

 Faculty Of Pharmacy, Nursing And Health Professions

Program Of Doctor Of Pharmacy

Industrial Pharmacy PHAR 411

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**Sieve analysis, density tests, and angle of repose**

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**Experiment No**. : 3+4+5

**Objectives**:

The aim of this experiment was to test the granules for several properties according to the guidelines. These tests are sieve analysis which was made to determine powder size, angle of repose to determine flowability property and bulk and tapped densities.

**Abstract**:

The following experiments are part of in process quality control tests, which were done to determine any problems that might occur in future processing of tablet. These tests are angle of repose to see the flowability characteristic of the powder, sieve analysis to classify powder and granules by particle size distribution and bulk and tapped densities to calculate Carr's index. The angle of repose was found to be ……., the distribution of powders displayed ……. Of granules with a size between …….. and Carr's index being ……

**Introduction**:

Development of a drug product is a long process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. To further enhance the effectiveness and safety of the drug product after approval, many regulatory agencies such as the United States Food and Drug Administration (FDA) also require that the drug product be tested for its identity, strength, quality, purity and stability before it can be released for use. IPQC stands for in process quality control. These are checks that are carried out before the manufacturing process is completed. Granulations tests are small part of those tests, among the huge number of tests on them there is a particle size test, bulk density and flowability test.

One of the most important things to consider when making tablets is uniformity of particle size. A good powder formulation has a uniform particle size distribution. If the particle size distribution is not uniform, the powder can segregate according to the different particle sizes, which may result in inaccurate dosing or inconsistent performance. A uniform particle size distribution insures uniform dissolution rate if the powder is to dissolve, a uniform sedimentation rate if the powder is used in a suspension, and minimizes stratification when powders are stored or transported. That is why sieve analysis is performed, as while vibrating, granules are separated through sieves with different pores sizes by their size.

Another important factor to consider is flowability of the granules, this will affect the ability to transfer materials, the worse the flowability, the more material will be lost and the process will become harder. The angle of repose is a characteristic related to interparticulate friction or resistant to movement between particles, and it is done by pouring amount of material in a funnel on a flat surface.

Another important factor to be tested prior to tablet production is compressibility of a powder mixture. The bulk density is calculated by dividing the mass of the powder by the bulk volume. The bulk volume of a powder includes the volume occupied by the particles as well as the volume occupied by the intraparticular and interparticular voids. It can be determined easily using a graduated cylinder and a balance.

The tapped density of a powder can be calculated by dividing the mass to the tapped volume. The tapped volume is the volume the powder occupies after being tapping the container it is in as to reduce the interparticular spaces as much as possible by arranging the particles so. This tapping is done using a device called a tapped density tester, which taps a graduated cylinder a number of times, until the volume of the powder decreases no longer, meaning the spaces between particles were reduced as much as possible. Using the bulk density and tapped density of a powder, one can determine the compressibility index, or Carr's index, which gives an idea about the flowability and compressibility of the powder or granules.

**Experimental:**

* **Procedure:**

**Exp3: sieve analysis;**

First, the weight of each empty sieve and the collection pan were recorded.

Then the sieves were arranged in a sequential nest: smallest mesh number at the top, largest mesh number at the bottom. The collection pan was added to the bottom of the nest. (We did not use the sieve with a mesh number of 125).

100 gm of the powder was weighted and added to the top sieve, and was covered.

Then the nest of sieves were agitated for 10 min at speed of 50.

Each sieve was carefully removed from the nest without losing material.

And the sieve was reweighted and the weight of material on each sieve was determined.

Lastly, the weight of material in the collecting pan was determined in a similar manner.

**Exp 4: BULK+TAB+TRUE density;**

**Bulk density:**

A graduated cylinder was weighed while empty, then using a funnel, a quantity of granules was filled into the graduated cylinder without any type of tapping. The weight of the cylinder and the granules recoded and the weight of the granules alone was then calculated to be 50.09 g

The volume of the granules was then observed (87 ml), the bulk density was then calculated by dividing the mass by the volume (0.575 g/ml)

**Tab density**:

The filled cylinder was tapped 100 taps for three times using an automated tap density apparatus. The volumes occupied by the sample was recorded after each 100 tap and the repetitions of the tapping stopped when the readings of the volume appeared to be steady and no longer decreasing (72 ml)

The tap density was calculated by dividing the weight of the sample by the volume at which the readings was steady (50.09/72=0.695 g/ml)

**True density**:

A quantity of granules was weighted and was added gradually using afunnel to a graduated cylinder after filling it with a known volume of an inert liquid (paraffin oil), then the difference in volume was observed and the true density was calculated by dividing the weight of the sample by the difference in volume.

**Exp 5: ANGLE OF REPOSE;**

A funnel was fixed to the stand using a clamp and a piece of paper was placed under the funnel to help with recording the diameter of the formed circle.

4 trials was done, the first one was to adjust the funnel height and make sure that the powder is flowing through the hole of the funnel effectively.

The height was adjusted to be 5 cm from the bottom of the funnel to the center of the paper.

The granules sample was poured into the funnel while closing the bottom opening , the funnel was tapped to ensure that granules flow through the hole.

The bottom opening of the funnel was opened, and the granules was allowed to flow to the paper.

The base of the formed circle was marked to measure the diameter, and the height of the pile was measured using a ruler.

The granules was removed and the diameter was measured also using a ruler.

The process was repeated 3 times and the average of the diameter and the height was calculated.

Then, by using the tan-1 of the height divided by diameter, the angle was calculated.

* **Ingredients**
1. the granules that was formed during the previous experiment
2. paraffin oil: was used as an inert liquid to measure the true density

Quantity: 55 ml

* **equipment:** beaker, graduated cylinder, funnel, ruler.
* **Machine / Instruments**

| **Machine Name** | **Model and/or S/N** | **Function** | **Parameters**  |
| --- | --- | --- | --- |
| Precision Balance KERN kb2000-2N | W1206981 | It is needed to obtain an accurate mass of each ingredient being used. |  |
| Tap Density Tester | AT 2000 | Diminish spaces between particles to help determine the tapped volume and density  | Number of taps Initial volume and mass  |
| Angle of repose funnel | ------ | Used in determining the angle of repose and the flowability of the granules. The granules are inserted into the funnel and allowed to be dropped after opening the bottom opening and forming a cone like shape.  |  |
| Retsch Sieve Shaker | AS200 | Particle Size Analysis (Sieve Analysis) works by the principle of vibration | Vibration speed  |

**Discussion:**

Sieving results:

| **Opening size (μm)** | **Sieve weight(g) empty**  | **Material and sieve weight(g)** |  **Weight retained on each sieve (g)** | **% weight retained on each sieve**  | **Cumulative % of sample retained**  |
| --- | --- | --- | --- | --- | --- |
| 1.7 mm | 379.38 g | 380.08 g | 0.7 g | 0.7% | 99.99% |
| 850 μm | 340.2 g | 365.73 g | 25.53 g | 25.57% | 99.29% |
| 600 μm | 290.0 g | 307.61 g | 17.61 g  | 17.64% | 73.72% |
| 300 μm | 269.1 g | 293.00 g | 23.9 g | 23.94% | 56.08% |
| 250 μm | 249.8 g | 254.2 g | 4.4 g | 4.41% | 32.14 % |
| 150 μm | 244.9 g | 250.2 g | 5.3 g | 5.31% | 27.73% |
| 90 μm | 238.8 g | 243.3 g | 4.5 g | 4.51% | 22.42% |
| 25 μm | 277.8 g | 292.8 g | 15 g | 15% | 17.91% |
| Pan  | 348.8 g  | 351.7 g | 2.9 g  | 2.91% | 2.91% |
| Total  |  |  | 99.84 g | 99.99 |  |

Table 1: Sieving results



Figure 1: Cumulative % retained on each sieve VS sieve opening size



Figure 2: mass retained on the sieve VS opening size VS cumulate weight retained on each sieve

The original weight of the sample was 100.00 g, there was a little bit lose probably during the weighing step.

Calculations:

* Cumulative %retained= %Weight retained on sieve 1 + % weight retained on sieve 2

 Sieves (600 μm – 300 μm) = 17.64% + 23.94% = 67.85%%

* % Finer= 100% - Cumulative % retained

 Sieve 600 μm: 100% - 43.91% = 56.09%

* Loss/Gain during sieving= (Initial sample weight – total sample weight after sieving)\*100%

= (100-99.84)\*100%

= 0.16 %

* Mean pore opening= (Opening size of mesh 1+ opening size of mesh 2)/2

= (0.85 + 1.7mm) /2= 1.275mm

* Weight retained on each sieve= (weight of material and sieve -weight of sieve)

For example, 1.7mm sieve (380.08-379.38g)

= 0.7g

* % weight retained on each sieve= weight of material on each sieve/ total weight of sample \* 100%

0.7/100 \*100%= 0.7%

Sieving was done to separate granules according to their size, and to know the size distribution which is very important in the process of compression. A number of sieves are stacked above each other, from the smallest mesh number (with the biggest holes) being on top to the biggest mesh (smallest holes) being at the bottom with a closed pan at the end. As the vibration starts, the granules start to pass through sieves until the granule is big for the sieve so they stop by it. This test will give an idea where the majority of the granules are located in relation to their particle size.

According to our results that are shown in figure 1, there was a variation in granules size. The largest percent of granules were in the sieves of opening from 850-300 micrometers, another high portion is presented in sieve with opening size 25 micrometer which may be because of using the mesh size 20 while screening in the wet granulator. So, the distribution wasn’t ideal because to be ideal there must be a peak in the middle which is somehow appeared in our results ( 23.9 g on opening size 300 mcm) with a distribution of articles to the left and right of it( in our results there is a high peak on the opening size 850 mcm) which means that there is a large quantity with large size according to the rest of granules.

 Bulk density was measured for the paracetamol granules prepared and it was 0.58g/ml, when the initial volume was 87ml. Tap density was measured 3 times and the least volume was taken and it was 72ml, tap density= 0.70g/ml. As we noticed that tap density is higher than bulk density, and this is because there are air voids between the granules without tapping so the volume would be bigger and the density lower compared to when the granules are tapped, as the volume decreased because of getting rid of the voids (spaces between granules) density increased. True density was also measured by adding the 49.44g of the granules to a 55ml paraffin oil with continuous stirring to avoid sticking of granules to each other, and the final volume changed from 55ml to 90ml. But there was a mistake here than a lot of granules was added, 25g would have been enough to measure true density in 55ml oil to avoid caking of granules, also final volume should be recorded immediately after finishing the addition of all granules to avoid dissolving any of the granules. Paraffin oil was used in this measurement because it’s inert (does not react or dissolve the API used).

| Bulk density | Tap density | True density |
| --- | --- | --- |
| Weight of powder= weight of cylinder+powder- weight cylinder= 195.04-144.95= 50.09g | Weight of powder= 50.09g | Weight of powder= 49.44g |
| Volume of untapped powder= 87ml | Volume of tapped powder= 72ml | Volume of oil= 55mlVolume of oil+granules= 90mlDisplaced volume= volume of oil+granules – volume of oil= 90ml-55ml= 35ml |
| Density= mass/volume= 50.09g/87ml= 0.58g/ml | Tap density= 50.09/72ml= 0.7g/ml | True density= weight of granules/ volume of (oil+granules)-volume of oil= 49.44g/35ml= 1.4g/ml |

Table 2: Density calculations

Angle of repose was measured to determine the granules flowability, flowability is a very important factor in compression, in order to fill the dies completely and avoid any sticking of the powder to the machine. The height and base of the granules pile was measured 3 times and the average was taken to calculate the angle of repose.

| Trial number | Height  | 0.5Base  | Average Height/0.5base | $θ$= Tan-1 (height/0.5base)  |
| --- | --- | --- | --- | --- |
| Trial 1 | 2.7cm | 5.2cm | 0.498 | 26.5º |
| Trial 2 | 2.6cm | 5cm |
| Trial 3 | 2.3cm | 5.05cm |
| Average | 2.53cm | 5.083cm |

Table 3: Angle of repose calculations

This angle indicates that the granules have excellent flowability, so there’s no need to add

any more lubricant to facilitate the compression process.

**Conclusion:**

Sieving analysis is a very important test for granules as it indicates whether the size distribution of granules is wide or narrow, if it was wide this would cause segregation and cause variations in tablets and affect compression process. The size distribution of the granules prepared was narrow in the coarse range (1062.5µm). Also, bulk density , affects compression by affecting flowability and increasing hardness of tablets as the density of granules increases. Angle of repose indicates whether the granules have bad or good flowability, which further affects compression process, better flowability prevents sticking of granules in machine and helps in complete filling of dies as desired.

**Questions:**

**Exp 3: sieving analysis**

1. **Describe as many limitations as you can think of for particle size determination by sieving. What particles could not be sized by sieving?**

It’s not a very precise size determination method, as it gives us the range of particle size and not the exact size. Also, sticky powders or very coarse and very fine powders size can’t be determined by sieving.

1. **If a large percentage of powder were deposited on the top sieve or the bottom pan, is the particle size you determined representative of the powder sample. Justify your answer.**

No, it’s not. The powder particles may be even bigger than the biggest pore sized sieve, or smaller than the smallest size sieve. So, we need to use a bigger pore size to get a whole size distribution and not an accumulation of powder in the biggest sized pore sieve or a smaller pore size sieve so it does not accumulate in the pan to determine the accurate size of the powder particles.

1. **Would you expect to get the same mean-sieved diameter if you performed the experiment described above but made the following changes? Justify your answer.**

No, I would get different results because the powder particles may have even a bigger size than the biggest sieve pore size used at first so the diameter would be bigger and the opposite if the powder was all in the pan and we used a smaller sized sieve the powder particles may have a smaller diameter when we use a smaller sieve.

1. **What are the other methods that can be used to identify the size of particle rather than sieving process?**
2. Microscopy
3. Sedimentation Technique
4. Electrical Sensing Zone Method
5. Laser Diffraction Method
6. Surface Area Measurement Technique
7. **What is the importance of size particles analysis in formulation?**

Particle size analysis will determine particle size distribution, and particle size distribution is important to estimate the amount of segregation that may occur with a mixture. The less variation in particle size, the less segregation will occur during tableting and uniformly dosed tablets will be formed.

**Exp 4: bulk and tapped density**

1. **A granulation has been prepared with a bulk density of 0.73 g/ml. If the granulation is tableted with 10mm diameter, flat faced tooling (circular), and the lower punch drops to a depth of 8 mm in the die cavity, what will be the theoretical weight of the resulting tablet?**

Bulk density= 0.73 g/ml

 Diameter= 1 cm

 Height= 0.8 cm

 **Volume of the tablet** = cylinder volume= πr2 h

 = 3.14\* (0.5cm)2 \* 0.8 cm = 0.628 cm3= 0.628 ml

 **Theoretical weight** = Volume of the Tablet \* Density

 = 0.628 \* 0.73 = 0.458 g

1. **Give reasons why the actual tablets weight might deviate from the theoretical weight.**

Due to the loss of granules in different steps in the manufacturing processes like dusting of powder when pouring it or while mixing, and sticking of the granules and powder to the tableting machine.

**Experiment 5: angle of repose**

1. **What factors will influence angle of repose for the materials?**
2. Particle size, the finer the granules, the smaller the angle of repose
3. Moisture content, the higher the moisture content, the larger the angle of repose.
4. Friction and interparticular forces between particles
5. **What other method can be used to calculate the angle of repose for the materials?**
6. Tilling box method: this method is used for fine-grained, non-cohesive materials with particle size less than 10 mm, The powder material is put in a box and the box is then slowly tilted until the powder begins to slide in bulk and then the angle is measured.
7. Revolving cylinder method, The material is placed within a cylinder with at least one transparent face. The cylinder is rotated at a fixed speed and the observer watches the material moving within the rotating cylinder [1]

**References**:

1. Breslin, A. (2017, April 24). Methods of Determining the Angle of Repose. Retrieved October 18, 2018, from https://sciencing.com/methodsdetermining-angle-repose-8380160.html
2. Shtaya, H., & Samaro, A. Industrial Pharmacy Lab. Manual. Birzeit: Faculty of Pharmacy, Nursing and Health Professions .