Creation of Dissolvable Strips

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Date of Experiment:

OBJECTIVES

- Students will learn about the commonly used processes for industrial thin film production
- Students will learn and use basic quality control testing methods
- Students will gain insight into energy requirements for drying thin films

INTRODUCTION

Dissolvable strips have become an important mechanism for drug delivery. Orginially created as candy, dissolvable strips fill a niche role, providing rapid-release drug delivery. Due to the drug being dissolved directly into the blood stream through the tounge, it bypasses the metabolism of the body, which can cause drugs to lose some of their bioavaliability (the amount of drug that will circulate through the body). Other advantages of using thin films include not having to take the drug with water, no risk of choking, and reduced dose size because the drug is more bioavailable sublingually (tissues under the tounge).[1]

The ingredients of a dissolvable strip will vary, depending on the desired drug release rate, the sensitivity of the drug, and several other factors. However, all strips will contain the following ingredients; an active pharmaceutical ingredient (API), polymers, placticzers, and sweetners/flavoring.[2] A polymer is often determined based on its reactions with water. The more hydrophilic (attraction to water) the polymer is, the faster the film will dissolve and release the API. The plasticzer helps improve flexibilty and prevent brittleness in the strip, while the sweetners and flavorings help to improve palatability and increases patient compliance.

On an industrial level, dissolvable strips are primarily made with either a solvent-casting film system or a film extrustion system. Solvent-casting systems are the most common process, as they do not require heat, which could damage an API, and are relatively inexpensive to construct. A typical setup for a solvent-casting system can be seen on the next page.[3] The drawbacks to solvent-casting techniques can include variances in film thickness and non-uniform drying.

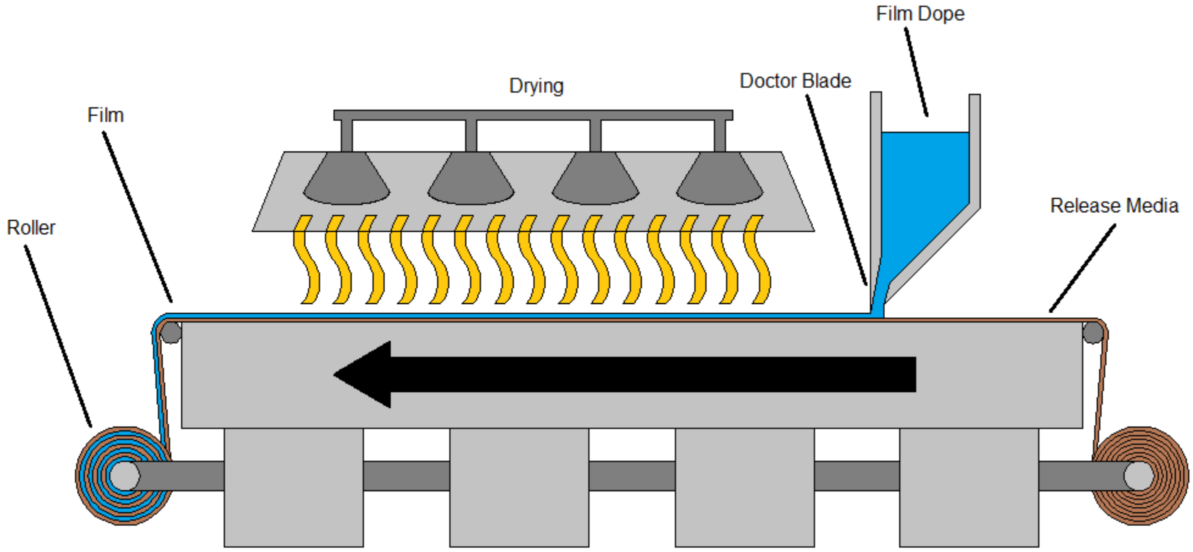

Figure 1. A diagram of a solvent-casting system as adapted from Particle Sciences.[3]

Alternatively, hot melt extrusion is also used to create strips. The advantages to extrusion are a simpler design and the lack of water needed to run the process, but the materials used in the dissolvable strip must be heat resistant and be able to flow as a dry powder. A sample of both of these systems can be seen in Figures 1 and 2.

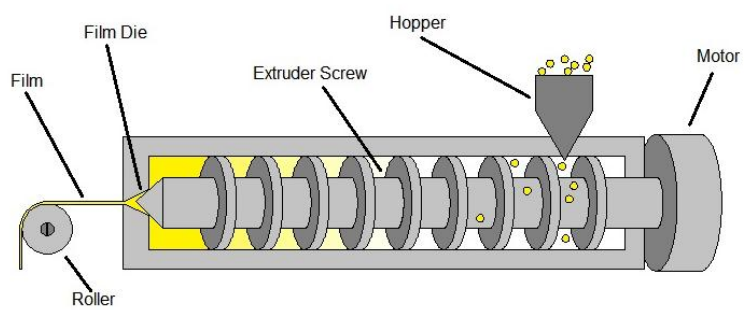

Figure 2. Screw-forced extrusion of dry feedstock as adapted from Particle Sciences.[3]

In this lab, you will be creating your own dissolvable strips. This procedure is based on the solvent casting method described above. Through this lab, you will have a better understanding of the way that dissolvable strips are created, and some of the engineering principles behind the process.

SAFETY CONSIDERATIONS

Make sure to wear safety goggles at all time. Laboratory safety gloves should also be worn.

MATERIALS NEEDED

- 1000 mL beaker
- Hot plate and mixer
- Magnetic stir bar
- CMC (carboxymethylcellulose)
- Pectin
- Xanthan gum
- Sodium lauryl sulfate
- Citric acid (anhydrous)
- Glycerol
- Sucrose
- Blue Food Dye (Blue #40)
- 3 drops of Peppermint oil
- Dropper
- Deionized water
- 3 mL syringe
- 2 Büchner (vacuum) flasks
- Funnel
- Fine mesh screen
- Vacuum tubing
- Vacuum source
- Spatula
- Petri Dish
- Teflon-lined sheet/plate apparatus with thickness guiding bars
- Analytical scale
- Tubing and stopper

PROCEDURE

CMC Method

Table 1: CMC preparation

Species	Weight (g)	Weight %
CMC	7.7	1.6
Glycerol	2.6	0.6
Peppermint oil	0.5	0.1
Citric acid	1.0	0.2
Sodium lauryl sulfate	1.0	0.2
Sucrose	1.5	0.3
Water	500	97
TOTAL	514.3	100

1. Weigh out the appropriate amounts of all powdered ingredients.
2. Add the required amount of deionized water to the large beaker. Reminder: density of water = 1 g/mL.
3. Place the beaker on the hot plate and add the stir bar. Set the heat to the lowest setting and set the stir to a low-medium rate (4 out of 10).
4. Add the CMC to the water at a very slow rate, dusting the powder over the surface of the water and waiting for it to be absorbed. Once most of it is mixed in, the solution will become very viscous and trap air bubbles. Once the viscosity increases, you will need to increase the stirring intensity. Do this slowly.
5. Add the glycerol to the solution with the 3 mL syringe. You will need approximately 2 mL of glycerol to correspond to the weight shown in Table 1.

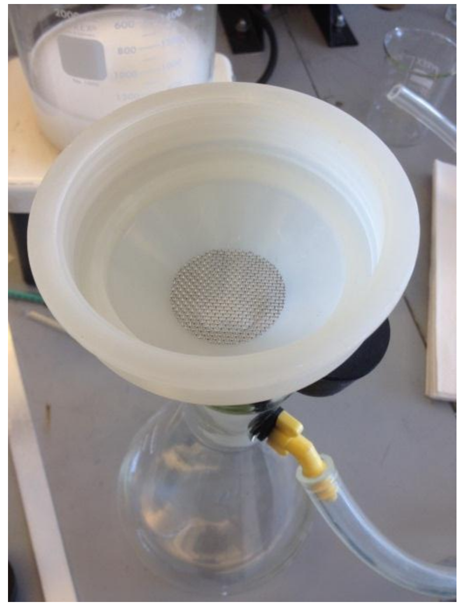

Figure 3. Funnel and screen setup for pouring into flask.

6. Add the remaining components to the solution similarly to how the CMC was added. At this point, the solution should be extremely viscous and appear opaque white.
7. Add three drops of peppermint oil to the solution.
8. Add one drop of blue food dye. The mixture should now be a light blue color.
9. Transfer the solution into the vacuum flask with the mesh and funnel, pouring through the mesh, to catch any large clumps of solidified product and the stir bar. Discard the solidified product.

Figure 4: The setup that should be used when using the vacuum.

10. We will now make a vacuum filtration system. The purpose of this is to de-aerate the mixture. This minimizes the bubbles in the solution. Hook the vacuum flask up to a tube and place a rubber stopper in the top of the flask. Then, connect the tube to the other vacuum flask. Next, place a stopper with an attachment into the top of the other flask and connect this to the vacuum source.

See Figure 4 for the appropriate setup. This second beaker will stop any foam from entering the vacuum.

11. Turn on the vacuum and wait approximately 30 minutes for the gas to leave the solution. The solution should slowly turn clear and may get frothy. The froth will subside.
12. Turn off the vacuum and disconnect the tubing from the vacuum source. Then, remove the beaker with solution from the setup.
13. Carefully pour some of the solution into a 500 mL graduated cylinder. This will make it easier to transfer the solution to the Teflon sheet or petri dish.
14. Take a petri dish and weigh it. Record this weight.
15. Prepare a sample of the film in the petri dish by adding 10 mL to the dish. Do this by using a small graduated cylinder (10 to 25 mL). If any bubbles remain on top of the solution, be sure to draw solution from under the surface.
16. Weigh the wet petri dish and record this weight.
17. Pour out 400 mL of the remaining solution onto the sheet using the 500 mL graduated cylinder.
18. Allow 1-2 days for the samples to dry. The batch should appear much thinner and have a glossy finish on its surface. Take a final weight of the petri dish sample and record its weight.

QUALITY ANALYSIS

How uniform is your batch? In industry, this is done by sampling a batch and testing it in several ways to ensure that specifications are met. Several samples are taken and their results are averaged. Quality analysis is critical to the success of a company, so that deviations can be caught and fixed before they become a costly problem.

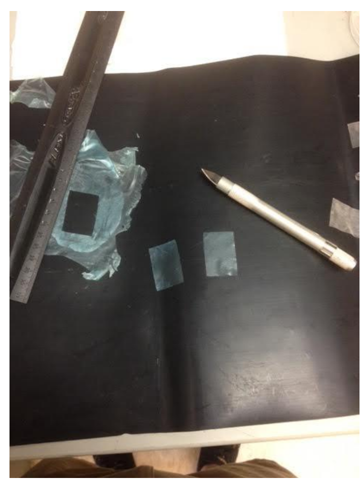
Figure 5. Strips being cut

Sample Creation

1. Carefully peel the strip out of the mold with a spatula.
2. Take a ruler and measure 4 samples with dimensions of 1” x 1.5”. Try to find room for samples from each of the four corners so that the samples are representative of the entire batch.
3. Using a scalpel carefully cut out the four samples.

Thickness Measurements

1. Using a caliper, take each sample and place it in the jaws of the caliper.
2. Adjust the jaws so that the sample fits snugly between them. Do not over tighten the caliper so that the sample tears. The sample should be pinched, but also be able to slide out from between the jaws when a small force is applied to it.
3. Record your results and repeat for all samples.

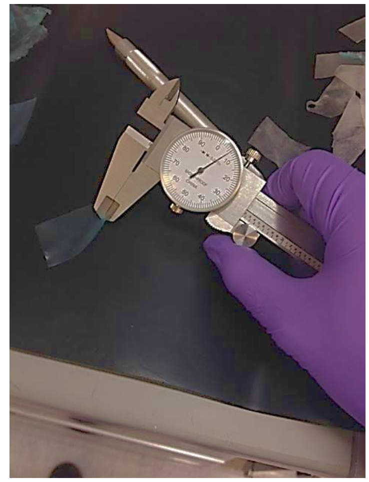

Figure 6. How to use the calipers to determine thickness

Folding endurance

1. Take a sample and fold it in half along the 1.5” face (At the 0.75” mark). Pinch the folding point with your fingers so that a distinct crease is formed.
2. Unfold the strip and flip it over. Carefully fold the strip in the opposite direction, along the same crease and pinch. This has now been 2 folds.
3. Repeat steps 1 and 2, counting the number of folds that you perform.
4. Record the final number of folds, and repeat for the rest of the samples.

Surface pH

1. Using one of the halves from each sample, use a pipette to drop a small quantity of DI water on the strip.
2. Place a broad-range litmus paper strip in the drop.
3. Compare the color of the strip to the package to determine the pH of the sample.
4. Record your results and repeat for the rest of the samples. Again, you only need to measure the pH from one half of each sample.

Figure 7. Ensure a good fold by pinching the strip

Analysis

1. Average the results from each test.
2. Find the range of results for all tests. Was there significant variance in the data you collected?
3. Do you think that the average pH of the samples would be dangerous to ingest? What about the highest/lowest pH sample?

4. The average number of folds it takes to break a Sheets® brand strip was found to be in the range of 15-20 folds. Does your average fall in this range? If not, why do you think it didn't?
5. What could be a dangerous consequence from a lot of variance in the thickness of each sample? Would you sell the strips you made to pharmacies?

Moisture Content Analysis

In this section, you will use the initial and final weights of the petri dish sample, as well as an introductory energy balance, to find the energy required to dry the sample and the amount of water remaining in the sample.

1. Find the change in mass of the sample. Assume that the mass that evaporated was 100% water.
2. Find the moisture content with the following equation:

$$\%_{moisture} = \left[1 - \left(\frac{m_1 - m_0}{m_0}\right)\right] * 100$$

   Where,
   m_1 = final weight of the sample
   m_0 = initial weight of the sample

3. You will now calculate the amount of energy required to evaporate all of the water that was lost. This energy was transferred into the sample from its surroundings, so the balance of energy transferred appears as such:

$$Q = m_{vap} * L_{vap}^{H_2O}$$

   Where,
   Q = energy required to dry the sample
   m_{vap} = mass of water vaporized, $(m_1 - m_0)$
   $L_{vap}^{H_2O}$ = Latent heat of vaporization for water, 2260 kJ/kg
   Make sure to watch your units!

4. Where do you think this energy came from?

QUESTIONS

1. For the following APIs, research the drug's therapeutic value and determine if a hydrophilic or hydrophobic polymer matrix would be best suited for drug delivery:
   a) Salbutamol
   b) Zolpidem tartrate
   c) Ondansetron
   d) Fentanyl citrate
2. Your boss approaches you with a new design project. The pharmaceutical company you work for has recently signed a contract with a client, requiring that you produce 800,000 dissolvable strips/year of a new API designed to treat the common cold. The API, referred to as DK-12, is potent in very small doses, but degrades rapidly when it hits stomach acid. Therefore, a dissolvable strip is the perfect method for introducing the drug into the body. The film must be fast-dissolving.
   a) Before any equipment can be decided upon, you must create the formulation. The required ingredients are:
      - DK-12 (10% w/w)
      - Water soluble polymer (40-50% w/w)
      - Plasticizers (0-20% w/w)
      - Sweetening agent (3-6% w/w)
      - Saliva stimulating agent (2-6% w/w)
      - Colors and flavors (1-10% w/w)

      Find a suitable chemical for each of these components and compile a list for your boss.

   b) Now that you've selected the ingredients for the strip film, you have to select whether you are going to use a hot-melt extruder or a solvent casting system. The material dissolves easily in water and polar solvents, and is not friable (does not degrade from heat). It must be noted that since DK-12 is new, it is very expensive, and therefore it is important to minimize wasted API. Explain your reasoning.

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