Design of a Transdermal Delivery System: A Case Study in Product Design and Multi-scale Design

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Introduction

The profession of chemical engineering is in the midst of a change. Biology is joining math, chemistry, and physics as an "enabling science." Chemical engineers are more often required to design new products rather than new chemical processes. The past generation has seen enormous research advances in the enabling sciences in colloid-scale, nano-scale, molecular-scale, and atomic-scale technology.

In response to this expansion of the skills and knowledge required of the 21st century chemical engineer, it is necessary to adopt a new paradigm for chemical engineering education. For example, many programs are now requiring biology classes in addition to the traditional chemistry and physics classes. An increasing number of departments are changing their names to include some reference to biology (*e.g.*, chemical and biochemical engineering, chemical and biomolecular engineering). Product design is either replacing part of or complementing process design in the capstone experience. There is a strong movement to alter the fundamental chemical engineering curriculum common to virtually every program to include the colloid-scale, nano-scale, molecular-scale, and atomic-scale technologies that are at the forefront of chemical engineering research.[1] This curriculum would replace a significant portion of the macro-scale technology that has been taught in chemical engineering for most of its history as a profession with multi-scale technology, while retaining a sufficient amount of the traditional technology to permit teaching and learning of manufacturing. Traditional course titles may change, reflecting a rearrangement of topics based on length scales.[1]

In any new curriculum paradigm, there will still be a need for a capstone experience. In the new curriculum paradigm, the capstone experience may include design of a product at multiple scales, from the product at the atomic through the colloid scales, as appropriate, and the manufacture of the product at the macro scale. Therefore, a new class of design projects will be needed to replace the traditional continuous chemical manufacturing process that is most often the subject of the capstone design class. This paper describes one such design project assigned to the West Virginia University class of 2004.

The Problem

This class was assigned the task of investigating transdermal drug delivery systems. They were to identify potential pharmaceutical products for use in a transdermal patch and suggest opportunities for a profitable venture to manufacture such a product. They were to learn the components of transdermal patches, including their chemical composition, their function, and their mechanism of action, and their location in a manufactured patch. Finally, they were to

learn how a transdermal patch is manufactured. The final deliverable was a detailed analysis of the transdermal patch and a process for manufacturing the patch.

From the perspective of the instructors, three overarching themes exist within this assignment. One is the notion of product design in contrast and in addition to more traditional process design. A product must be designed, but a manufacturing process that differs from a traditional chemical process must also be designed. Another is solving the assigned problem by explicitly addressing phenomena at different length scales. The final theme is the ability of students to teach themselves new material, not normally taught in class, to demonstrate the ability for lifelong learning.

Product Design

It has been suggested that a general framework for chemical product design includes four steps: (1) need, (2) ideas, (3) screening, and (4) manufacture.[2] Students identified the **need** for a transdermal delivery system by learning its advantage over traditional delivery systems. To this end, they learned about the general pharmacokinetics of an orally administered drug vs. that for a transdermally delivered drug. **Ideas** were developed for potential drugs by identifying the physical properties (molecular weight, potency, solubility) that make a drug amenable for use in a transdermal delivery system. A **screening** method was used that permits the weighting of several criteria in selecting the best alternative.[3] These criteria included the status of the drug on patent (The client, a role played by one instructor, is presumed to own a generic drug company.), the market for the drug (For example, scopolamine patches for motion sickness do not have a very large market compared to nicotine patches.), and the loading of the drug on the patch (There is more drug on the patch than is absorbed, which is needed to maintain approximately constant flux. The amount depends on rates of transdermal transport.). Finally, the method for **manufacturing** the product was outlined.

Multi-scale Design

In terms of multi-scale analysis, design of a transdermal drug delivery system requires design from the molecular scale through the macroscopic scale. At the molecular scale, the drug itself is designed. This is beyond the scope of this project. However, after significant screening, the students chose the design and manufacture of a transdermal, birth-control device containing ethinyl estradiol and norelgestromin. At either the molecular or nano scales, there is the presence of excipients and/or enhancers in the patch. Excipients are additives to all types of drug formulations (including tablets) that are not pharmaceutically active. For transdermal systems, the excipients are usually emollients to keep the skin moisturized while the patch is in place. Enhancers facilitate transport of the drug through the skin.

The adhesive to hold the transdermal patch to the skin could involve design at multiple scales. Since the drug is mixed with the adhesive in the most common formulation, if there were a molecular interaction between the drug and adhesive, it would have to be understood. For an adhesive to stick, it must wet the skin, so an understanding of colloid-scale wetting phenomena is required. It must be removed without significant discomfort, yet not become detached in the shower or during physical activity that causes sweating, both macro-scale phenomena.

At the microscopic scale, the mechanism of transport of the drug through the skin must be understood. Modeling drug transport through the skin layers is standard transport phenomena, which chemical engineers have been using for approximately one-half century. At what we will define as the mesoscopic scale (between microscopic and macroscopic), pharmacokinetics of the drug in the body can be modeled.

Finally, at the macroscopic scale, the components must be combined appropriately, manufactured into the desired product, and packaged for sale.

Student Results

Nano scale. It was determined that typical excipients in a transdermal patch include mineral oil and colloidal silicon dioxide. The former is an emollient or lubricant for the skin, while the latter is a viscosity-increasing agent. An example of an enhancer is crospovidone, which draws water to the surface of the skin, causing swelling, providing more surface area for transdermal transport. For the transdermal, birth-control device, oleic acid was chosen as a lubricating excipient and crospovidone was chosen as a necessary enhancer.

Colloid Scale. Students were required to understand the mechanism of adhesion to choose an appropriate adhesive. They learned that adhesion requires the adhesive to wet the surface to which it is to adhere. This requires the critical surface tension of the surface (skin) to be lower than the surface tension of the adhesive.[4] Typical adhesives satisfying this criterion include silicones, acrylics, and rubber-based adhesives (polyisobutylene). Polyisobutylene was chosen as the adhesive for the transdermal device.

Micro scale. An understanding of the mechanism of drug transport through skin layers was required. Students modeled the transport through multiple immiscible layers, resistances in series. There are also potential parallel transport mechanisms (intracellular vs. intercellular), and it was understood that the path of least resistance would dominate. Ultimately, it was learned that the stratum corneum (outermost layer of skin) usually dominates transdermal transport, resulting in a relatively simple transport model.

Meso scale. The pharmacokinetics of the chosen drug can be modeled. This usually involves stirred tank or stirred tank with dead space models. A two-stirred-tank model has been chosen. Students will be designing (but not actually performing, due to time constraints) an *in vitro* experiment that can be used to demonstrate the efficacy of transdermal delivery both on model drugs and on the drugs used in their system.

Macro scale. Students are designing a process to manufacture the chosen product. One step involves processing (but not manufacturing) the raw materials, which consist of the drug, excipients, enhancers, the adhesive, and the paper. Another step involves assembling the raw materials into the final product. A final step includes packaging of the final product. Detailed manufacturing procedures are being enumerated. Finally, the unit cost is determined by an economic analysis.

Table 1 summarizes the length scales listed above with their application to the current problem.

Table 1: Length Scales and their Application to the Transdermal Patch Problem

nano scale	the action of enhancers and excipients at a molecular level on the skin surface
colloid scale	mechanism of adhesion
micro scale	transdermal transport phenomena
meso scale	pharmacokinetics
macro scale	product manufacture

Lifelong Learning

This project and similar vague, initially open-ended projects require students to demonstrate the ability for lifelong learning. Students must demonstrate this ability and the instructors have the opportunity to assess this ability. This subject is discussed in more detail elsewhere.[5,6] A brief synopsis follows.

In the senior year in chemical engineering at West Virginia University, the entire class works on a large project for two semesters under the direction of a student chief engineer. Faculty members play roles in this exercise. One is the client, for whom the students are "hired" to complete a design project (RT for this project). Another is the "vice-president" of the students' company, who helps the students with technical matters (JAS for this project). The chief engineer divides the class into groups, each headed by a group leader. The role of the chief engineer is to represent the entire team to the client and to provide leadership from the "big picture" perspective. The group leaders receive assignments from the chief engineer and are responsible for completing the work within their groups. Assignments are deliberately vague and open ended. The goal is to force students to define their own work statement, with input from faculty members, and to learn material not normally taught in class. The exact topics students must learn are a function of the project. It is less important what they learn year to year. The goal is to make students realize that they will have to continue learning new material throughout their careers and that they have the ability to do so.

Assessment

Two assessment measures were used. In one, the two instructors use a rubric to evaluate, separately, all aspects of the final design report and oral presentation submitted by the students each semester. This rubric was developed in the context of more traditional chemical engineering design problems. For example, since biology is not required in our curriculum, it is not listed as a science which students are expected to demonstrate an ability to apply. The ability to learn and to apply biological concepts as needed is evaluated under the ability to learn new material not taught in class. The complete rubric is available on the Web.[7] Table 2 shows the results, averaged for the two instructors, for the fall semester. The score of 3 indicates *meets expectations*, and the score of 4 indicates *exceeds expectations*. Clearly, our assessment of the students suggests that they exhibited superior performance in the ability to teach themselves new material.

Table 2: Assessment Results for Fall Semester Design (Assessment by Faculty)

Design of equipment, understand interrelationship between equipment in process	3.0
Apply chemistry, math, physics, engineering science	3.0
Resolve complex problem into components	3.0
Apply economic, physical constraints and optimization methods to obtain solution	3.0
Use of computer-based and other information systems	3.0
Demonstrate ability to learn new material not taught in class	4.0
Demonstrate ability to function in assigned role	3.0
Demonstration of ethical behavior	3.0
Demonstrate understanding of societal impact and need for assigned design	3.0

In our student evaluation of instruction, it is possible for the instructor to add an individually defined question, usually specific to a class. One question asked of the class was: *I feel that my experience with the group design taught me the importance of and the need for continuously learning new material.* The results were a 4.17 on a 5-point scale, which demonstrates that students appreciate and value this experience.

A synopsis of the final student report is posted on our design project Web site.[8]

Discussion

This is one example of a multi-scale, product design project. In this case, students were required to learn and to organize the multi-scale phenomena, since most of that material was not included in their more traditional curriculum. This is also an example of how to incorporate lifelong learning into a capstone experience both to provide students with the opportunity to teach themselves new material and to provide the faculty with the opportunity to assess that skill in students.[6] However, in a new curriculum, this type of project might be a capstone experience of topics contained in the curriculum.

One can envision similar projects based on the direction of chemical engineering research over the last few decades. One example might be design of a microprocessor and a process for its manufacture. Another might be design of a material, polymer, polymer composite, nano-material, etc., with specific properties, and a process for its manufacture. A good source of these design projects might be the research being performed in one's department.

It may seem that design projects of this type are too different from typical capstone design projects for traditionally trained instructors to use in their classes. One method that we have found useful is to invite an expert in the topic of the project to meet with the students to act as a one-time consultant. We usually try to incorporate this visit as part of the graduate seminar series. As early in the project as is possible is best; however, it should be after students have begun research on their own. The consultant meets with the instructors and fills in their knowledge gaps. The consultant also meets with the students to help "jump-start" their research, to suggest sources of information, and to be a general resource for student questions based on their initial research. For this project, the consultant was an alumnus who works in transdermal delivery system development for a generic pharmaceutical company.

Conclusion

Design of a transdermal drug delivery system was used as a project in a traditional capstone design class. Students were required to teach themselves the necessary information to complete the design. A transdermal drug delivery system involves product design, design aspects at all scales from molecular to macro, plus it is a biologically related topic. Therefore, it is a useful prototypical design of the future. As the chemical engineering curriculum changes in response to the changes being seen in our profession, similar design projects will find their way into capstone experiences.

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