Effective Concentration of Antibiotics on Dissolvable Polymer Sutures

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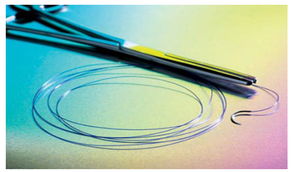
Abstract

Concentrations of triclosan, a common antibacterial drug, at the surface of an antibacterial polymer dissolvable suture were tested with a COMSOL model of a helical suture, measuring average concentration in the wound area and flux of molecules to the rest of the body to determine appropriate concentrations that were high enough to be effective in the local wound area but delivered a low enough amount of material to the rest of the body as to not cause side effects. The concentration range was found to be $10^{3.7}$ to $10^{4.7}$ mol/m^3; results were normalized for a 60kg patient.

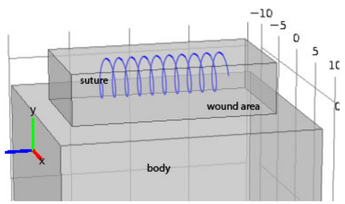
Introduction

- To minimize the risk of infection at the wound site following surgery, antibacterial regimens are often used locally[1].
- Drug delivery often comes in the form of an absorbable polymer suture, coated with antibacterial molecules[2].
- These sutures, which most commonly elute triclosan, dissolve gradually by hydrolysis[3].
- Limited information is available regarding the optimal initial Triclosan concentration for loading. Constraints on this parameter include the minimum effective concentration (~0.1mol/m^3) in local wound area[4] and maximum non-toxic concentration in body (~0.038 mol)[5]; normalized to 60kg male.
- Finite element processing in COMSOL can be used to model and recover the concentrations of triclosan in the wound area
- Compartmental modeling can be used to explore the systemic concentrations at which effects of triclosan become toxic.
- Approximating flux as relatively constant (an observation supported by the results), the concentration in the body can be found and used to evaluate loading concentrations
- Triclosan concentration is relevant over 14 days[2].



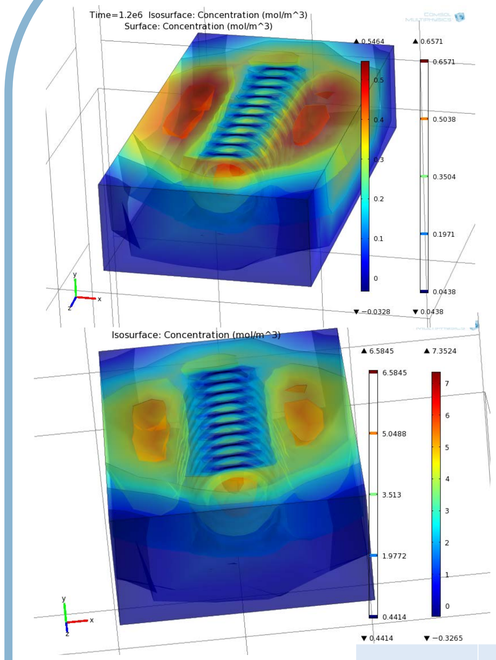
Methods

- Drug release concentration profiles were modeled using COMSOL 4.1 time-dependent convection and diffusion physics module.
- A 10-stitch, gauge 2, polyglycolide suture was modeled as a helix with major and minor radius of 1.5cm and 0.025 cm respectively, and an axial pitch of 1.0 cm.
- The wound was approximated as a partially insulated 6cm x 16cm x 4cm box because for tissue to be much closer to capillaries on one side[6].
- The body was modeled as a prism with contact area 96cm^2 with the body.
- Concentration profiles were obtained for models after 14 days.



- Toxicity threshold was found using the lowest end of L_{50} in concentration for intraperitoneal injection[5]. The data was normalized to an average weighted man (60kg)[6].
- The average concentration in the would area then used to determine the effectiveness of suture concentrations.

Results



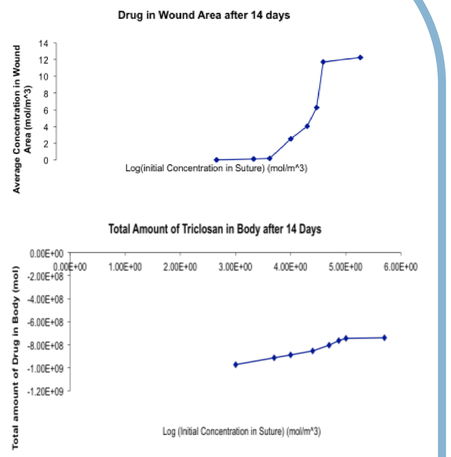


Figure 1. (top left) surface concentration profile for suture surface concentration of 10^5 mol/m^3. **Figure 2.** (bottom left) surface concentration profile for suture surface concentration of 10^4 mol/m^3 **Figure 3.** (top right) average concentration in wound area after 14 days as a function of initial suture concentrations **Figure 4.** (lower right) total moles of triclosan diffused into the body after 14 days as a function of the log of the initial suture concentration Table 1. (below) determinants of effectiveness and toxicity for each initial concentration tested

- Highest concentrations appeared adjacent to and in the center of the suture, tapering off quickly as distance from the source grew.
- Almost all of the triclosan eluted after 14 days but with much retention in the wound area

Log(Initial Concentration in Suture) (mol/m^3)	Average Concentration in Wound Area (mol/m^3)	Log(Flux of Drug into Body) (mol/m^2/s)	Total amount of Drug in Body (mol)	Comment on Usability of Initial Suture Concentration
3.00E+00	0.0213713	-1.17E+01	1.80E-04	low
3.70E+00	0.1045329	-1.10E+01	8.73E-04	ok
4.00E+00	0.2178501	-1.07E+01	1.84E-03	ok
4.40E+00	2.5340906	-1.03E+01	4.58E-03	ok
4.70E+00	4.0529842	-9.67E+00	1.79E-02	ok
4.88E+00	6.253529	-9.15E+00	5.92E-02	high
5.00E+00	11.672357	-8.95E+00	9.25E-02	high
5.70E+00	12.244875	-8.90E+00	1.04E-01	high

- Out of the concentrations tested, initial concentrations on the scale of $10^{3.7}$ to $10^{4.7}$ mol/m^3 at the suture produced average concentrations in the wound area above the effective 0.1 mol/m^3 threshold while limiting body concentrations to remain below the 0.038 mol toxic threshold.
- Results approximated that all molecules of triclosan at the wound edge entered the body immediately after reaching the edge. It was found that triclosan partition coefficient into the tissue was close to 1[7].

Discussion

It appears that the window of permissible concentrations gives a range of approximately one magnitude. While this seems like a small selection, this range was created with several limitations in mind.

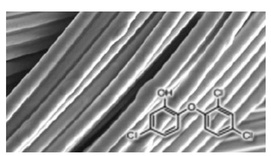
Foremost, the design of the model estimated suture size, length and other aspects of the geometry. The variance of wound size and relative suture length used in surgeries is high, and may change the acceptable ranges of concentrations.

Additionally, the toxicity limit was obtained using the lower limit of L_{50} values, which may be more than one would risk for a surgery[2,5]. However, this is offset by the fact that excretion rates, which, although low on average, may also vary highly over time and lower body concentrations.

Since most of the triclosan remains in the wound after 14 days, there will be continued delivery to the body as time goes on. However, it can be assumed that the flux of molecules does not increase any more than levels observed, since the triclosan has already eluted from the suture.

Nevertheless, if the drug delivered to the body concentrates, side effects may come with the drug eluting suture use. When triclosan is well-spread through the body, the elucidated range of concentrations for suture use should be safe. This is a fair assumption, considering sufficient circulation and given the favorable tissue/plasma partition coefficient characteristic of small molecules. It should also be noted, however, that acceptable ranges shrink due to the toxicity levels with lower body weight.

Conclusion



Acceptable initial concentrations of triclosan at the surface of a dissolvable suture are between $10^{3.7}$ to $10^{4.7}$ mol/m^3 normalized to a 60kg man. The results are slightly inaccurate when longer sutures are used or with patients with varying body weight due to the higher chance of side effects from high toxicity levels.

Future work may include models of different geometries of suture stitching, suture length and effective wound size. Furthermore, the model can be further refined by considering the breakdown of drug in the local drug area by both cellular and local environmental factors (a reaction mechanism).

Another factor for consideration is the effect of high Triclosan levels to the endemic cellular population in the wound. This research would have to extend beyond the scope of this simple helical suture- wound box model.

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