# Development of a Web-based Computing Platform to Teach Controlled-Release Technology

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*Abstract*— **Traditional drug-delivery techniques, such as oral formulations and injections, fail to establish continuous, targeted release of a medication to specific sites. In addition to problems associated with poor patient compliance, several injections may be necessary to keep a desired plasma drug concentration. These factors have led researchers to explore alternatives such as controlled-release dosage forms. One advantage of the new technology over conventional tablets, for example, would be to better control the pharmacokinetic profile of the formulation. Although these systems have been studied extensively and resulted in breakthroughs, significant challenges remain. Several cost-prohibitive experiments may be required to match a release pattern. The drug transport mechanism is not well understood, in some cases, which delays the introduction of new devices into the marketplace. Our group has developed theory-guided methods to teach students the necessary skills to meet the challenges facing the pharmaceutical industry. By modeling the transport phenomena occurring during the release of medication, students learn to identify the key factors driving the amount and rate of drug released from a system. They are also able to make design recommendations. In addition to modeling methods, solution procedures are particularly important for performing reliable simulations. We have devised a web-based computing platform that can be accessed by undergraduates, graduates, controlled-release device producers and scientists who may or may not have advanced knowledge of mathematics. The programs are coded in webMathematica®.**

***Index Terms*— controlled release, iontophoresis, membrane, webMathematica**

## I. Introduction

TEACHING fundamental concepts, through mathematical constructs and simulation, is an approach that has been adopted in courses such as transport phenomena and unit operations. Simulation, an essential component of an engineering course, encourages students to address design issues. Modeling helps to understand underlying phenomena, including the main variables that drive performance. Several pedagogical studies outline the benefits of interactive learning through computer simulations [1-3] and the importance of visualization in retaining information [4-6]. Simulations also assist to anchor abstract knowledge to daily activities. In addition, the influence of an array of conditions on a process can be assessed immediately. However, learning through simulation, alone, has disadvantages, such as a lack of insight into the mechanisms of action, but will suffice if students are only expected to have a superficial knowledge of a concept. To become effective designers, learners will need a well-rounded understanding of basic transport phenomena principles. This is facilitated through the combination of modeling and simulation that enables students to have a broad-based view of their discipline.

Our group has introduced new mathematical formulations and simulations to teach students controlled-release technologies and to ensure accurate, cost-effective polymer-based delivery of drugs to their target sites. Drug-release profiles can be varied by regulating several factors; such as: drug loading, polymer compositions and membrane thickness. Although optimal experimental designs (e.g. sequential simplex delivery method or response surface experiments) are valuable tools in the development of drug-delivery devices, they are costly and offer only limited predictive capabilities. The ability to weigh the contributions of convection, axial and radial diffusion in elucidating transport mechanisms is a skill that needs to be developed and perfected in engineering students who will be responsible for designing new controlled-release devices and improving the efficiency of existing products.

A set of dynamic educational modules (*Laboratory Online*: http://laurentsimon.com/softwaretools.htm), were designed to accept user data and to generate graphics. The website contains several remote-access, web-based learning modules. Two examples are presented to illustrate the development and use of this tool.

## II. webMathematica

webMathematica (current version 3.2) is a Wolfram product that allows researchers to introduce interactive computations and visualization to their websites. This tool uses the features of Mathematica to carry out calculations and display the results on the web. There are several stages involved in installing webMathematica. The first step is to set up a servlet container, such as Apache Tomcat, and Java. Support documents are available at www.wolfram.com. Additional steps involve the configuration of Mathematica and the installation of the webMathematica Web application.

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A rudimentary knowledge of HTML is necessary to deploy a module. Part of the code incorporates functions and commands in Mathematica. As a result, a basic or in-depth understanding of the software is mandatory depending on the complexity of the procedures. Several examples are given at www.wolfram.com to guide new users and make their experiences more rewarding.

## III. DRUG DIFFUSION ACROSS A MEMBRANE

An algorithm is written to estimate the cumulative amount of drug released through a membrane at the membrane/receptor cell boundary. Such experiments are routinely conducted to study drug permeation through a device. Studies reveal that the polymer content, solvent composition and film thickness influence the release kinetics. A two-chamber Franz cell apparatus, consisting of two cells, a donor and receiver compartments, is employed. The membrane separates the cells. A saturated drug solution is added to the donor chamber while an equal volume of the fresh solvent is placed in the receiver cell. For the mathematical analysis, molecular transport is assumed to occur through a homogeneous layer (thickness $h$) and can be described by Fick's second law of diffusion. The setup is drawn in Fig. 1 where $D$ represents the diffusion coefficient, $t$ is the time, $C$ is the concentration and $x$ is the spatial variable. The goal is to solve the equations and plot the cumulative amount of drug released per unit area ($Q$) and the flux ($J$).

The governing equation is

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{1}$$

and the boundary conditions are

$$C(0,t) = C_s \tag{2}$$

and

$$C(h,t) = 0 \tag{3}$$

where $C_s$ is the concentration on the surface of the membrane. Initially, the membrane is devoid of drug:

$$C(x,0) = 0 \tag{4}$$

Simulations are designed to allow students to investigate the effects of $C_s$, $D$ and $h$ on $Q$ and $J$. The series solution was programmed in webMathematica. After giving a brief description of the topic, the following screen (Fig. 1) appears in http://webmath.njit.edu/webMathematica/mathsimon/transder1.jsp

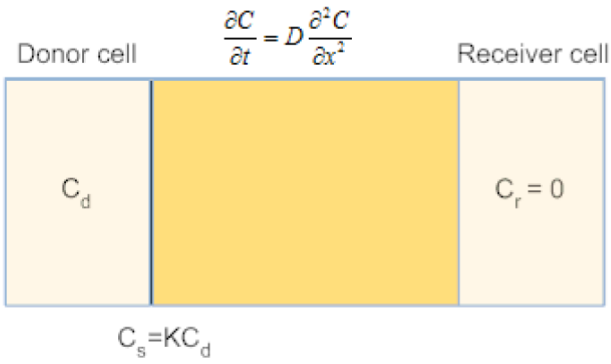


Fig. 1. Drug transport across a membrane.

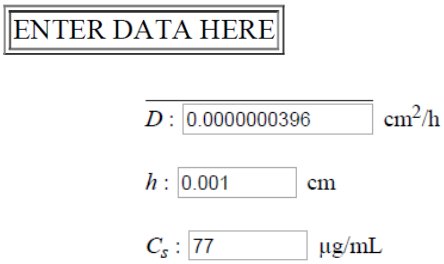


Fig. 1. Screenshot of the "Drug released across a membrane" module.

The result is displayed for this particular set of data after pressing a red-shaded button near the bottom of the page (Fig 2.).

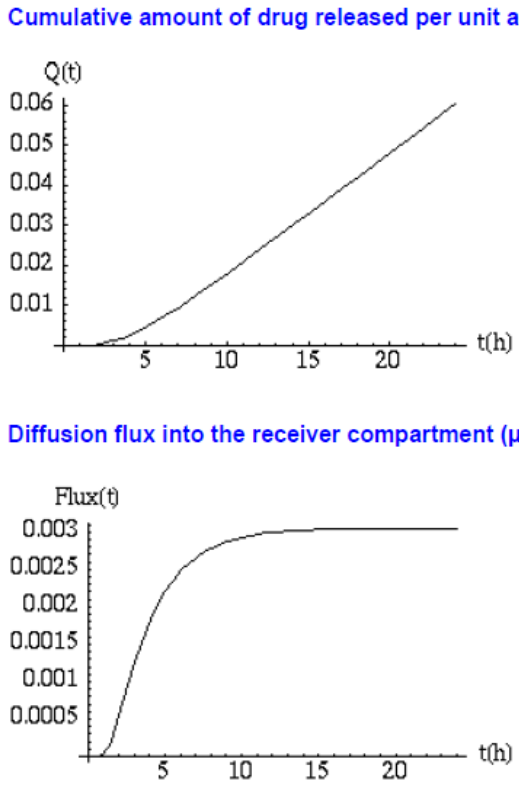


Fig. 2. Simulation of for passive diffusion.

## IV. IONTOPHORETIC TRANSDERMAL DRUG DELIVERY

Transdermal drug delivery can be difficult for some pharmaceutical ingredients because of the formidable barrier to penetration posed by the *stratum corneum*. Iontophoresis is an alternative technique used for enhancing transport across the skin layers. This physically-enhanced method involves a mild electric current applied to the delivery system. Positively charged drugs are placed in the anode chamber while therapeutic agents, that are negatively charged, are placed in a cathode reservoir. The electrodes (e.g., anode: Ag and cathode: AgCl) are connected to a controller (i.e., Iomed Phoresor II Auto) to complete the circuit.

When convective solvent flow or electroosmosis is negligible, electro-diffusion through the skin is represented by [7, 8]

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} - \frac{\upsilon D}{h}\frac{\partial C}{\partial x}, \tag{5}$$

where $\upsilon$ is

$$\upsilon = \frac{zFE}{RT}. \tag{6}$$

The potential difference, $E$, is applied across the membrane; $z$ represents the charge on the ionized drug molecule; $F$ is the Faraday constant; $T$ is the absolute temperature and $R$ is the universal gas law constant.

A program was written to examine the effects of the model parameters on $Q$ and $J$. Figure 3 shows a portion of the webpage:
http://webmath.njit.edu/webMathematica/mathsimon/ionto1.jsp

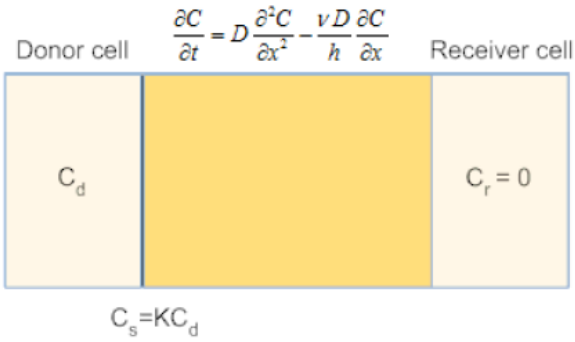


Fig. 1. Iontophoretic Drug transport across a membrane.

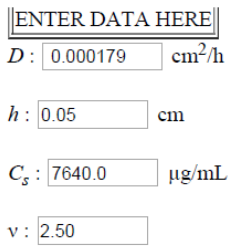


Fig. 3. Screenshot of the "Iontophoretic transdermal drug delivery" module.

The result is depicted in Fig. 4.

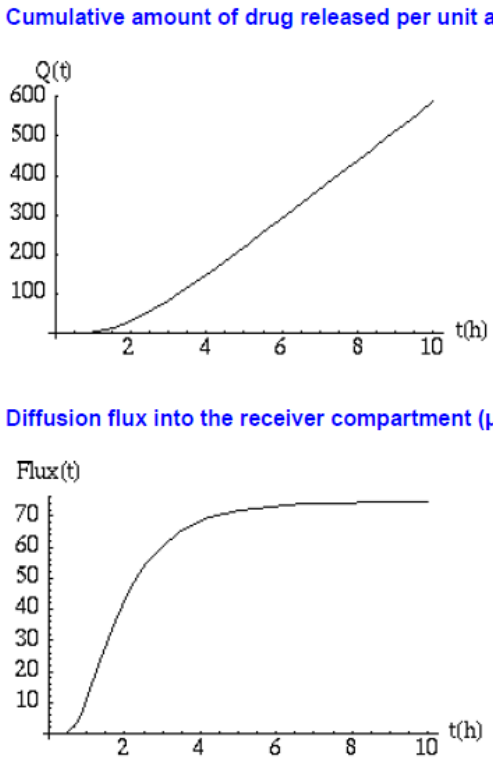


Fig. 4. Simulation of drug transport following transdermal iontophoresis.

## V. CONCLUSION

Two illustrations of educational and interactive modules on controlled release were provided. The web applications were created with webMathematica®. Users can access the site to investigate the influences of key membrane/drug properties on the release kinetics.

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