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Modeling the Effects of Drug Delivery Systems and Nerve Growth Factor (NGF) on Damaged Nerve Regeneration

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Abstract. Nervous tissues are one of the most important body tissues and any disorder in their performance will cause serious complications in trend of one's life. Today, these types of disorders can be repaired and restored using drug delivery systems and presentation of effective growth factors at the damaged area. In this study, mechanisms of effect and degree of efficacy of Nerve Growth Factors (NGF) have been modeled during nerve regeneration process. Then, with changing initial value of one of parameters, some changes, which are formed during restoration trend of tissue, have been modeled at two various modes, details of which have been compared in two ideal modes.

Keywords: Nervous Tissues, Drug Delivery Systems, Growth Factors, Nerve Growth, Factor (NGF)

1. INTRODUCTION

Biomaterial structures are the networks with the capability of absorption of high amount of water. Therapeutic applications of biomaterial hydrogels were highlighted with synthetizing of Poly-Hydroxyl Ethyl Methacrylate (PHEMA). On the other hand, engineering strategy of the tissue for repair and restoration of patient's tissues was initiated by Alex Carl and Charles Landenberg in 1900 for the first time and results of their study led to the production of artificial skin. (khosei et al., 2012) Today, the damaged tissues can be repaired and restored easily with presentation of exogenous growth factors. With the interaction of growth factors released from biomaterial structures, repair and restoration of the damaged tissue is possible both physically and chemically.

2. MATERIALS AND METHODS

Extracellular matrix in the complex form is consisted of carbohydrates, proteins and minerals which have been surrounded by tissue constituent cell. This matrix helps cells bond with each other and regulates cellular performances including differentiation, proliferation and cellular bonding. Macromolecules inside this structure can be bonded with growth factors with high affinity. (wood et al., 2009) In response to the changes of physical conditions of the environment such as wound, cells secrete an enzyme that can cause release of growth factors. This matrix includes two classes of macromolecules as follows: 1- glycols l amino glycan, 2- Fibrous proteins such as collagen and fibronectin. (Kouyoumdjian et al., 2006) Heparin–Glycols

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amino glycan are bonded to the growth factors by electrostatic interactions. In natural matric of blood coagulation, fibrin has been considered as a basic material and peptides include domains that form cross- link matrix with fibrin in covalent form. With their specific domains, these peptides can be bonded with heparin as well and these two themselves are bonded with the growth factors. (maxwell et al., 2005)

Fibrin ⟶ Peptide ⟶ Heparin ⟶ Growth Factor

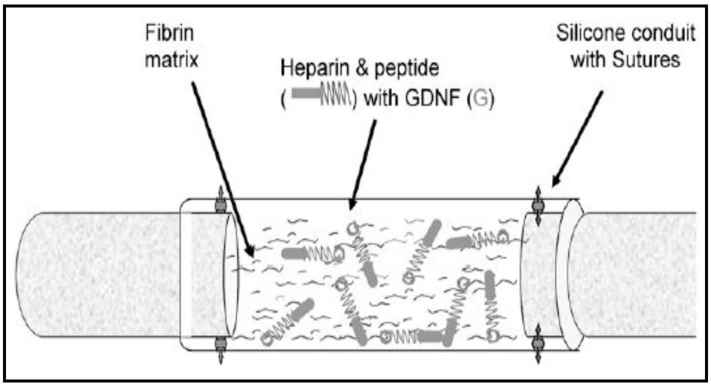


Figure 1. Damaged nervous Tissue on the Verge of Being Repaired (maxwell et al 2005).

Figure1. indicates a damaged nervous tissue which is being repaired and heparin and peptides are bonding to the growth factors. As it is specified in Figure 1, three areas are involved for repairing the damages tissue as follows: 1- Nerve cell tissue, 2- biomaterial network structure, 3- peripheral environment.

2.1. Existing Components

d: Nerve Growth Factors (NGF) which have been considered as "drug".

p: represents as "Peptide".

m: represents "heparin network structure"

e: represents "enzyme secreted from the tissue".

mp: represents heparin bonded to peptide

mpd: represents bonding of heparin, peptide and growth factor

"mp" and "mpd" are the components bonded and connected to the network which are active under the biomaterial network structure environment.

Optimum effect of Nerve Growth Factor (NGF) is observed when ratio of peptide–heparin to peptide– heparin–NGF is 1:1. Mechanism of growth factor release from biomaterial network is taken after as follows: the growth factor is first separated from peptide–heparin site and then, biomaterial network structure is destructed, based on which, one enzyme is secreted from nerve cell tissue and components with growth factor –peptide are released as well. Consequently, drug will be analyzed as well. It should be noted that "p", "d", "pd" and "e" will be appeared at the bond-free component environment (maxwell et al., 2006).

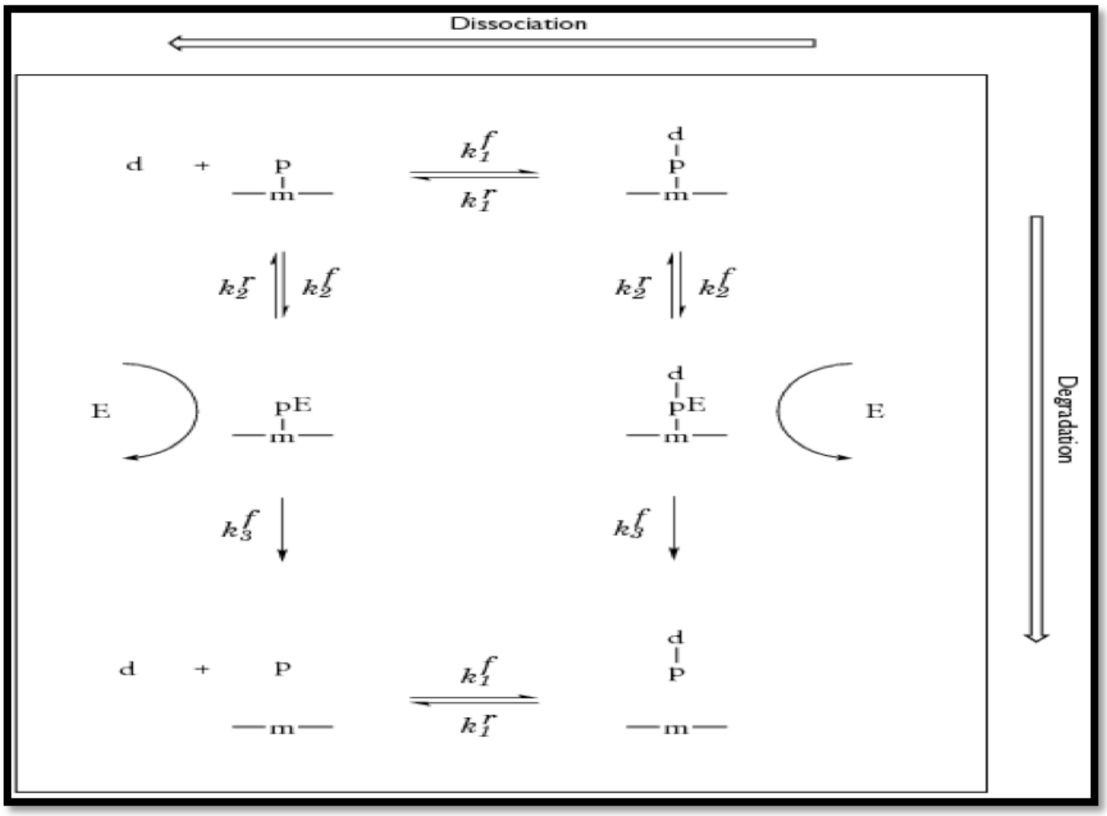
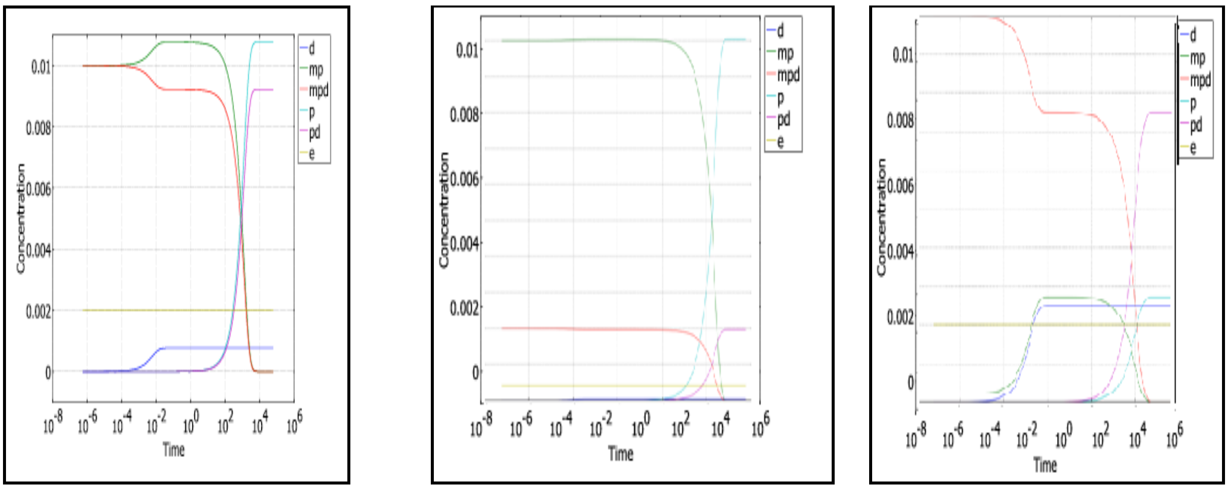
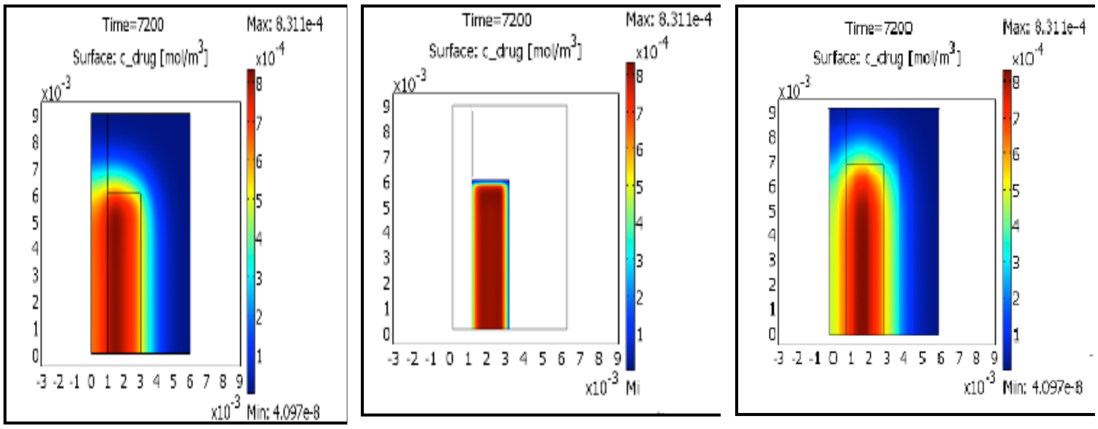


Figure 2. General Schematic of Dissociation of Growth Factor (Horizontal Line) and Network Degradation Reactions (Vertical Line).



A) mp:mpd B) mp:1.2mpd C) mp:2mpd

Figure 3. Concentration of all Reactant Components as a Function of Time.



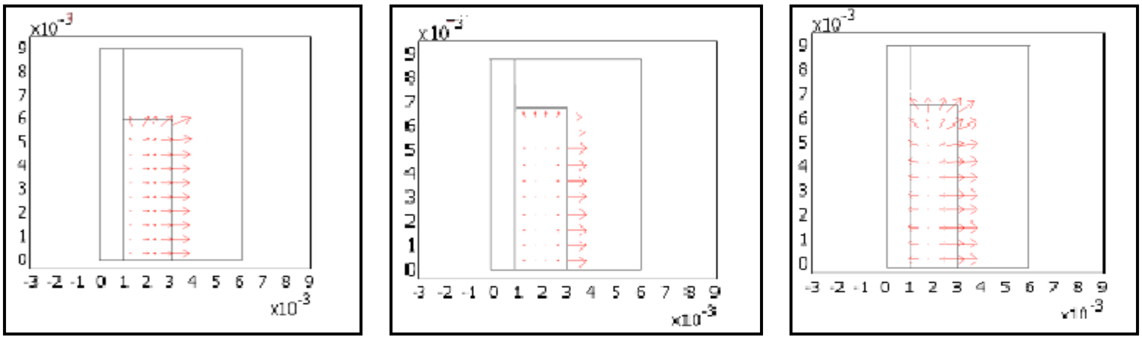
A) mp:mpd B) mp:1.2mpd C) mp:2mpd

Figure 4. Concentration of all Reactant Components as a Function of Time.

In Model (4-A), maximum and minimum concentration of Nerve Growth Factor (NGF) has been specified. Given the release of enzyme in nerve cell environment, concentration of growth factors is increased at the environment as compared to its surrounding area. In this case, ideal condition is provided for repairing nervous tissue and this result is observed in simulated model as well. But at the second condition, the concentration of peptide–heparin became "half", (Model, 4-B) Given the change that formed in value of growth factors, it is expected that the drug delivery system did not show any effect on repairing the tissue and such expectation is specified in the formed model and it is shown that biomaterial has no effect on repairing or restoring the tissue under this condition. But at the third mode i.e.mp: 2mpd (Model 4-C), although rate of concentration of growth factors had turned 'doubled', the effect observed from this system at the damaged tissue environment has been reduced as compared to the optimum mode. In the following three models, distribution of concentration of growth factors has been shown at the end of simulation process i.e. 7,200 seconds in each of three modes and is comparable.

3. RESULTS

The results indicate that drug delivery system uses a fibrin matrix as a framework for restoration and repair of nervous tissue inside a nerve guidance conduit and causes increased cellular adhesion. Moreover, Nerve Growth Factor (NGF) is used as increasing factor to repair nervous tissue as well. Therefore, penetration of NGF inside fibrin matrix has synergic effect. (Tuoi et al., 2011) and increase of NGF in each two forms released and bonded with drug delivery system will improve its repairing effect. Generally speaking, fibrin is a natural material which plays an important role in healing wounds. Sakiyama-Elbert-Habbell presented drug delivery system which included two-domain peptides during polymerization of fibrin and can bond interaction with heparin and growth factors as well. (wood et al., 2008) With elapse of time and continuation of interactions, the damaged tissue will be restored and repaired. In the same direction, three models were presented for the damaged tissues (on the verge of repair) using results of their studies and inferred result is as follows: if ratio of initial concentration of mp to mpd is excluded from 1:1 mode, drug delivery system has no special effect on restoration of tissue according to the carried out modeling process. This study, in its turn, explains effect of gradual process of destruction of network structure on the way of release of factors as a function of time and geometrical structure of material carrying growth factor. The following three figures show the value of NGF transferred from surface unit at the time unit and their direction manifest the explained results.



A) mp:mpd B) mp:1.2mpd C) mp:2mpd

Figure 5. NGF distribution flux at the environment

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