

Development of experiments in strip film drug delivery and manufacture

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ABSTRACT: Experiments were developed for the use in an introduction to engineering course that focuses on presenting principles of dissolvable strip drug delivery technology, while also reinforcing general engineering concepts. These experiments were designed to be used as individual laboratory exercises or as part of a semester-long project for more in-depth learning. Several laboratory experiments focus on formulation and properties (related to function and performance) of strip films used in pharmaceutical applications. The experiments introduce students to manufacture of strip films, using a simple bench-scale casting device to create solid polymeric thin films from a liquid feed solution. Students explore how results can be modelled and used in scale-up.

Keywords: Drug delivery, dissolvable strips, pharmaceutical engineering, experiments

INTRODUCTION

The pharmaceutical industry has been going through shifting paradigms over the last few years. The interests of the pharmaceutical sector now focus on shortening drug development timelines and streamlining processes [1]. While there are several factors for this change, one of the most substantial is pharmaceutical companies feeling pressure to improve their manufacturing efficiency. With profits shrinking from drugs going generic, a diminishing pipeline of new products and a need to understand processes faster, the pharmaceutical industry is looking for more R&D engineers with new ideas [1].

With this demand for more engineers in the pharmaceutical sector, many universities have developed curricula to educate their students in pharmaceutical engineering. Pharmaceutical engineering can be defined as any applied science or technical aspect from research and development through design and manufacturing of a pharmaceutical product [2]. This discipline is not a typically taught four-year degree major, like chemical or mechanical engineering and, therefore, the pipeline of trained students is limited. There has been work in developing educational materials for both the graduate and undergraduate level instruction. Institutions such as Rutgers University, University of Michigan and New Jersey Institute of Technology all offer graduate degrees in pharmaceutical engineering. While most undergraduate academic programmes offer specialisations in pharmaceutical engineering for students of traditional engineering majors, some schools, such as University of Basel in Switzerland, offer undergraduate degrees specifically in pharmaceutical engineering [3].

With undergraduate specialisations, emphasis is typically placed on developing special topic courses for upper-level students. For example, courses that focus on drug transport and drug design and delivery have been developed by New Jersey Institute of Technology and Georgia Institute of Technology, respectively [4][5]. There has also been some work on developing material for lower-level undergraduate curricula. Rowan University has developed problem sets that can be used in material and energy balance courses that contain concepts of pharmaceutical manufacturing [6][7]. The University has also developed several laboratory experiments that can be used in lower-level engineering courses that present basic pharmaceutical manufacturing principles and general engineering educational objectives. Pharmaceutical concepts discussed in these laboratories include drug delivery theory, pharmaceutical product design product manufacturing, and product testing [8][9]. The authors are currently exploring educational materials in emerging areas of pharmaceutical technology. Strip film drug delivery methods are among these emerging areas, and they are the focus

of this article. One of the novel approaches to drug delivery is dissolvable thin films or strip films. Thin films are starting to gain popularity for use in transmucosal drug delivery. Transmucosal is the method by which the drug diffuses through a mucous membrane, like on the surface of the tongue. Thin films negate some of the drawbacks of traditional tablet medications, including degradation of the active pharmaceutical ingredient (API) in the gastrointestinal tract [10]. Thin films are also more effective for patients that have difficulty swallowing (dysphagia) [11]. It is this last factor that has made thin films a popular area of research for paediatric medicinal applications. Research has been conducted on creating oral strips that could be used for immunisations, which could prove useful in paediatric medicine. Preliminary studies have shown that this is achievable, and can provide advantages in both cost and safety [12].

Dissolvable strips are also being researched for use in cancer therapies. In these therapies, thin films are loaded with antiemetic (anti-nausea) drugs to reduce the effects of nausea and vomiting for patients taking potent opioid analgesics [13]. The main advantage that thin films have in this capacity is that this form of drug delivery reduces the time it takes for the drug to take effect. Previous research has found that thin films can deliver a full dosage of the antiemetic prochlorperazine in as little as two minutes [14]. Other research, including clinical trials, has demonstrated the potential for this method [15][16].

DEVELOPMENT OF EXPERIMENTS

Eight experiments were developed for use in a lower-level undergraduate course. These laboratories were designed to introduce students to dissolvable thin films and to reinforce basic engineering concepts that would be discussed outside of the laboratory; including topics such as working individually and in teams to identify and solve engineering problems, design and conduct experiments, as well as analyse and interpret data [17]. These experiments include: Creation of Dissolvable Strips Lab, Initial versus Final Height of Formulation Lab, Viscosity and Commercial Products Lab, Degradation of Dissolvable Strips Lab, Computer Modelling of Evaporation Lab, Hydro-Properties Lab, and Design of Experiments and Thin Films Lab #1 and 2. The student audience can be multidisciplinary or from a particular major, like chemical or biomedical engineering. These experiments were designed to be completed during our typical laboratory period (approximately 2.5 hours) and to meet the safety standards of an undergraduate laboratory. They were also designed to not rely on highly specialised equipment and to keep operating costs low.

The experiments were developed so that they could be used as a semester-long project or on an individual basis. To help an instructor determine if they would feel comfortable performing these experiments as a semester-long project, a hand-out that highlights the overall objectives for the series of laboratories and the individual objectives for each laboratory was prepared. A tentative schedule was also developed for a 15 week semester that would include these experiments. Also included in this hand-out were selection guidelines for any equipment necessary for the laboratory, along with purchasing information for each of the chemicals that were to be used in the laboratories. One of the equipment guides included how to make the special casting tray that are needed for these laboratories. The dimensions of the casting tray and material for construction were given, along with a diagram of what the tray should look like (Figure 1).



Figure 1: The casting tray that needs to be made for the thin films experiments. The dimensions for this are 30 cm by 25 cm with a height of 2 cm and it is constructed of stainless steel.

Laboratory write-ups for each of these experiments are available on PharmaHUB (www.PharmaHUB.org), a Web site dedicated to sharing educational materials about pharmaceutical science and engineering. To access these laboratories, simply type in *experiments* in the search bar on the left: *Experiments in Thin Films* contains all eight of these experiments. There are two types of write-ups for each of the experiments: a student version and an instructor's version. The student versions contain information that would be standard to a laboratory write-up (e.g. objectives, introduction, procedure, questions, etc). The instructor's version contains all the sections of the student version, but also contains an answer key, including sample data, and some tips or suggestions that are specific for the laboratory. Of the eight experiments, three will be discussed in this article; the Creation of Dissolvable Strips Lab, the Initial Versus Final Height of Formulation Lab, and the Computer Modelling of Evaporation Lab.

EXPERIMENTS

Creation of Dissolvable Strips Lab

The Creation of Dissolvable Strips Lab was developed to introduce students to the processes used to make thin films. Students follow a procedure for making dissolvable strips [9]. This requires students to add a polymer (carboxymethylcellulose or CMC), a plasticiser (glycerol), a surfactant (sodium lauryl sulphate), a sweetener (sucrose) and a saliva stimulant (citric acid) to water kept between 80 and 90 °C, and vigorously stir. The required amounts of each ingredient and their weight percentages are shown in Table 1. Different flavours and colours are provided to add customisation to the laboratory for each student group. If experiments are conducted in a food-grade sanitary laboratory environment, using proper food safety protocols and food-grade ingredients, the strips may be sampled after being formulated. Once the solution has been properly mixed, it is placed in a deaerating apparatus (Figure 2) and put under vacuum to remove any air bubbles. After approximately 15 minutes, the students pour the mixture into the casting tray and allow to dry for one to seven days to form the thin films.

Table 1: The ingredients and required amounts needed for creating dissolvable strips. Also included is the mass percent of each material. Adapted from Mandeep, Rana and Nimrata [11].

Ingredient	Mass (g)	Mass %
CMC	7.7	1.6
Glycerol	2.6	0.6
Peppermint oil	0.5	0.1
Citric acid	1.0	0.2
Sodium lauryl sulphate	1.0	0.2
Sucrose	1.5	0.3
Water	500	97
Total	514.3	100



Figure 2: The vacuum apparatus used to remove air bubbles from the thin film mixture.

Once the strips have formed, students prepare four samples with dimensions of 2.54 by 3.81 cm [9]. These samples are then used in a quality analysis procedure. In this portion of the laboratory, students perform three quality analysis tests that were chosen from the literature based on using commonly available equipment and their ease of setup [11]; thickness measurements, folding endurance and surface pH. Thickness measurements are taken using a calliper and measuring the thickness of each side of the samples. The folding endurance was found by folding the sample in half repeatedly until it breaks. Surface pH was determined by drop-wise adding one drop of water unto the surface of a sample, then placing litmus paper on the wetted surface. Students are then tasked with finding the mean, range and standard deviation of the results, and then asked to comment on their findings (e.g. *Is the surface pH is acceptable for human ingestion?*, *How does the folding endurance compare to a commercial brand strip?*, and *What dangers are there for large variances in strip thickness?*) [9]. Typical student data of these quality measurements are shown in Table 2. Students will most likely find that their pH is safe for human ingestion, considering that lemon juice has a pH around 2, and milk of magnesia has a pH between 10 and 11. Students can also think critically about potential side effects for products that are either acidic (heartburn) or basic (imbalance of salts in the blood). Students should also realise that large variances in strip thickness would also mean large variances in the API that would be administered. In some cases,

this could lead to not enough medicine delivered or could possibly lead to overdosing. Students are also given ranges of thicknesses for different types of thin film products, depending on their intended release (e.g. flash, short or long). These values, obtained from literature, are standard thicknesses for products of the intended release times [11], and students are asked to determine what kind of product their strips would be intended for based on their thickness measurements and the polymer used.

Table 2: Student results from the quality analysis section for the Creation of Dissolvable Strips Lab.

Sample	Thickness (mm)	Folds endured	Surface pH
1	5.5	8	4.3
2	4.9	6	4.3
3	4.2	5	4.3
4	3.9	3	4.3
5	5.5	6	4.3
6	4.0	3	4.3
Average	4.7	5	4.3
Standard deviation	0.67	1.8	0

Questions were included in this experiment to reinforce critical thinking. *Industrial scenario* questions are used to give an idea of what a *practicing engineer* might be asked to do in the profession. For this laboratory, a scenario question was used that had students determine a thin film formulation based on a list of criteria. As an example, the theoretical API that was used in this scenario question had to take up 10% by weight of the film, while the water soluble polymer had to take up 40 to 50% by weight of the film. Once the students came up with their own formula, they then had to determine what method of production they would use, solvent casting or hot-melt extrusion. Since the API did not degrade with heat, and was a rather expensive compound, hot-melt extrusion would be considered the best method for producing these strips.

Initial versus Final Height of Formulation Lab

In the Initial versus Final Height of Formulation Lab, students are introduced to advanced data analysis. In this experiment, students make dissolvable strip solution in the same manner as described in the Creation of Dissolvable Strips Lab. Each group of students is given a different volume of solution to pour into the casting tray: 200, 400, 600, 800 and 1000 mL. Students then calculate the thickness of the initial solution based on the dimensions of the casting tray. For example, the 200 mL solution volume produces an initial height of 0.01 cm. The solution is allowed to dry in the casting tray for 1 to 7 days, depending on the thickness. Once completed, six samples of the films were prepared, and thickness measurements were taken with a calliper on all sides of the sample (Figure 3).

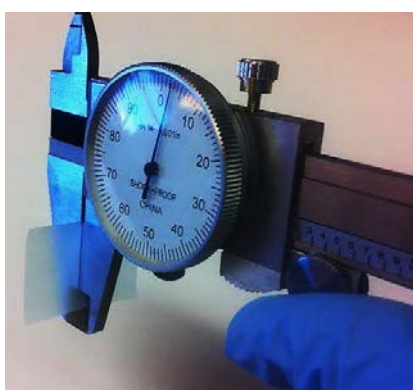


Figure 3: Thickness measurements taken using callipers during the Initial versus Final Height Formulation Lab.

Once data are collected, students then take the average of the results for that run and plot the initial height of the solution versus the final height of the strips. Students then analyse these data, and determine why final thicknesses are different between each of the samples, and the percent difference between the initial and final height. They develop an empirical model based on experimental data (Equation 1, with x being the initial height (cm) and y the final height (cm)), and use this model to determine a hypothetical final film thickness using an initial volume of 750 mL and a tray having a length and width of 45 cm and 30 cm, respectively. Students are not given instructions as to which type of regression to use for their data. This can lead to linear, exponential or polynomial equations being used, depending on which offers the best fit (highest correlation coefficient). It should be noted that polynomials should not be used because this would infer that

there is a minimum at a non-zero initial height. In the case of the data collected for this article, an exponential provides the best fit with a correlation coefficient of 0.8885.

$$y = 0.0088e^{0.8349x} \quad (1)$$

The students are introduced to the concept of a mass balance in this experiment through an exercise where they are asked to theoretically determine the final height of the strips, with the assumption that only water evaporates. Using a final moisture content of 2% (determined in a previous laboratory experiment or obtained from the instructor), the students are able to determine that there is about 3.4% difference between the theoretical final height determined via a mass balance and the final height found during experimentation. This experiment introduces the concept of empirical modelling and correlation of experimental data. Students also observe one of the important phenomena of casting polymeric films, the change in phase as the solvent (water) in the initial polymer-liquid solution evaporates and the solid polymer phase forms.

Computer Modelling of Evaporation Lab

The Computer Modelling of Evaporation Lab is closely related to the Initial versus Final Height of Formulation Lab. For this laboratory, students develop a spreadsheet in Excel[®] that can be used to determine the final height of a thin film batch based on the initial volume. This model will be based on material balances on the system and compared to the empirical correlation (Figure 4). The model assumes an initial volume of the solution and only water evaporating from the system, with the final moisture content of the strips being 2%. Students are provided with guidance on creating this spreadsheet and the assumption making process.

For example, the laboratory write-up shows students how to determine the fraction of water that evaporates from the casting tray using the total mass and component balances. Once the students develop this model, they are required to determine the equation that fits the data (Equation 2, with x being the initial height (cm) and y the final height (cm)). It is clear from the data gathered in the Computer Modelling of Evaporation Lab that a linear regression should be used. The correlation coefficient for Equation 2 was determined to be 1.00.

$$y = 0.02x \quad (2)$$

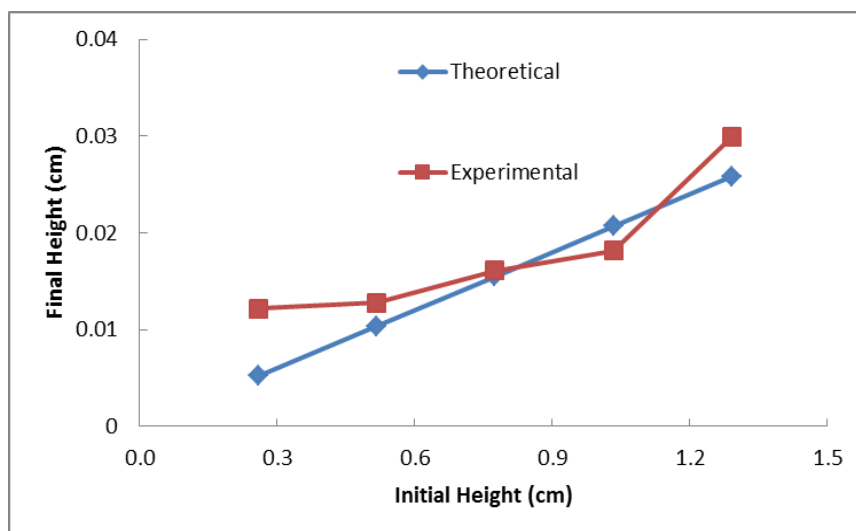


Figure 4: Student results showing experimental and theoretical data for the Initial versus Final Height of Formulation Lab and Computer Modelling of Evaporation Lab.

Figure 4 shows that the experimental values deviate somewhat from the theoretical model at both low and high-end initial casting heights. Students are asked to brainstorm the reasons behind the differences and how the results could be improved. They realise that one of the assumptions of a fixed final moisture content of 2% may not be true for all of the experimental runs. There are also discrepancies in how samples were obtained from the final films and in the drying conditions for the particular run. With the higher initial height, the slower the evaporation process, so the final strip may have been sampled before it reached its final equilibrium height (and thus has higher moisture content). The converse could also be true, yielding a lower value at lower initial pour heights.

Some of the other considerations are deviations in the feed composition and the ambient room environment for a particular run. The humidity and temperature in the room affect the drying rate and final film characteristics. It should be noted that the student data shown in Figure 4 were taken over the course of several weeks, as opposed to at the same time.

Students are given an industrial scenario question in this laboratory where they use their model to solve a *real-world* problem. Students act as engineers for a small consulting company advising a drug company on commercialisation of a new process. The drug company does not want to spend capital to build a pilot plant for scale-up testing and wants to rely solely on a model developed from previous experimental data. In this case, the drug company client wants to know if the scale-up calculations they did were correct, and if the final height of their strips will be within a given range. Using the model developed in laboratory, the students determine that the scale-up calculations were incorrect and that the final height will be out of range. This experiment shows the importance of developing accurate models and the assumptions used in creating them, along with the value of pilot-scale evaluation before commercialisation of a process.

CONCLUSIONS

With the increased interest in pharmaceutical manufacturing in engineering curricula, experiments have been developed for use in a lower-level undergraduate engineering course. These laboratories all focus on aspects of novel drug delivery through dissolvable strips. These laboratories can be used to introduce thin film technologies while also focusing on general engineering concepts. Three of the eight experiments are described in this article. Future work includes using these experiments in the classroom and obtaining assessment data from students. These laboratories can be found on PharmaHUB.org by searching for *thin film experiments*.

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BIOGRAPHIES



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