Asthma Drug Delivery Laboratory Experiment
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Date of Experiment:

OBJECTIVES

- Students will learn about intrusive laboratory experiments
- Students will gain experience in reverse engineering strategies and project designs
- Students will conduct a basic quality control analysis operation

Figure 1: Diagram of the dry powder inhaler

INTRODUCTION

ADVAIR® is a dry powder inhaler prescribed to patients with asthma and chronic obstructive pulmonary disease that uses two active pharmaceutical ingredients. Fluticasone propionate, one of the two, is a corticosteroid, which is used to reduce the inflammation of the lungs. Salmeterol xinofoate, the second, is a bronchodilator, which relaxes the muscles in the airways to help improve breathing.[1]

ADVAIR® is not only used as an option for people with asthma, but also can be used as a maintenance treatment for chronic obstructive pulmonary disease.[1] Chronic obstructive pulmonary disease (COPD) is a disease that makes it difficult to breathe. It also takes the form of chronic bronchitis, causing a long-term cough with mucus, and emphysema, which destroys the lungs over time. Most sufferers of COPD have a combination of the two symptoms.[2] Asthma occurs when the airways of the lungs tighten and narrow, which leads to wheezing, shortness of breath, coughing, and a tightening in the chest.[3]

ADVAIR® comes in three varieties: ADVAIR DISKUS® 100/50; ADVAIR DISKUS® 250/50; ADVAIR DISKUS® 500/50. The three varieties of ADVAIR® have different amounts of fluticasone propionate in the powder. For example, in an ADVAIR DISKUS® 100/50, there will be 100 µg (micrograms) of fluticasone propionate and 50 µg of salmeterol. The 250/50 prescription of ADVAIR® is used for COPD treatment.[1]

In this lab, the teams will be examining an ADVAIR DISKUS®, and conduct an invasive reverse engineering experiment on the diskus. They will then compare the dry powder inhaler to two other types of inhaled medication transport systems; a nasal spray and a traditional metered dose inhaler. The goal is to see the difference in the transport process that each system uses, and to also see if there is any way to improve the design of the diskus. A quality control study on the packaging of powder in the ADVAIR DISKUS® is also provided. This will include an average and a standard deviation of the powder packages.

MATERIALS NEEDED

- ADVAIR DISKUS®
- Small flathead screwdriver
- Analytical scale (able to read at least 1/10,000g)
- Albuterol metered dose inhaler (or suitable substitute)
- Fluticasone propionate nasal spray (or suitable substitute)
- Narrow-headed spatula
- KimWipes
- Weigh boats

SAFETY CONSIDERATIONS

All students should know that laboratory gloves and eyewear must be worn at all times to protect from sharp edges and medicines.

PROCEDURE

PART I - REVERSE ENGINEERING

1. Open up the diskus box and remove the information packets. Make general observations on the diagrams and information included.
2. Remove the inhaler from the tinfoil package. Based on its outside appearance, how do you think it works? Sketch the diskus.
3. With the flathead screwdriver, proceed to remove the outer shell of the inhaler. Be careful to not break or shatter any plastic.

Figure 2: Removal of outer shell

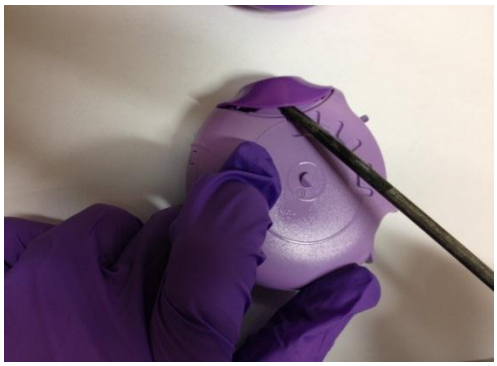

Figure 3: Proper removal of mouthpiece

4. Insert the screwdriver under the mouthpiece and use it as a lever to dislodge the mouthpiece.
5. Along the outside circumference of the diskus you will notice several slots and tabs that hold each half of the inhaler together. One by one, carefully depress each tab and pry the inhaler open.
6. This should expose the inside of the inhaler. Make observations on its appearance and the gears. Sketch the inside of the diskus.
7. Pull the lever down and reset it a few times. Discard the powder inside the blisters. Note how the gears move. Based on this, do you have any other ideas as to how the inhaler works?
8. Remove the foil strip. It will be stuck at one part after the foil has been split in half. Cut this section away to fully remove the rest of the foil strip.
9. The large white plastic mold that the foil fits into can be removed. Look for white tabs interlocking with the purple exterior shell by the mouthpiece. Push these tabs in to remove the white mold.
10. At this point, the gears should be fully exposed. Move the lever up and down. Was your hypothesis as to how the diskus worked correct? If not, what is actually happening?
11. Set the diskus aside and look at the aerosol inhaler and nasal spray. Compare and contrast these methods of asthma drug delivery to the diskus. (i.e. size, complexity, ergonomics, visual appeal, etc.)

Figure 4: Proper depression of the tabs

Figure 5: Inside the Diskus

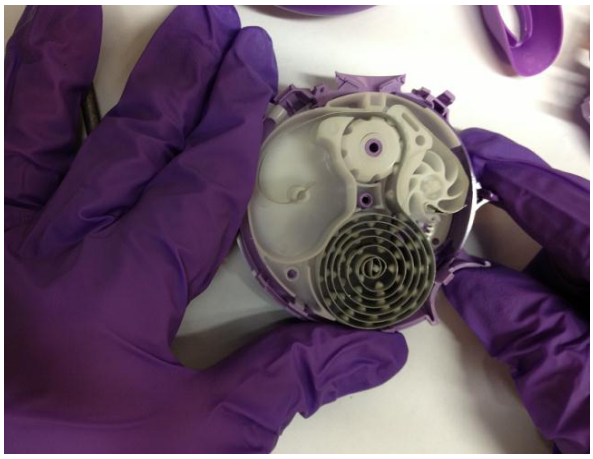

Figure 6: Operating the open diskus

Figure 7: Removal of the inner plastic layer

PART II - QUALITY CONTROL/MEASUREMENT

You may wish to place your findings in the table found in the RESULTS section of this experiment, but you should also record them in your laboratory notebook.

ADVAIR® Quality Control

1. Take the foil strip that was previously removed over to a weighing station that has a precise analytical scale.
2. Place a weigh boat on the scale and tare the instrument.
3. Remove the boat and pull back the foil strip exposing the powdered drug in one blister. Carefully empty its contents into the weigh boat using a spatula to scrape off any remaining powder.
4. Place the boat back on the scale and record the result. Tare the scale once again so the powder does not have to constantly be thrown out in between measurements. Repeat this nine more times so that the weights of ten blister packs have been recorded.
5. After all measurements have been taken, dispose of the boat and powder in the trash.
6. Reassemble the diskus and place it back in the box along with included pamphlets.

Figure 8: Proper removal of medicine from blister pack

Metered Dose Inhaler Quality Control (See Figure 9 for proper techniques for this section)

1. First, take a weight boat, and place it on the analytical scale.
2. Now, take a KimWipe and fold it until you have a small rectangle that will fit over the end of the metered dose inhaler. Place this folded KimWipe in the weigh boat, and then zero the analytical scale.
3. Take the metered dose inhaler, and shake well. Remove the KimWipe from the weigh boat, and place on the end of the inhaler where the propellant will exit.
4. With the KimWipe on the end of the inhaler, press down on the canister section of the inhaler, allowing the propellant to exit the inhaler and the KimWipe to capture it.
5. Quickly place the Kimwipe back on the weigh boat and take a mass measurement. (This may be difficult as the excipient, which acts as a propellant, will evaporate.) Take the measurement once the scale stays on the same value for at least a second.
6. Dispose of the KimWipe. Repeat steps 2 to 5 with fresh KimWipes until you have ten mass measurements.

Nasal Spray Quality Control (See Figure 9 for proper techniques for this section)

1. Once again, take a weight boat, and place it on the analytical scale.
2. Now, take a KimWipe and fold it. Place this folded KimWipe in the weigh boat so that it covers the bottom and most of the sides of the weigh boat. Once this is done, place the weigh boat back on the scale, and then zero the instrument.
3. Take another KimWipe or a paper towel and fold several times. Take the nasal spray and shake. Prime the device by spraying it a few times into this second wipe.

4. With the spray primed, take the weigh boat off the scale, and place on a slightly downward angle. Spray the propellant into the weigh boat once.
5. Place the weigh boat back on the scale and take a mass measurement.
6. Dispose of the KimWipe. Repeat steps 2 to 5 until you have ten mass measurements. (Step 3 may not need to be repeated every time, but once every 2 to 3 measurements.)

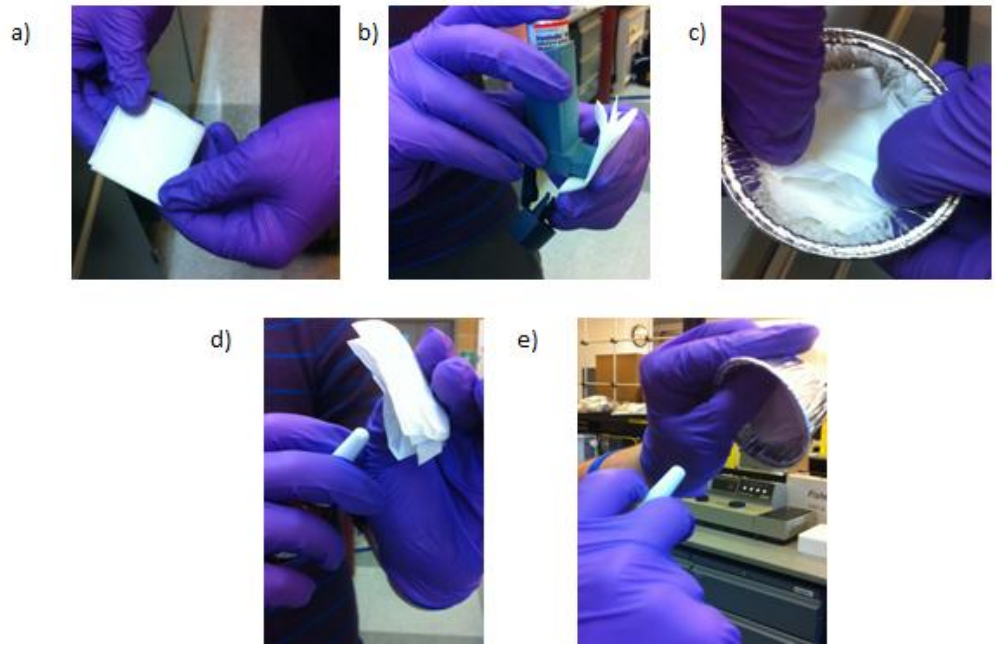

Figure 9: Different examples of the correct technique for metered dose inhaler (MDI) and nasal spray quality control measurements. a) The folding of the KimWipe before taking a mass sample of the MDI. b) The MDI cartridge being pushed down so that the medicine will be ejected into the KimWipe, and a mass measurement taken. c) The lining of a KimWipe on the bottom of a weigh boat far nasal spray mass measurements. d) Priming the nasal spray apparatus before taking a mass measurement. e) Taking a mass measurement using the nasal spray.

RESULTS

Make sure that the students record all results in a lab notebook, and that all members of the teams receive the data. These results can be placed in the table below and turned in along with solutions to the questions below. Questions were also asked throughout the procedure, and should be answered as well.

Table 1. Empty data table for collecting data in the Asthma Drug Delivery laboratory experiment

Diskhaler Trial	Mass (g)	MDI Trial	Mass (g)	Nasal Spray Trial	Mass (g)
1		1		1	
2		2		2	
3		3		3	
4		4		4	
5		5		5	
6		6		6	
7		7		7	
8		8		8	
9		9		9	
10		10		10	
Average					
Std. Dev.					

QUESTIONS

1. Compare and contrast the different styles of drug delivery that you examined in part I. Which of these systems did you think had the most appeal? Which do you think will work the best?

2. When comparing the MDI and the nasal spray, which of the two has a higher standard deviation? Compare all three standard deviations. Determine the highest and the lowest standard deviation. Explain what these results imply about the quality control measures of the three devices.

3. What were some sources of error in part II? How do you think you could fix some of these problems?

4. Based on the average weight of the blisters, what percentage of the powder are active pharmaceutical ingredients (API's) and what percentage is inactive? Assume that the amount of active ingredient from each sample is equal to the amount stated in the prescription dosage.

   The formula for finding the percentage of inactive ingredients is as follows:

$$\%_{Inactive} = \left(\frac{M_{total}^{avg} - \sum M_{API}}{M_{total}^{avg}}\right) x\ 100 \quad (1)$$

M_{API} *can be found on the package. Watch the units*!

   From this, find the percentage of active ingredients.

5. Do you think that the assumption made for problem 4 was a valid assumption to make? Why or why not?

6. The Advair dry powder inhaler, as described in the introduction section, contains two active ingredients, fluticasone propionate and salmeterol powder. There is one other ingredient listed on the label, lactose.
    a. What is lactose? Where else is lactose commonly found?
    b. Why would lactose be used in the inhaler? What type of excipient should it be considered?
    c. What are some negatives of using lactose?

    Be sure to site all references.

7. All metered dose inhalers (MDIs) need a propellant. A propellant makes up almost 99% of the dose of an inhaler. The propellant must have specific properties. Some of these include the boiling point, solubility of the API, toxicity and others. The API is suspended in the propellant and when the medication is dispensed the propellant creates an aerosol cloud, that the medication can be inhaled by the patient.[4]
    a. What is a CFC?
    b. Why are CFCs no longer used as propellants in inhalers?
    c. What type of propellant is used in the Ventolin inhaler? Which type of propellant did it replace?
    d. Compare the two propellants. Why do you think they replaced the propellant?

    Be sure to cite all references.

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4. Noakes, T. Medical aerosol propellants. The Journal of Fluorine Chemistry. Vol. 118, pp. 35-45. 2002.