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Study of the transdentinal diffusion of bioactive molecules

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ABSTRACT

In this work the mass transfer characteristics in a μ-tube that simulates a simplified dentinal tubule geometry are numerically investigated. The aim is to assess the key features that affect transdentinal diffusion of substances and consequently to define the necessary quantitative and qualitative issues related to a specific bioactive agent before its potential application in clinical practice. *CFD* simulations were performed in an *S*-shaped tapered micro-tube, while the code was validated using the non-intrusive optical measuring technique *Laser Induced Fluorescence* (*LIF*). As the phenomenon is one-dimensional, diffusion dominated and strongly dependent on the molecular size, the time needed for the concentration of released molecules to attain a required value can be controlled by their initial concentration. Thus, we propose a model, which is successfully verified by experimental data using a dentinal disc and which given the type of applied molecules and their critical pulpal concentration is able to estimate the initial concentration to be imposed.

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1. Introduction

In recent years research tends to be interdisciplinary, and in this context Chemical Engineering techniques and methodology are also applied to solve problems arising from other research areas. In this sense, the diffusion of therapeutic agents through the dentinal tubules, i.e. micro tubes (μ-tubes), is a challenge for potential, more effective treatment modalities in restorative dentistry that can be tackled using the principles of transport phenomena.

During the last decades clinical practice of dentistry has been oriented towards the development of modern treatment techniques that would ensure the healthy function of pulp-dentin complex, which is the basic skeletal structure (80% of the total volume of the tooth). The ultimate goal of an effective treatment modality would be to maintain vitality and function of the dentine-pulp complex [1,2]. Recent research is focused on the design and development of treatment strategies leading to tissue regeneration (reactionary and/or reparative dentin formation), which require tissue-engineering techniques based on specific stem cells and/or bioactive molecules [3]. In other words, the fact that the pulp-dentin complex can be repaired and regenerated by forming tertiary dentin, has led scientists to focus their research on developing optimal procedures and therapeutic agents for use in restorative dentistry. It is well recognized that in deep non-exposed dentinal cavities the transdentinal stimulation of odontoblasts, the highly differentiated cells which are responsible for primary dentin development and repair, can lead to focal secretion of tertiary dentin at the pulp-dentin interface. In experimental studies involving the implantation of the recombinant Bone Morphogenetic Protein–7 (*BMP-7* or *OP-1*) or EDTA-soluble dentinal components, transdentinal stimulation of odontoblasts was demonstrated [4,5]. Furthermore, diffusion of chemical substances which are released from traditional restorative materials and can be potentially involved in the healing process of pulp, requires the in-depth understanding of the transdentinal flow phenomena.

The idea of using the dentinal tubules for drug transfusion in pulp was originally proposed by Pashley [6]. According to the typical dental procedures those biological compounds are placed in completely restored (***enclosed***) cavities of the operated tooth and then diffuse transdentinally through the dentinal fluid to the pulp.

Given the above the ultimate goal of such research is the development of a model that would predict the mass transfer in the dentinal tubules, based on the measurement of the transport rate of selected molecules (e.g. *HEMA/TEGMA, TGFs/BMPs*) using an experimental methodology that could adequately simulate clinical conditions of dentin matrix. It is obvious that the minute dimensions of the dentinal tubules render the experimental study of the diffusion rate of therapeutic molecules inside the dentinal tubules practically impossible using conventional experimental techniques. Therefore, Computational Fluid Dynamics (*CFD*) seems to be a feasible method for studying the problem under consideration. In biomedicine, *CFD* has already proved to be a highly reliable

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Nomenclature

C	molar concentration, mol/m^3
C_L	molar concentration at the bottom end, mol/m^3
C_o	initial molar concentration, mol/m^3
C_∞	final molar concentration (for $t = L^2/D$), mol/m^3
D	coefficient of diffusion, m^2/s
j	concentration flux, mol/m^2 s
L	length, m
M_w	molecular weight, g/mol
R_s	stokes radius, m
r	radius of conduit, m
T	temperature, °C
t^*	Dt/L^2, *dimensionless*
t	time, s
x	distance, m
μ	viscosity, g/cm s

tool in hemodynamics, respiratory and cardio-vascular system research [7–12]. Recent studies [13,14] confirmed that *CFD* is also a powerful tool in the research of endodontic irrigation. *CFD* can be considered also useful in the study of flow phenomena inside the dentinal tubules.

In this study we tackle a simple case that concerns the diffusion of substances similar to typical molecules released from restorative materials or bioactive therapeutic agents used in the modern dental practice through a typical dentin tubule that has no obstructions or alterations of any type (μ-tube model). In this initial approach of the problem our model deals with the diffusion of molecules in a tubule without the presence of bacteria and/or inflammatory molecules released from pulp tissue. The rate of ion production from the therapeutic compound is also not taken into consideration. As the nature of the barrier between pulp and dentin and its permeability are still unknown [15], we consider it impermeable aiming to study only the transport of substances to the dentin–pulp junction. To verify the applicability of the model to the actual tooth structure additional experiments will be performed with a *dentinal disc*.

2. Diffusion in dentinal tubules

The dentin tissue consists of microscopic channels, called dentinal tubules, which radiate outwards through the dentin from the pulp to the exterior cementum or enamel border. Fig. 1 gives a typical representation of the tissues that form a human tooth (Fig. 1a) and the dentinal tubules (Fig. 1b and c). The dentinal tubules extend from the dentino-enamel junction (DEJ) in the crown area of teeth to the periphery of the pulp following an *S*-shaped path. Tapering from the inner to the outermost surface, they have an average diameter of 2.5 μm near the pulp, 1.2 μm in the middle of the dentin, and 0.9 μm at the DEJ, while the total tissue width is estimated to be about 2.5 mm [16]. Most of the dentinal tubules contain non-myelinated terminal nerves and odontoblastic processes (extension of odontoblast) that are placed in an environment filled with dentinal fluid [17–19].

In clinical practice biological compounds can be placed in ***enclosed*** cavities, whenever the dentin pulp complex is affected by caries, or trauma, and then diffuse through the dentinal fluid to the pulp. In the dental practice the fluid outflow is avoided by covering the surface of traumatized dentin tissue with suitable dental materials after the addition of the therapeutic agent and thus in our study the resistance to the internal diffusion will not be included in the computational simulations.

3. Materials and methods

3.1. Code validation

In this work we numerically investigate the diffusion of substances through a μ-channel (the dentinal tubule) using the commercial *CFD* code *ANSYS CFX® 15.0* for the simulations, i.e. for solving the incompressible Navier–Stokes and mass transfer equations. Although several equations that are derived from Fick's Second Law of diffusion are proposed in the literature [21], the theoretical and experimental study of the diffusion process in the actual dentinal tubules is practically infeasible due to the non-uniformity of the cross-section and the dimensions of the μ-channel, e.g. it is difficult to construct such a μ-tube and to use it for performing experiments. Thus the flow through a cylindrical μ-channel, i.e. a glass capillary, will be initially experimentally studied for the sake of simplicity while the acquired experimental data will be compared with relevant *CFD* results.

For the experimental study of the diffusion in μ-channels and for validating the *CFD* code, the non-intrusive micro Laser Induced Fluorescence (*μ-LIF*) technique was employed, the application of which is of primary importance in the field of microfluidics, where there is need to perform online measurements in situ. Laser-Induced Fluorescence (*LIF*) is a novel optical measuring technique used to indirectly determine instant whole-field concentration (or temperature) maps in liquid and gaseous flows by measuring the light emitted (i.e. fluorescence) by the tracer compounds that are used to mark the fluids. The experimental setup consists of a fluorescence *μ-LIF* system, available in our Lab, and a glass capillary (ID= 580 μm, L= 3 cm) as the μ-channel. The measuring section of the μ-channel is illuminated by a double cavity *Nd:YAG*

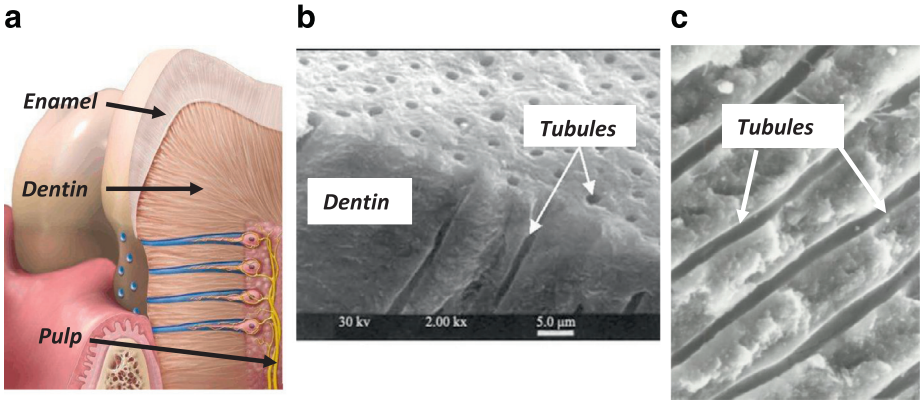

Fig. 1. (a) Typical cut-away representation of human tooth; (b and c) dentinal tubules running perpendicularly from pulpal wall toward DEJ [12].

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