

Creation of Dissolvable Strips – Instructor's Version

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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. Originally 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 tongue, it bypasses the metabolism of the body, which can cause drugs to lose some of their bioavailability (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 tongue).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, plasticizers, and sweeteners/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 plasticizer helps improve flexibility and prevent brittleness in the strip, while the sweeteners and flavorings help to improve palatability and increase patient compliance.

On an industrial level, dissolvable strips are primarily made with either a solvent-casting film system or a film extrusion 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.

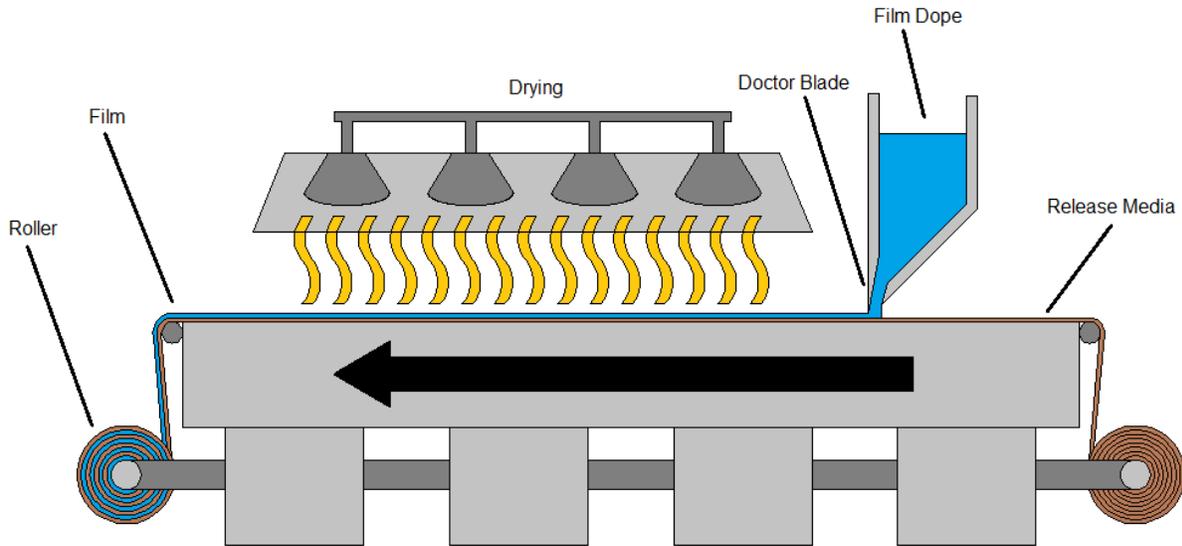


Figure 1. A diagram of a solvent-casting system as adapted from Particle Sciences.³

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.

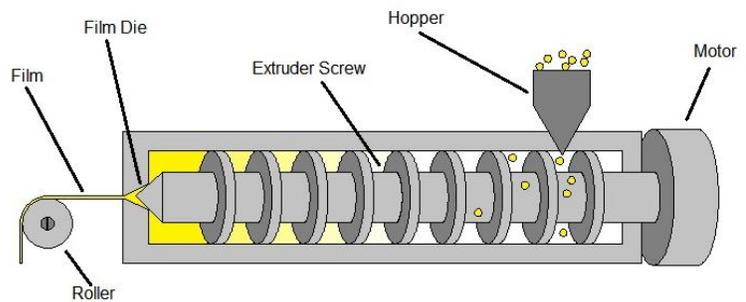


Figure 2. Screw-forced extrusion of dry feedstock as adapted from Particle Sciences.³

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.

INSTRUCTOR'S NOTE

In this experiment, no API is added to the dissolvable strips, as no drug modeling is being analyzed. If you wish to use an API, that is acceptable, and caffeine is recommended as an inexpensive API. In addition, it is possible to obtain food-grade versions of each of these chemicals. If possible, you may wish to do this in a food-safe area, and allow the students to try their strips once they are done the experiment. Lastly, the apparatus used in this experiment is a Teflon sheet that has metal thickness guides adhered to the surface. A model is shown below:



Figure 3. The sheet used to make dissolvable strips.

These thickness guides have dimensions as follows: Length of 31 cm, a height of 2.7 cm, and a thickness of 0.06 cm. The thickness guides were made from aluminum metal sheets. Note that the thickness guides are adhered to the surface. This was done through silicone adhesive caulk. The adhesive caulk takes time to dry (48-72 hours), so it is suggested to have these sheets prepared ahead of time for the experiment.

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)
- Sodium lauryl sulfate
- Citric acid (anhydrous)
- Glycerol
- Sucrose
- 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 guides
- Analytical scale
- Tubing and stoppers
- Blue food dye (Blue #40)

PROCEDURE

Table 1: Recipe for 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

* Instructor's Note: All chemicals can be obtained from Fisher Scientific. Peppermint oil can be found in specialty food stores or online.

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.
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.



Figure 4. Funnel and screen setup for pouring into flask.

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.
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 5 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.



Figure 5. The setup that should be used when using the vacuum.



Figure 6. Strips being cut

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.

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.

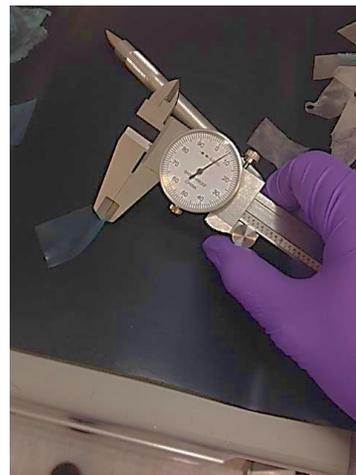


Figure 7. How to use the calipers to determine thickness

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.



Figure 8. Ensure a good fold by pinching the strip

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.

- 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.

Analysis

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

- Find the change in mass of the sample. Assume that the mass that evaporated was 100% water.
- 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

- 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?

INSTRUCTOR'S NOTE: For an in-class exercise, the averages from each group can be compiled on the board, and then used to create a control chart. Was the "process" of the student's lab activity in control or out of control? This can be used as an introduction to control charts, Western Electric rules, and Six-Sigma manufacturing.⁴

QUESTIONS

1. For the following APIs, research the drug's therapeutic use 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.

ANSWER KEY

The following data was used for the answer key:

Sample	Thickness (mm)	Folds endured	Surface pH
1	0.08	32	5.0
2	0.10	28	5.5
3	0.12	39	5.5
4	0.07	23	6.0
Average	0.09	30.5	5.5

The following data was for the petri dish portion of the experiment:

Initial weight of sample (g)	Final weight of sample (g)
20.65	0.335

Analysis

1. Average the results from each test.

ANS: See the above table.

2. Find the range of results for all tests. Was there significant variance in the data you collected?

ANS: "Significant" is used loosely here. This does not mean statistical significance, but the student should be able to relatively compare the ranges of the three tests against each other. For example, the ranges above are 0.05 mm, 16 folds, and 1 pH. A student should realize that the folding test generated inconsistent results.

3. Do you think that the average pH of the samples would be dangerous to ingest? What about the highest/lowest pH sample?

ANS: For this set of data, the strips would be safe to ingest. Humans can ingest foods such as lemon juice, which has a pH of 2. However, stomach discomfort or heartburn may result from ingesting something this acidic. A student thinking critically will realize the potential side effects.

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?

ANS: The strips in this mock scenario do not. The folding endurance study was found to be highly dependent on the humidity of the room. In very dry air, the strips will become brittle and shatter after 1 or 2 folds. In humid air, the strips can be folded a near-indefinite amount of times with little fatigue. Commercial strips are packaged in controlled climates so they always have ideal properties. Opening a commercial strip package and leaving the strip out to reach equilibrium with the surroundings should yield similar fold endurance to the experimental strips.

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?

ANS: Large variance means concentrated areas of API, and areas with little API. The highly-dosed strips could lead to an overdose, and the under-dosed strips could lead to diminished therapeutic value. Obviously, these strips would not be sold commercially. This question segues nicely into the importance of process control.

Moisture Content Analysis

1. Find the change in mass of the sample. Assume that the mass that evaporated was 100% water.

ANS: The $\Delta m = 20.315$ g.

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

ANS:

$$\%_{moisture} = \left[1 - \left(\frac{20.315 \text{ g}}{20.65 \text{ g}} \right) \right] * 100 = 1.63\%$$

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!

ANS:

$$Q = \frac{(20.95 \text{ g} - 0.635 \text{ g})}{1000 \text{ g/kg}} * 2260 \frac{\text{kJ}}{\text{kg}} = 45.91 \text{ kJ}$$

4. Where do you think this energy came from?

ANS: This energy was transferred into the liquid from the natural convection of the air.

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:
- Salbutamol

ANS: Because salbutamol is used for immediate relief of an asthma attack⁵, a fast dissolving hydrophilic polymer would be best suited for this application.

- Zolpidem tartrate

ANS: Zolpidem tartrate has only been shown to induce sleep, but not maintain it, unless it is in a controlled release form.⁶ Therefore, a hydrophobic polymer would be best suited for this application. The strip would most likely be applied sublingually or to the cheek.

- Ondansetron

ANS: Again, ondansetron is used primarily for immediate relief of nausea in chemotherapy patients.⁷ Therefore, a hydrophilic polymer would be best in this application.

d) Fentanyl citrate

ANS: Being a highly potent opioid analgesic that is used for moderate to severe pain relief,⁸ it can be found in both hydrophilic and hydrophobic polymer matrices. It may even be found in a layered strip that uses both types of polymer.

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.

ANS: *Make sure the ingredient is safe for consumption!*

- DK-12 (10%)
- Pectin, HPMC, hypromellose, etc. (40-50%)
- Glycerol, etc. (0-20%)
- Sucrose, dextrose, aspartame, etc. (3-6%)
- Ascorbic acid, malic acid, citric acid (2-6%)
- Peppermint oil, various esters, Red No.40, etc. (1-10%)

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.

ANS: Hot melt extrusion would be the best operation for creating the strips. They do not degrade from heat, and extrusion minimizes product lost. While a more expensive process, it is worth it if a contract has been made with a client.

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