Quantifying Disruption in Flow Through Dry Powder Insufflation (DPI) Device

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1 Background

Aspergillosis is a fungal disease that targets the respiratory system of birds and mammals, especially those whose environments are moist and warm. The fungal infection develops from numerous species of fungus, such as: *Aspergillus fumigatus, A. flavus, A niger, A nidulans, A. terreus*, to name a few, however, contraction of the infection is commonly from *A. fumigatus*. Due to its ubiquity, A. fumigatus is a common threat to wildlife-patients in wildlife rehabilitation centers [1]. To prevent wild-life patients from contracting the infection, they are typically treated with oral prophylactics. However, due to their compromised immune systems, —as a result of previous injury—vulnerability to contracting aspergillosis remains. In addition to the remaining chances of infection, these birds are handled for large periods of time—twice a day, every day—to be medicated, causing additional stress that further immunocompromises them. Alternate treatments include intravenous and dry powder delivery of the medication.

Dry powder delivery is a method employed to of deliver medication to the respiratory system of patients suffering from respiratory diseases. In this case, delivering powdered medication allows for both control of the distribution and less interaction between the wildlife patients and wildlife clinicians. Delivery of this dry powder is done through the development of a novel dry powder insufflation device. This treatment option relies on both macro- and micro-scale design. Microscale design focusses primarily on the inherent physicochemical properties of the aerosol. These properties are inherited from manufacturing practices that are used to develop the powder or simply from the chemical structure [2, 3]. These properties influence the flow, fluidization and dispersion of the powder, all of which factor into the success of the device [2]. Success of said device will be determined by the proper distribution and deposition of the medication into the pulmonary parenchyma. The desired distribution of the powdered medication has been unattainable with existing devices due to agglomeration or clumping of the powder and clogging of the device. Thus, we developed an experimental set up that will allow metrics to be defined to asses agglomeration or clumping of the dry powder and clogging of the device. This will be measure, eventually, using a differential pressure sensor and scanning electron microscopy in conjunction with laser diffraction. Quantifying this factor will allow us to better determine the effectiveness of future solutions, improve device design, and alter experimental protocols to optimize distribution.

2 Physicochemical Properties

As aforementioned, physicochemical properties influence the flow, fluidization and dispersion of the powdered medication. This influence is a result of the chemical structure of the medication and the physical aspects of the particle. Although there are plenty of factors and properties of the aerosol, our focus has been placed on the physicochemical properties that

influence agglomeration of the powder. Such properties include crystallinity, size and shape, and hygroscopicity.

2.1 Crystallinity

The crystallinity of a powder can be described by both the crystal system and crystal habit—morphology of the particle. The crystal system is defined by the interatomic or intermolecular spacings within each particle. These variations are typically seen in the bond lengths and angles between atoms or molecules [2]. If more than one crystal system exists within a single chemical entity, then this is referred to as a polymorph. As a result of the varying crystal structure, polymorphs display variances in particle shape, solubility, and hygroscopicity [2, 3]. These changes affect agglomeration due to changes in interactions such as: electrostatic charge, capillary forces and mechanical interlocking forces [2]. These various mechanical or chemical forces can cause interactions between the powdered molecules that hinder proper distribution.

2.2 Size and Shape

Particle size is an important feature of any particle that is intended to be aerosolized into the pulmonary system for therapeutic use. To reach the lower respiratory tract and optimize the deposition of the medication in the pulmonary parenchyma, aerosols normally have aerodynamic diameters that fall between 0.5 and 5μm [3, 4]. Bioavailability is another factor that influences the size of the aerosols. In order to improve bioavailability, particles typically have aerodynamic diameters > 3μm, once deposited into the lungs. Additionally, particle size influences the flow, fluidization, and dispersion of the powder. To fit within these acceptable constraints, powdered particles have aerodynamic diameters that are typically < 5μm [2, 4].

Particle shape also plays a role in the success of the powder successfully depositing into the lungs. The ideal shape of choice for powdered pharmaceuticals is a sphere. This can be achieved by manufacturing processes or by reducing the size of the particle to a point where the morphology may be considered negligible. Maintaining a spherical shape reduces mechanical interlocking forces, however, allowing rugose particles causes a reduction in the effect that interparticle forces have on the powder agglomerating [2]. Maintaining a balance of both rugosity and sphericity, or smoothness, is necessary since both can affect the fluidization of the particles [2].

2.3 Hygroscopicity

The hygroscopicity of the powdered medication is an important characteristic of the drug. It indicates its reaction to the surrounding temperature and humidity. Temperature and humidity play a role in moisture uptake which can result in local dissolution and recrystallization, thus

effecting the fluidization of the particles [2, 3]. This aggregation—through solid bridge formation— is induced by the strong relative forces that are confined between the particles [3]. Those forces generated are capillary forces which can affect the interactions within the molecules themselves and the surrounding enclosure of the loading capsule [2, 5]. Aside from the changes in adhesive and cohesive properties, hygroscopicity can substantially affect particle size. With an increase in relative humidity, there is an increase in relative growth of the particle [3]. In the case of aerosols, this can cause irreversible changes in agglomeration. The instability of the aerosol leads to the inability to generate particles that are respirable [3]. This can significantly affect the success of the device and the success of the treatment.

3 Particle Interactions and Forces

The above properties are all factors that influence the interactions that occur and cause agglomeration of the powder. These properties play a role in the relative strengths of the following interactions. Such interactions and forces are Van der Waals and mechanical interlocking interactions and electrostatic and capillary forces.

3.1 Van der Waals Interactions

Van der Waals interactions are one example of the molecular interactions influenced by the above properties. All other forms of agglomeration can be influenced by synthesis adjustment, except Van der Waals forces. These interactions are ubiquitous and are a result of the attraction between dipole-dipole, dipole-nonpolar, and nonpolar-nonpolar molecules [6, 7]. The strength of these interactions is proportional to the radius of the two spherical particles interacting with one another [7]. In addition to the size of the particle, the shape also alters the Van der Waals interactions. Surface contact can significantly be altered, either decreasing or increasing based on particle morphologies [4, 7]. Because, spherical provides the weakest interaction—due to the least amount of surface area to interact with—it is the most preferrable shape for this reason [7].

3.2 Mechanical Interlocking Interactions

Surface rugosity or particulate morphology offer chances for mechanical interlocking between aerosols that prevent particle dispersion. These interactions are related to the diameter of pores between particles and tension arising from hydrogen bonding [4]. The interlocking can cause physical interactions that prevent proper dispersal of the medication.

3.3 Electrostatic Forces

Electrostatic charging of particles is another factor associated with particle interactions that can cause agglomeration. These interactions are a result of a buildup of charge due to collisions

between particles and the surrounding surfaces, such as the surfaces encapsulating the medication within the DPI device [7]. The accumulation of these charges influences the cohesion of powders, resulting in a stronger interaction between each contact [7].

3.4 Capillary Forces

The structure of the molecule is another indicator of the molecule's possible interactions. Polymorphism has a large impact on hygroscopicity or the molecules likeliness to uptake moisture from the environment. This chemical property itself is heavily influenced by the relative temperature and humidity. It is this uptake of moisture that allows capillary forces to occur. These forces of attraction are further increased when relative humidity is higher than 65% [7]. These forces can further cause agglomeration of the powdered medication, influencing its dispersal. As the relative humidity increases, a layer of water molecules forms, increasing the cohesive and adhesive forces. These changes in moisture uptake can result in recrystallization, which can lead to irreversible aggregation through solid bridge formation. This can negatively affect the aerosol's ability to deposit into the lungs [4].

3.5 Summary

In summary, powder properties can influence the success of the device. Physicochemical properties and the environment can dictate the types of interactions that the powder will encounter. These interactions ultimately affect the powders likeliness to agglomerate, which in turn effects the distribution.

4 Problem Statement and Future Expectations

Lacking the necessary resources to fully quantify all these aspects of our powder, we have decided to focus on examining metrics of occurrences in our experimentation to have quantitative data that can influence design of the device, design of protocols, and evaluate future solutions.

4.1 Hypothesis

Developing a technique to quantify the clogging of the device and the clumping of the powder will allow us to better evaluate future solutions to reduce agglomeration, evaluate device design, and evaluate experimental protocol, ultimately improving our distribution.

4.2 Objective

The objective of our project is to develop a dry powder insufflation device that can distribute powdered liposomal amphotericin B, intratracheally and bilaterally, to the lung parenchyma of avian patients.

4.3 Success Criteria

Success will be achieving an equal dispersion and deposition of the selected medication into both lung compartments.

5 Technical Approach

To acquire the needed information, the following experimental approach has been designed. This technical approach will include the use of sensors being aggregated to the device to measure clogs in the device and the use of optical techniques to measure agglomeration of the particles. This section will discuss the equipment being used and a bill of materials in addition to the experimental approach that will be taken.

5.1 Budget and Selection of Sensors

To ensure the most appropriate and the most cost-effective sensors and microcontrollers were chosen, a number of sensors were compared against each other. Upon looking at the differences in capabilities and prices, the sensors desired for this project were chosen.

5.1.1 Differential Pressure Sensors

The differential pressure sensor is an essential piece of this project. This sensor is responsible for defining a clog in our system and so we need to choose the most appropriate sensor that will best quantify this metric. Below different differential sensors were compared against one another. The chosen sensor was the ASDXRRX005PGAA5 Honeywell differential pressure sensor based on cost, size, and voltage supply. The response time is slower by a few seconds, as shown in Table 1, but this is not a problem.

Pressure Sensors	ASCX Series Compatible	5 PSI-D-HGRADE-MINI	ASDXRRX005PGAA5
Metrics	Value	Value	Value

Cost	$90.55	$16.07	$78.06
Size (Volume mm)	27.4 x 12.2 x 27.9	10.16 x 22.1996 x 21.971	14.02 x 24.81 x 9.68
Accuracy	—	—	2%
Vs	4.5 to 5.5 Vdc	16 Vdc	5 Vdc
Response time	100us	2-4s	2-4s
Humidity Limits	0 to 95% RH	—	0 to 95% RH

Table 1. Demonstrates the selection criteria that went into selecting the pressure sensor for the project.

5.1.2 Humidity Sensor

The humidity sensor is another part of the project that will be important for characterizing the conditions that are appropriate for the device's use. Powder tends to be influenced by any humidity above 66%. The relative humidity experienced will be in the wild so the environment will have an influence and we need to be able to identify this influence. This influence could be interpreted as more consistent clumping than normal, as a result of the hygroscopicity of the molecule and the capillary forces involved. To document the chances of this occurring, we need a humidity sensor to provide us information on the surrounding environment in which it is being used. The ideal sensor for our use is the AHT20 humidity sensor which has a high detection of relative humidity, low cost and low error in accuracy.

Humidity Sensor	DHT11	AM2302	AM2311A	AHT20
Metrics	Value	Value	Value	Value
Cost	$5.00	$15.00	$4.99	$4.50
Vs	3.3-5.5 Vdc	3.3-5.5 Vdc	3.3-5.5 Vdc	2.0-5.5 Vdc
Humidity Accuracy	+/-5%RH	+/-2%RH	+/-3%RH	+/-2%RH
Humidity Range	5~95%RH	0~99.9%RH	0~99.9%RH	0~100%RH

Temperature range	-20~+60℃	-40~+80℃	-40~+80℃	-40~+85℃
Temperature accuracy	+/-2%	+/-0.5℃	+/-0.5℃	+/-0.3℃

Table 2. Demonstrates the selection criteria that went into selecting the humidity sensor for the project.

5.1.3 Microcontroller

The microcontroller is the power source of our devices and the tool that will be capturing the information sent by the sensors. This device needs to have an available voltage supply that will provide the right power to the previous components. With this in mind the most adequate device would be the Arduino Uno. This device is compact, has the correct voltage range, has a lower cost than other devices with the same voltage supply capabilities. For these reasons the Arduino Uno will be the microcontroller of our choice.

Microcontrollers	Arduino Uno	Arduino Mega	Arduino Nano 33 BLE Sense	Arduino Nano 33 BLE
Metrics	Value	Value	Value	Value
Cost	$23.00	$38.50	$29.50	$19.00
Length	68.6 mm	101.52 mm	45 mm	45 mm
Width	53.4 mm	53.3 mm	18 mm	18 mm
Vs	5V	5V	3.3V	3.3V
Clock Speed	16MHz	16MHz	64MHz	64MHz
Flash Memory	32KB	256KB	1MB	1MB
Weight	25g	37g	5g	5g
Analogue I/O	6	16	14	14

Table 3. Demonstrates the selection criteria that went into selecting the humidity sensor for the project.

5.1.4 Bill of Materials

Component	Vendor	Description	Catalog Number	Cost per Order	# Units per Order	# to Order	Total Cost
ASDXRRX 005PGAA5	Honeywell	Board Mount Pressure Sensors Differential 0 psi to 5.0 psi	ASDXRRX005P GAA5	$78.06	1	1	$78.06
Humidity Sensor	Adafruit	The AHT20 is a nice but inexpensive temperature and humidity sensor	4566	$4.50	1	1	$4.50
Arduino Uno	Arduino	14 digital input/output pins, 6 analog inputs, a 16 MHz ceramic resonator, a USB connection, a power jack, an ICSP header and a reset button	A000066	$23.00	1	1	$23.00
OLED Display	Adafruit	Monochrome 1.3" 128x64 OLED graphic display - STEMMA QT / Qwiic	938	$19.95	1	1	$19.95
						Sum Total	$125.51

Table 4. Demonstrates the sum total for the sensors and microcontrollers that will be purchased for this project

5.2 Experimental Set Up

5.2.1 Determining the Loading Capacity

The first experiment is intended to determine the loading capacity and efficiency the of dry powder liposomal amphotericin B (5 mg/mL; AmBisome, Astellas, Northbrook, IL) in the dry powder insufflation device. The first trial will require 20mg of the dry powder liposomal amphotericin B to be loaded into the loading capsule of the dry powder insufflation device. Before aerosolizing the medication, a small pouch will be placed on the outlet of the device to

capture the medication. The medication will then be aerosolized through the DPI device. The differential pressure sensor will monitor the change in pressure through the device's channel system from before the loading capsule to the outlet channel. The greater the value calculated the more disruption of flow is occurring in the system. Thus, the least difference in pressure calculated signifies optimal loading capacity. After each aerosolization, the captured medication will be noted, and efficiency will be calculated by dividing the amount of drug that made it into the pouch versus the drug that was loaded. The pressure difference read on the OLED display will be noted and averaged over 3 repetitions. In addition, to ensure similar conditions. The humidity of the present environment will also be noted for each trial. The following trials will increase the amount of powder by increments of 20mg till 100mg is reached, for a total of 5 trials for 3 repetitions each. The trial that clogged the least, as measure by the pressure differences, and had the greatest efficiency, will be the chosen as the loading capacity.

5.3 Determining the Agglomeration and Size Distribution

To quantitatively define agglomeration, medication will once again be aerosolized into a pouch. The aerosolized medication will then be observed under a scanning electron microscope to determine the size of the powder agglomerates. The process will be repeated for 10 trials, noting each agglomerate in each set of powder collected. The resulting data will be analyzed and trended alongside the relative humidity at the time of collection.

In addition to capturing the varying sizes of agglomerates found in our dispersal, the distribution of size will also be calculated. This will be done so using laser diffraction. The size distribution will be calculated following protocol from Miranda M.C. van Beers et al. [8] who used this technique to assess size and agglomeration of microparticles. The Particle size distributions were measured by using a Malvern Mastersizer 2000 laser diffraction instrument equipped with a Micro Precision Hydro 2000μP sample dispersion unit (Malvern Instruments). Three measurements will be performed to make this calculation [8].

6 Project Plan

6.1 Schedule

- Month 1:   Record loading, efficiency and pressure differences with ambient humidity
- Months 2-3:   Scan and accumulate data on agglomerates and particle size distribution
- Month 4:   Move on to next phase of experimentation

6.3 Facilities

The DPI device has been manufactured using machining tools located at the Engineering Student Design Center at the University of California, Davis. Testing protocols will be completed at the Genome and Biomedical Sciences facility at the University of California, Davis.

7 Conclusion

Conducting this experiment will allow for a more quantitative approach towards determining the most efficient loading capacity. "Efficiency" is defined as causing the least amount of clogging and the most amount of medication being delivered. Our lab currently lacks the necessary equipment to characterize or quantify parameters of our powdered medication that cause agglomeration. Thus, indirectly quantifying the "clogging" through pressure differences at different points of the channel that is aerosolized and quantifying the agglomeration and size distribution will provide a deeper understanding of our device and the powder's agglomeration based on varying the loading size. This will allow us to avoid previous efforts that required visual inspection to determine clogs in the device or clumping of the powder. This previously used method lacks depth and has too much variability. Thus, we hypothesize that by adding these metrics to our data collection will enable us to better determine future solutions, device design, and protocol.

References

[1] Aspergillosis, The Department of Natural Resources (2020).

[2] C. A. Dunber, A. J. Hickey, and P. Holzner, KONA Powder and Particle Journal 16, 7 (1998).

[3] M. J. Telko and A. J. Hickey, Respiratory care 50, 1209 (2005).

[4] G. Pilcer and K. Amighi, International journal of pharmaceutics 392, 1 (2010).

[5] T. M. Crowder, J. A. Rosati, J. D. Schroeter, A. J. Hickey, and T. B. Martonen, Pharmaceutical research 19, 239 (2002).

[6] M. Trunec and K. Maca, Advanced Ceramics for Dentistry, pp. 123–150, (2014).

[7] H. Kinnunen, Ph.D. thesis, University of Bath (2012).

[8] M. M. V. Beers, C. Slooten, J. Meulenaar, A. S. Sediq, R. Verrijk, and W. Jiskoot, European Journal of Pharmaceutics and Biopharmaceutics, vol. 117, pp. 91–104, (2017).a