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In Silico Simulation of Porous Geometry-Guided Diffusion for Drug-Coated Tissue Engineering Scaffold Design

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Abstract: Recent research works have shown the effect of nutrient concentration on cell activity, such as proliferation and differentiation. In 3D cell culture, the impact of scaffold geometry, including pore size, strut diameter, and pore shape, on the concentration gradient within scaffolds under two different loading conditions—constant fluid perfusion and non-fluid perfusion—in a perfusion bioreactor is investigated by developing an in silico model of scaffolds. In this study, both triply periodic minimal surface (TPMS) (with gyroid struts) and non-TPMS (with cubic and spherical pores) scaffolds were investigated. Two types of criteria are applied to the scaffolds: static and perfusion culture conditions. In a static environment, the scaffold in a perfusion bioreactor is loaded with a fluid velocity of 0 mm/s, whereas in a dynamic environment, perfusion flow with a velocity of 1 mm/s is applied. The results of in silico simulation indicate that the concentration gradient within the scaffold is significantly influenced by pore size, strut diameter, pore shape, and fluid flow, which in turn affects the diffusion rate during drug delivery.

Keywords: tissue engineering; drug-coated scaffold; diffusion–convection simulation; perfusion bioreactor

Academic Editor: Süleyman Ergün

Received: 14 February 2025
Revised: 1 April 2025
Accepted: 9 April 2025
Published: 27 April 2025

Citation: Awad, E.; Bedding-Tyrrell, M.; Coccarelli, A.; Zhao, F. In Silico Simulation of Porous Geometry-Guided Diffusion for Drug-Coated Tissue Engineering Scaffold Design. *Organoids* **2025**, *4*, 8. https://doi.org/10.3390/organoids4020008

1. Introduction

In tissue engineering, functional tissues are created by combining scaffolds, cells and biochemical signals. These functional tissues are then used to restore or repair the damaged structures in the human body [1]. Cellular functions and tissue regeneration can be enhanced by the addition of drugs, which are also referred to as signaling molecules, growth factors, proteins, and bio-active molecules, that support cell growth and tissue regeneration. Thus, by incorporating drug delivery mechanisms into scaffolds, tissue repair and regeneration are stimulated further. In tissue engineering, instead of a burst release of drugs, controlled and sustained release is encouraged so as to accelerate the cellular activity and tissue regeneration. Controlled drug release is achieved with any one of the techniques such as drug encapsulation within the scaffold, absorption of the drug onto the scaffold and by embedding drug delivery systems into the scaffold [2]. The process of a drug encapsulating a scaffold leads to a drug-coated scaffold. The main challenges of such drug-coated scaffolds in 3D scaffold structures, such as microspheres, nanospheres, nanofibrous mesh, 3D porous matrix and hydrogels, have been fabricated for controlled sustained drug release for long durations [3]. There are many research works that have been carried out to demonstrate the effectiveness of drug-coated scaffolds in

tissue engineering. For example, Jin et al. [3] proposed a drug-coated scaffold for treating bone defects. The scaffolds are made of biodegradable zinc fabricated by the additive manufacturing technique. The osteogenic and antibacterial properties of the zinc scaffold make it suitable for bone treatment applications. Soundrapandian et al. [4] studied the effect of drug-coated porous glass scaffolds for the treatment of osteomyelitis. The porous glass scaffolds are loaded with two types of drugs: antibacterial (Gatifloxacin) and antifungal (Fluconazole). The glass-based scaffolds are further coated with chitosan solution, which is a natural polymer. The results show that the controlled release of both the drugs was achieved with chitosan-coated scaffold when the drug concentration was higher.

Once the scaffolds are fabricated and prepared with drug coating, the next step in tissue engineering is the selection and maintenance of living cells, called cell culture, which are to be used with scaffolds for tissue regeneration and repair. To culture the cells in three dimensions (3D), the cells need to be seeded on scaffolds. Even though 3D cell culture is expensive, it is the better choice for cell cultivation since it mimics the mechanical and spatial properties of the donor tissue [5]. Cells are usually cultured in either static or dynamic conditions. Static cell culture involves growing cells in a fixed and stable environment such as a dish or well, whereas in dynamic cell culture the cells are cultivated within a bioreactor (such as a perfusion bioreactor). Even though dynamic cell culture is expensive, this method is mostly adopted in tissue engineering because in dynamic cell culture, the cells are exposed to realistic physiological stimuli such as fluid flow, mechanical shear stress and oxygen concentration gradients [6]. The geometrical configurations of the scaffold, such as pore size, porosity and pore shape, play a major role in the mass transport within scaffold [7,8]. However, the influence of scaffolds' porous geometry on the drug delivery under both static and dynamic culturing conditions has not been fully understood yet.

Therefore, the main goal of this study is to use an in silico approach for investigating the effect of scaffold porous geometry (i.e., pore size, porosity and pore shape) on drug delivery within scaffolds under static and dynamic culturing conditions. The in silico model is based on the diffusion–convection equation, which is solved by finite volume method (FVM) in ANSYS 2023 R2—CFX (version 23.2, ANSYS Inc., Canonsburg, PA, USA). The output from this study is expected to improve the design of drug-coated scaffolds for tissue engineering.

2. Materials and Methods

In this study, a computational fluid dynamics (CFD) model coupled with the diffusion–convection equation has been developed for simulating drug delivery within different scaffold designs. The mathematical modeling for the transport of the drug molecule within the scaffold is defined by the diffusion–convection equation, which is governed by the concentration gradient as given in Equation (1):

$$\frac{\partial C}{\partial t} = D\nabla^2 C - v\nabla \mathrm{C} \quad (1)$$

where C is the concentration of the drug molecule at a time t and D is the diffusion coefficient. Due to the mathematical analogy with thermal conduction, in ANSYS CFX, a thermal conduction model is used for representing the mass diffusion–convection process in Equation (1).

A schematic diagram of the cubical scaffold in a perfusion bioreactor with a fluid velocity of 0 mm/s (static condition) and 1 mm/s (perfusion culture condition) is shown in Figure 1. In a static environment, the scaffold in a perfusion bioreactor is loaded without fluid flow, whereas in a perfusion culture environment, it is loaded with a fluid flow of

1 mm/s velocity. In the CFD model, the scaffold is placed in a perfusion bioreactor under two different loading scenarios: constant fluid perfusion and non-fluid perfusion. The fluid is assumed to exhibit laminar flow, a smooth and orderly flow in parallel layers within the model. The fluid flow is modeled by the Reynolds number, a dimensionless quantity used to predict whether the flow regime of the fluid is laminar or turbulent. A low Reynolds number indicates the dominance of viscous force over the inertial force, resulting in a laminar flow regime through the scaffold region. The entire energy model is activated to study the drug molecule diffusion–convection process within the scaffold structure. The fluid inlet velocity is set at 0 m/s and 1 mm/s, enabling the simulation of two distinct flow conditions: static and dynamic (i.e., perfusion). To prevent the back flow of fluid, a reduced reverse flow condition is applied. The scaffold walls are maintained at a normalized drug concentration of 100%.

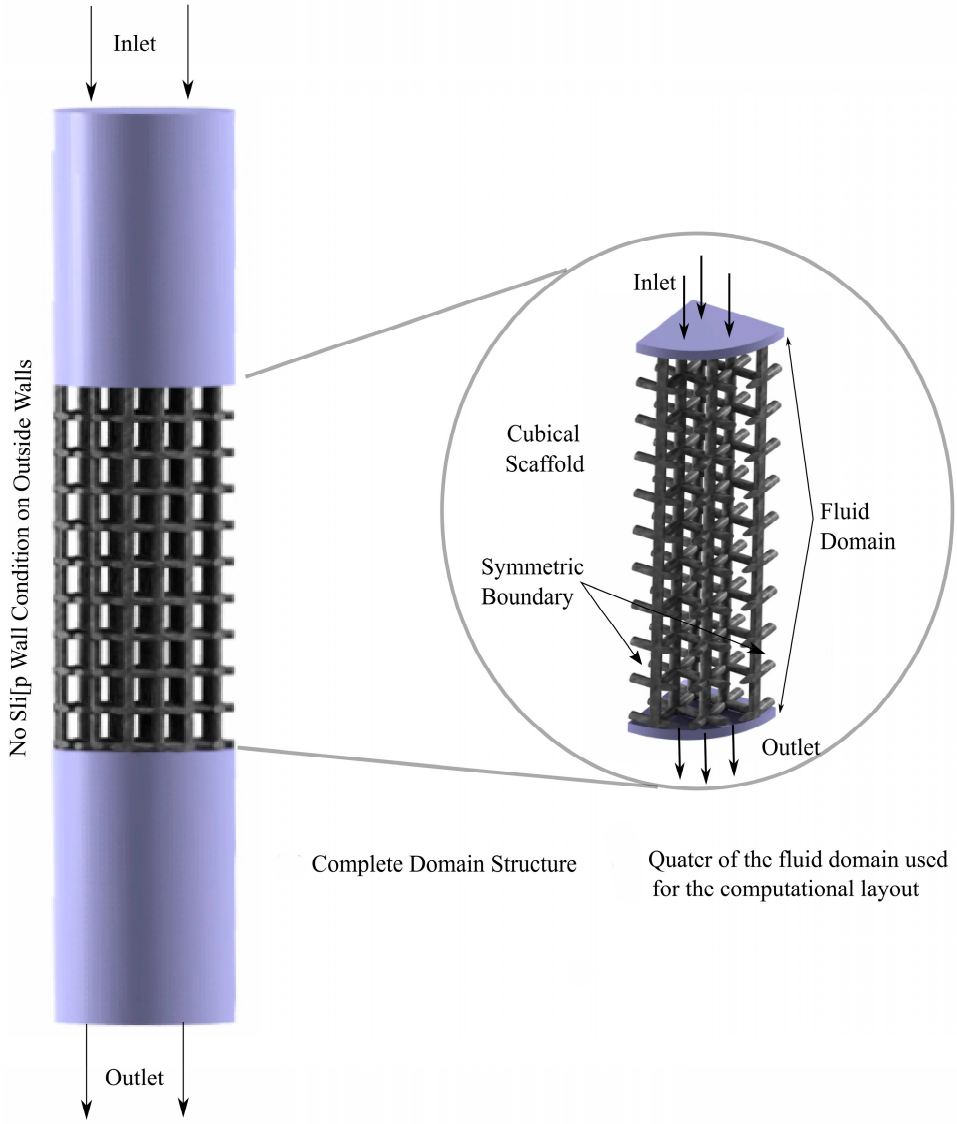

Figure 1. Boundary conditions of CFD model for the scaffold under perfusion flow.

In this study, the pore size, strut diameter and shape of the scaffolds are varied, and the effect of the geometrical parameters on the drug (such as concentration of calcium ions for enhancing bone regeneration) concentration gradient under both static and dynamic conditions is investigated. The parameters taken for this study are given in Table 1. The gyroid is a type of TPMS scaffold. TPMS is a minimal-area surface and is periodic in three

dimensions, with a closed curve boundary. The unit cell is created by adding thickness to the surface, and the final TPMS scaffold is formed by combining these unit cells periodically in three dimensions.

Table 1. Summary of geometric parameters of scaffold design.

Parameter	Range
Strut Diameter	0.2, 0.3, 0.4 mm
Pore Size	0.6, 0.7, 0.8, 0.9, 1.0 mm
Applied Fluid Velocity	0 mm/s, 1 mm/s
Scaffold shape	Cubical, Spherical, Gyroid

3. Results

Figure 2 shows an obvious effect of varying pore size and strut diameter on concentration gradient within the cubical scaffold under static conditions (Figure 2a) and dynamic conditions (Figure 2b). Normalization of the concentration gradient is performed with respect to its maximum value.

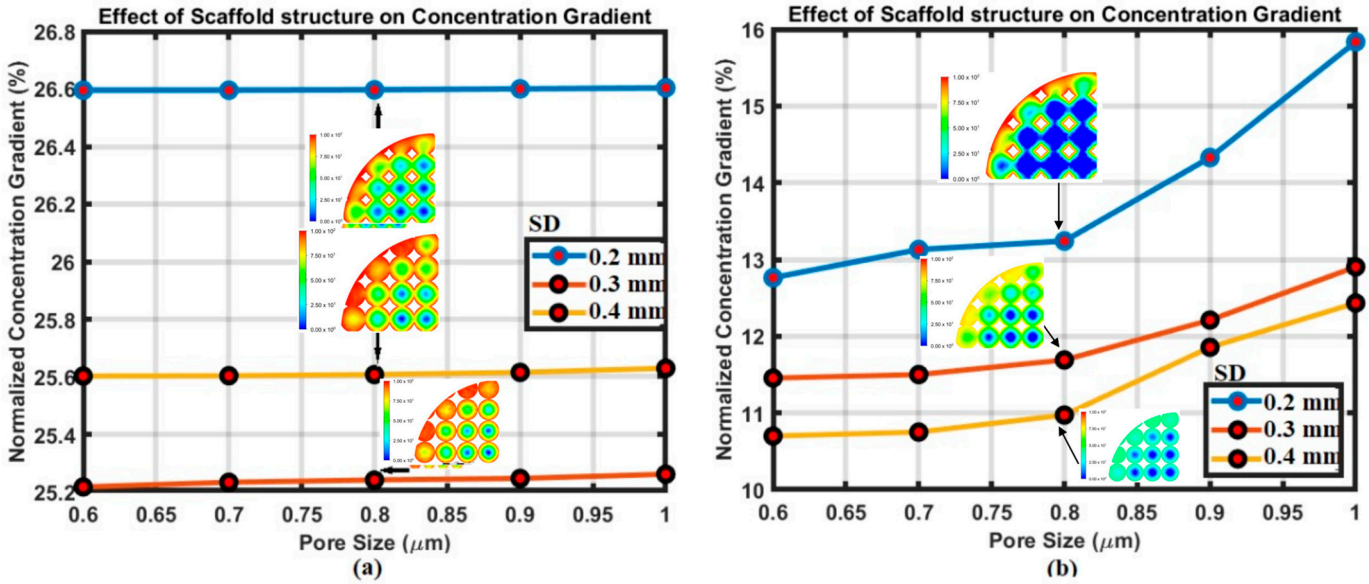

Figure 2. Effect of scaffold geometry (cubical pores) on drug molecule concentration gradient: (**a**) without fluid velocity (static condition) and (**b**) with fluid velocity (dynamic condition).

Under static conditions ($v = 0$ mm/s), the drug molecule concentration gradient almost remains constant. On increasing the strut diameter, concentration gradient also increases. Under dynamic conditions ($v = 1$ mm/s), the concentration gradient increases upon increasing pore size and strut diameter.

In Equation (1), the first term, $D\nabla^2 C$, depicts diffusion and the second term, $v\nabla$C, represents convection. Under static fluid flow conditions, the drug delivery is governed by diffusion only. Under dynamic fluid flow conditions, the drug delivery is driven by diffusion and convection. Thus, on referring to Figure 2a,b, it is shown that the concentration gradient under fluid flow is less (11% approx.) than that under no fluid flow (25% approx.). Under zero fluid velocity, the concentration gradient remains almost constant irrespective of the pore size. This is because, under no-flow conditions, the drug delivery is mainly governed by diffusion, the rate of diffusion being proportional to the concentration gradient and not the pore size. Unlike convective transport, which depends on the pore size, the transport by diffusion is less sensitive to changes in the pore size.

Under fluid flow (Figure 2b), it can be seen that the concentration gradient increases upon increasing pore size and strut diameter. This is because, under fluid flow, if the pore size of the scaffold is increased by keeping other parameters constant, the porosity also increases. The increase in porosity results in the reduced flow rate inside the scaffold as the pressure of the fluid is dropped [9]. As the flow rate reduces, then there will be difference in the drug concentration at different points in the scaffold, resulting in the increase in the concentration gradient.

The results of the scaffolds with spherical pores (Figure 3a,b) are also similar to those of cubical pores, where the concentration gradient increases upon increasing pore size and strut diameter (under fluid flow conditions), and the same remains constant under zero fluid velocity. The results of the TPMS scaffold (Figure 4a,b) show that the TPMS shape has a considerable effect on the concentration gradient. The concentration gradient of the TPMS scaffold is less than that of cubical and spherical scaffolds under similar loading conditions and geometric parameters. However, the effect of fluid flow is not significant, as the concentration gradient increases at the same rate in both loading conditions and upon varying geometrical parameters. The effect of strut diameter on concentration gradient is as follows: In cubical and spherical scaffolds, the increase in strut diameter reduces the concentration gradient of the drug (Figures 2a and 3a). This occurs because, as the strut diameter increases, the surface area to unit volume ratio decreases, reducing the porosity, leading to spatial restriction for diffusion. As a result, the rate of diffusion of the drug from the interior of the scaffold to the culture medium decreases, reducing the steepness of the concentration gradient. This results in a lower concentration gradient [9]. In contrast, in TPMS gyroid scaffolds, the increase in strut diameter increases the concentration gradient (Figure 4a). This is because, in TPMS scaffolds, the pores are interconnected with a complex gyroid structure, which makes the drug diffusion harder, thereby increasing the steepness of the concentration gradient. Therefore, on increasing the strut diameter, the rate of diffusion of the drug increases, resulting in increased concentration gradient [10].

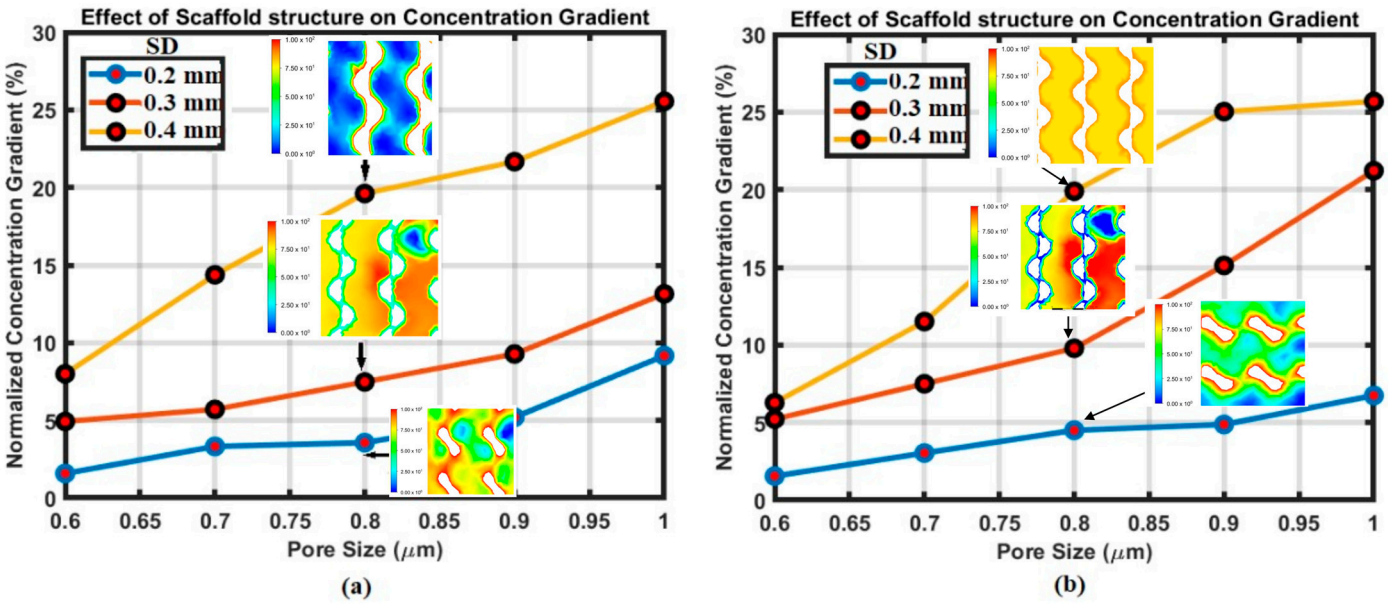

Figure 3. Effect of scaffold geometry (spherical pores) on drug molecule concentration gradient: (**a**) without fluid velocity (static condition) and (**b**) with fluid velocity (dynamic condition).

The contour plots show the concentration gradient across the cross-sectional plane of the scaffold, which differs from the concentration gradient observed at the inlet and outlet and along the scaffold.

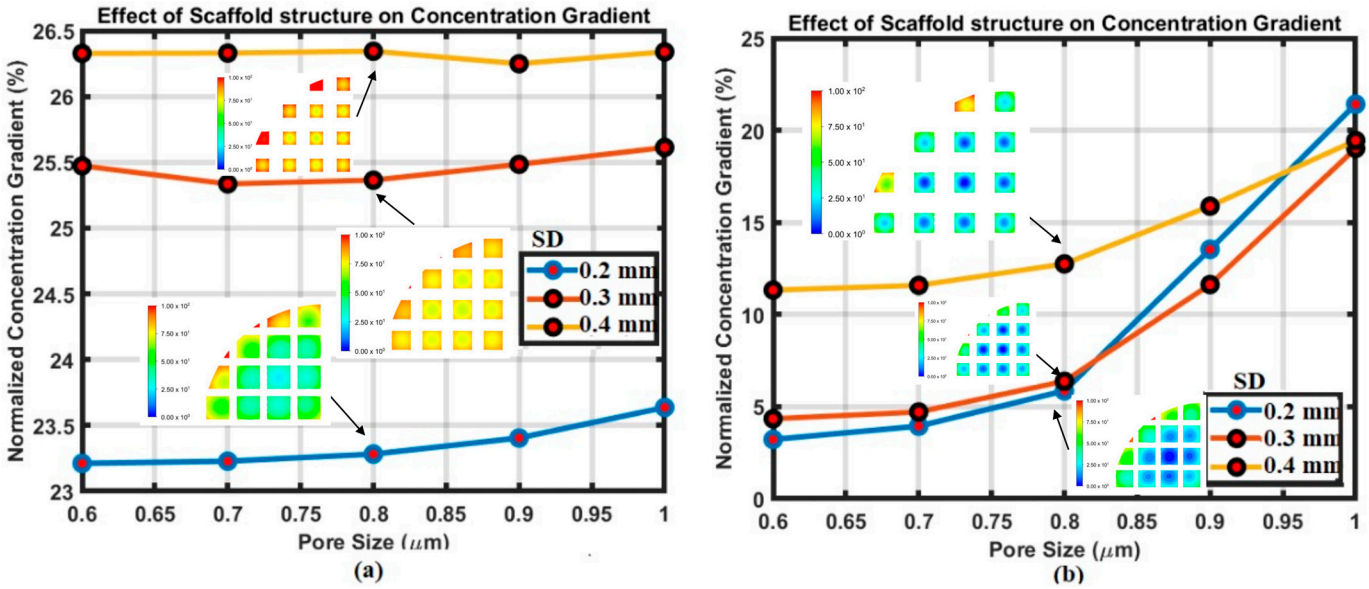

Figure 4. Effect of TPMS scaffold geometry (gyroid pores) on drug molecule concentration gradient: (**a**) without fluid velocity (static condition); (**b**) with fluid velocity (dynamic condition).

The drug concentration near the scaffold walls is higher than at the inlet, and hence there will be steeper concentration gradient at the inlet. Along the scaffold walls, a radial concentration gradient is created because the drug is released from the scaffold walls into the fluid, and this radial gradient becomes less steep than at the inlet. At the outlet, the concentration gradient becomes flattened as the transport of the drug reaches equilibrium [11].

4. Discussion

The results show that under fluid flow conditions, the transport of the drug is enhanced as the fluid flow carries the drug throughout the scaffold, equalizing the concentration, thereby reducing the concentration gradient. Thus, for uniform drug delivery within the scaffold, it is recommended to have the scaffold in a perfusion bioreactor with fluid flow. On investigating the pore size of the scaffold, the results show that increasing the pore size under fluid flow conditions increases the concentration gradient. This is because, on increasing the pore size, the fluid perfusion rate reduces, thus relying on diffusion for the mass transport within the scaffold. In considering the geometric parameters, the increase in pore size and strut diameter increases the concentration gradient. This increase in concentration gradient results in the increase in the rate of diffusion of drug delivery. The increase in concentration gradient enhances the cell migration along the gradient area and is useful in processes like wound healing. The cells migrate along the gradient direction until they reach a zone where they begin to divide, a process referred to as proliferation. Thus, an increase in the concentration gradient enhances the cell activities such as cell migration and proliferation [12]. However, there is one drawback if the pore size is too large. For scaffolds with a large pore size, the porosity also increases, assuming that the other parameters are constant. The increase in porosity reduces the fluid velocity within the scaffold, thereby reducing the shear stress [7], if shear stress is needed in mechanobiological experiments. However, if the pore size is higher, then the surface area to volume ratio is less, leading to a reduction in the area required for cell culture. Thus, an optimum pore size is recommended. From our in silico simulation results, it is observed that if the pore size and strut diameter are high, then the concentration gradient is also high. This results in an increased rate of diffusion. Drug delivery relying on diffusion is a slow process, and for uniform distribution of a drug throughout the scaffold, it takes longer. Thus, an optimum

pore size and strut diameter of 0.8 mm and 0.3 mm, respectively, are recommended. The results obtained are similar to those of the existing works [13,14].

From this study, it can be inferred that both high and low concentration gradients are desirable depending on the purpose of drug distribution. For uniform drug distribution, the concentration gradient should be low so that the drug levels are consistent throughout the scaffold, and for targeted drug distribution, the concentration gradient should be high to focus the drug at the localized sites that require treatment. Additionally, the high concentration gradient also enhances cell activities and the low concentration gradient provides consistent cell behavior. Uniform drug distribution is typically required for applications such as bone regeneration and cartilage repair, while targeted distribution is suitable for applications such as cancer therapy and wound healing [13,14].

On investigating the shape of the scaffold, it can be seen that the effect of fluid velocity on concentration gradient is not distinct in the TPMS structure. Also, the net concentration gradient within the TPMS scaffold is less than that of the cubical and spherical scaffolds under similar parameters. If the concentration gradient is lower, then the rate of diffusion is also reduced. This shows that uniform drug delivery is achieved at a faster rate in TPMS scaffold than with cubical and spherical scaffolds. The lower value of the concentration gradient results in uniform drug distribution throughout the TPMS scaffold volume, which is suitable for sustained drug release applications.

For sustained drug release applications, a lower concentration gradient reduces the likelihood of drug depletion regions within the scaffold and hence a consistent therapy is achieved. This is particularly important for applications such as bone regeneration or cartilage repair, which require uniform exposure of cells to molecular drugs, and promotes uniform cell growth and proliferation. From the in silico results, it can be inferred that scaffold architecture plays a crucial role in the diffusion of nutrient transport and cell growth [13,14]. In this study, the perfusion bioreactor was used because the fluid flow induces shear stress on cells, which enhances their response to drugs, thereby promoting cell adhesion and proliferation. To overcome the disadvantage of drug depletion caused by perfusion, slow, controlled or sustained drug release mechanisms that prevent rapid depletion can be adopted [15].

In this work, in silico modeling and simulation of different 3D scaffold designs within a perfusion bioreactor was conducted. The results are yet to be validated by future experiments. Nevertheless, the findings of scaffold porous geometry's influence on drug delivery may inform the design of drug-coated scaffolds for tissue engineering applications. The study also has some limitations. Our study is focused on typical scaffold strut topologies: non-TPMS (i.e., cubical, spherical pores) and TPMS (with gyroid struts). The impact of other pore geometries, such as triangular, hexagonal, octagonal, etc., on drug diffusion might be different from the findings of this study. However, the pore geometries can have numerous possibilities. This study utilizes a fluid velocity of 1 mm/s in dynamic conditions, which is suggested in Reference [16], which is for bone tissue engineering application. Instead, the impact of a wide range of fluid flow velocities could be studied for other tissue engineering applications as well. Cell behaviors (such as adhesion, proliferation, differentiation and matrix production) usually have large variation among different types of cells; therefore, to reduce the complexity, cells are not modeled in this study. However, to refine the scaffold design for specific cell/tissue types, cell behaviors could be included in the computational model, once the model parameters (such as drug concentration-dependent proliferation and migration rates) are determined. To improve the computational model in the future, drug solubility, osmotic effects and water capillary transport are suggested to be considered in the model.

5. Conclusions

The effects of scaffold geometry on drug diffusion under different loading conditions and geometrical parameters of non-TPMS (i.e., cubical and spherical pores) and TPMS structures are explored in this study. According to our in silico simulation, TPMS scaffold shows a significant effect on drug concentration gradient. A uniform drug distribution throughout the scaffold is achieved faster in the TPMS structure than the other two non-TPMS structures. By examining the effect of pore size and strut diameter, it has been found that both strut diameter and pore size have a significant impact on the concentration gradient, which is essential for drug delivery by the diffusion process. Therefore, it is suggested that these two parameters (i.e., strut diameter and pore size), together with the struct topology, need to be considered in future tissue engineering scaffold design.

Author Contributions: Conceptualization, F.Z. and E.A.; methodology, E.A., M.B.-T. and F.Z.; software, E.A. and M.B.-T.; validation, E.A.; formal analysis, E.A.; investigation, E.A.; resources, E.A. and F.Z.; data curation, E.A.; writing—original draft preparation, E.A. and M.B.-T.; writing—review and editing, E.A., A.C. and F.Z.; visualization, E.A.; supervision, F.Z.; project administration, F.Z. and A.C.; funding acquisition, F.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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