thoroughly being explored in diverse areas of science including medicine and healthcare. 3D printing of metal [2], polymer [3] and hydrogel [4,5] materials are currently underway using unique 3D printing techniques [1]. The 3D printed scaffolds offer 3D spatial distribution of the drug molecules in the scaffold. Stereolithography was the first 3D printing technique developed, where a photosensitive liquid resin was exposed to a laser that cures each exposed layer and is processed into stackable two-dimensional layers to form a 3D structure [6]. Fused deposition modeling (FDM) is currently a widely used 3D printing technique where a thermoresponsive polymer filament of polylactic acid [3], poly(lactide-co-glycolide; PLGA) [5] polycaprolactone [7], polyvinyl alcohol [8], and other polymers are melted beyond glass transition temperatures and deposited onto a solid medium to create 3D structures. Powder bed 3D printing is another technique where biocompatible metal or ceramic powders are bonded together using a binder solution resulting in a solid 3D shape [9]. Bioprinting is another technique where cell-laden hydrogels are extruded through a syringe and deposited into a binder solution that gels and solidifies the hydrogel into a 3D structure. For a detailed explanation of the materials and methods used for 3D printing, the readers are advised to see [1]. These techniques provide fast fabrication of 3D structures at a layer resolution of 20–100 μm and are widely employed for developing 3D printed drug delivery systems [10]. However, none of these 3D printing techniques can print submicrometer structures with nanometer resolution.

Two-photon polymerization (TPP) is a sophisticated 3D printing technique that can fabricate microscale 3D structures. TPP offers the freedom to design and develop novel and complex architectures. TPP works on a principle where a near-infrared femtosecond laser moves spatially according to the computer-aided design model with a resolution beyond the optical diffraction limit in the light-sensitive liquid resin and solidifies it instantly resulting in a 3D structure. The resolution of the printed structures solely depends on the strength of the laser and photoinitiator concentration. Unlike other 3D printing techniques, TPP assisted micron-sized 3D scaffolds has potential applications in tissue engineering and drug delivery [4,11,12].

Three-dimensional printed drug delivery systems

Three-dimensional printed drug delivery systems have evolved rapidly in the last decade. The holy grail of drug delivery is to deliver drugs to the disease site with minimal systemic delivery to avoid side effects. Nanotechnology has advanced the mode of delivering drugs clinically. Nanoparticles as carrier vehicles have the capacity to deliver chemotherapeutic drugs without passive dissolution in the human body. Our group has been extensively working on drug delivery systems that span from controlled drug release nanoparticles [13,14] to pulsatile drug release

PDMS chips [15] and scaffolds [4]. Nanoparticles made from natural and synthetic biocompatible polymers were investigated for their ability to deliver chemotherapeutic drugs [13], gene-activated plasmids [16] and antigens as vaccines [17]. Three-dimensional printing of tablets has demonstrated its potential for controlled drug release [4]. Three-dimensional printing also helps to develop more complex and customized doses of medication. Three-dimensional printed drug delivery systems facilitate localized, controlled and sustained release of different active pharmaceutical ingredients that perform specific functions in the body [10]. Spritam[®] (Levetiracetam) is the first US FDA approved 3D printed orodispersible tablet. We have developed different drug delivery systems using different 3D printing techniques such as extrusion-based core-shell printing, FDM, and two-photon polymerization 3D printing to achieve unique sequential, sustained and controlled drug delivery.

Extrusion printed drug delivery system

Sequential release of drugs at the diseased site will have significantly prolonged therapeutic effects. Consequently, extrusion-based bioprinting of alginate–PLGA core-shell structures was tested to provide sequential delivery of model drugs fluorescein and rhodamine B [5]. These core-shell structures were fabricated using a coaxial syringe that extrudes core PLGA inside the alginate sheath [5]. Such structures provided a great benefit of loading hydrophilic and hydrophobic drugs, fluorescein and rhodamine B in alginate and PLGA. Natural polymers such as alginate exhibit burst release patterns. The sequential release of fluorescein from alginate followed by rhodamine B from PLGA was observed by sustained release of both dyes for 168 h. The organization of the alginate sheath over the PLGA core provided a sponge-like effect, absorbing the drugs released from PLGA, thus facilitating a sequential and sustained drug release. Moreover, faster drug release of fluorescein and rhodamine B was observed from alginate and PLGA alone, respectively. The random porosity of the extruded materials can change the kinetics of sustained drug release. Hence, the defined porosity with enhanced surface area-to-material interactions can provide sustained drug release.

FDM printed drug delivery system

FDM-based 3D printing often provides the definitive structural features and porosity which will facilitate sustained and controlled drug release. Polylactic acid structures with 70% porosity were 3D printed and surface modified with polyethyleneimine and then conjugated with citric acid. Citric acid mediates calcium phosphate deposition onto the surface of 3D printed scaffolds when immersed in simulated body fluid. The deposited calcium phosphates were characterized as calcium-deficient hydroxyapatite and showed improved bone regeneration [3]. Calcium-deficient hydroxyapatite 3D printed scaffolds yielded a sustained and controlled release of calcium for over 10 days. The sustained release of calcium has resulted in augmented bone regeneration. Irrespective of its advantage in providing sustained delivery of desired moieties, the fabrication of drug delivery systems with micrometer dimensions is a limitation.

TPP drug delivery systems

TPP facilitates researchers to design and develop complex microscopic, infusible structures at a resolution of 100 nm [18]. The effect of manipulating various 3D printing parameters on controlled release were explored recently [4]. Using TPP, polyethylene glycol dimethyl acrylate devices were printed with varying settings in slicing, hatching and pore size and their effects on drug release kinetics were investigated [4]. The sustained release behavior was validated with different drug dissolution kinetics models. The model drug rhodamine B was loaded in the 3D printed scaffolds with varying pore diameters for drug release studies. The release profiles of rhodamine B showed the best fit for the Korsmeyer–Peppas model ($n \leq 0.45$ – Fickian diffusion; $0.45 > n < 0.8$ – non-Fickian diffusion). All polyethylene glycol dimethyl acrylate scaffolds demonstrated 'n' values from 0.14 to 0.35 which signifies diffusion-based drug release. Although polymers are known to deliver a sustained drug release in the non-Fickian diffusion kinetics manner, the structural features of the 3D TPP printed scaffolds here showed a different diffusion-based drug release mechanism. The structural elements of the scaffolds hence played a role in determining drug release behavior. The noncovalent interaction of rhodamine B with the polymer will also affect the drug release behavior.

TPP was also employed to fabricate different device architectures as drug delivery systems. Chitosan-based magnetic swimmers were fabricated to provide light-triggered doxorubicin drug release in a controlled manner [19]. A porous cylindrical cage with dimensions of 0.34×0.9 mm (d $\times$ h) was fabricated with the aim of generating a controlled and localized drug delivery device [20]. Fluorescent particles were loaded into an agarose gel inside the

cylinder which was then capped with cyanoacrylates. The fluorescence dye was released in a sustained fashion for over 24 h.

Future perspective

Three-dimensional printing offers significant potential for designing and fabrication of unique drug delivery systems personalized to a patient's disease. The extruder based core-shell and FDM 3D printing techniques can generate a customized device with specific drug release profiles at the millimeter scale. TPP is the most sophisticated 3D printing technique that has enormous potential in developing novel drug delivery systems at the micron scale. The intricate architecture fabricated with TPP is an added asset when it comes to achieving controlled drug release. Future studies by our group and other groups in 3D printed drug delivery systems should focus on controlling various structural parameters of the 3D printed systems, while also focusing on the drug interactions with the polymer. Such studies will provide more insight into developing novel and unique drug delivery systems with tailored release profiles.

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