

Faculty Of Pharmacy, Nursing And Health Professions

Program Of Doctor Of Pharmacy

Industrial Pharmacy PHAR 411

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**Granulation and Mixing**

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**Experiment No**. : 1 + 2

**Objectives**: the aim of this experiment was to learn how to weigh the active pharmaceutical ingredient (API) and excipients needed to make a paracetamol tablet, and to do wet granulation method using a slow shear mixer. Also to learn what each excipient is used for, and what problems can face us during manufacturing of a tablet and how to solve or avoid them during manufacture.

**Abstract**: Paracetamol tablets contain many excipients including; the acetaminophen itself, lactose, starch, mannitol, PVP K30, avicel PH101,sodium croscarmellose, and magnesium stearate. Each of these materials was weighed carefully and then they were mixed together using a low shear mixer, the PVP was used as a binder and it was dissolved in water using a homogenizer,wet granulation was performed in a slow shear mixer and then magnesium stearate was added and mixed using a cube mixer. The granules obtained were small and spherical, they were screened at a mesh #10, and sieving results were that most of the granules had a 1275micrometer diameter which is considered very coarse granules. The moisture test was done before adding PVP and after drying it was 4.26% and 5.12% respectively.

**Introduction**:

 Oral dosage forms excluding orodispersable tablets are usually preferred by patients as they don’t require injections, feeling pain, visiting hospitals and they don’t increase risk of infections compared to parentral dosage form so they are more convenient. And compared to oral liquid dosage forms like solutions or suspensions there’s no need for taste masking.

 Paracetamol tablets are used very commonly as an analgesic for mild to moderate pain, also as an anti-pyretic. When people suffer from a headache or a flu, they usually prefer taking paracetamol as it’s considered safer and has milder side effects compared to other analgsics like ibuprofen or tramadol. The main techniques used in this experiment were wet granulation by low shear mixing, cube mixing and sieving to determine the size distribution of the granules. Wet granulation is usually the last choice in tablet manufacturing, direct compression is usually preferred but some API’s have bad compressibility so dry granulation should be performed instead, but if the material has no inherent cohesive properties it would be difficult to accomplish dry granulation, so wet granultion is performed, but in this technqiue the matrial should be heat and moosture stable to avoid its degradation during adding the liquid binder or the dryig process. Paracetamol can be manufactured by all the methods mentioned previously, but wet granulation was performed as it includes more steps, for learning purposes. In addition to this, granulation has many advantages as it decreases dust production and increases compressibility of the powder.

 The API and each excipient were weighed carefully, acetaminophen (50mg per tablet), lactose, starch and avicel were all weighed and mixed together. Then PVP was dissolved in water then it was dissolved using a homoginizer, and added to the 4 materials in a low shear mixer, then the other excipients were added excluding magnesium stearate which was added in the last step of addition, due its hydrophobic chracter and its function as a lubricant which may decrease disintegration, dissolution and bioavailability if it was added earlier and mixed for a longer time. Then sieve analyis was performed to determine the size distribution of the granules prepared, which has a great effect on compression, if it was wide it can cause segregation and tablet variation during compression.

**Experimental**

1. Procedure
2. **Granulation (Exp 1)**

1-The actual quantity of each excipient for the experiment was weighted

2-The following ingredient were mixed using plastic sack (Acetaminophen, Starch, Lactose, Mannitol powder, one part of Avicel PH101)

3-The mixture was transferred to the bowl and mixed for 15 min at impeller speeds.

4-A sample was taken to measure moisture contents (1.5 gr).

5-The granulating solution was prepared by adding the PVP K30 to purified water (28% w/w PVP K30 in P.W) and it was mixed until the PVP K30 dissolved. (Granulating liquid)

6-The liquid binder (Granulating liquid) was added to the powder by pouring it via a port in the lid of the granulator, while impeller was running at a low speed.

7-Once a satisfactory granule has been produced; the granular product was discharged, passing through a wire mesh #10.

8-The granules were transferred on stainless steel tray to the oven and were dried for one week.

9-A sample was taken to measure moisture contents (Loss on Drying)

1. **Mixing (Exp 2)**

1-The granules from Exp 1 was screened from sieve Mesh #16 for 2 min at speed of 70

 2-The second part of Avecil PH101 and Actasol were added.

3-The mixture was added to a plastic bag and shaken for 10 min.

4-Magnesium Stearate was added to the plastic bag and shaken for 2 min, after that the mixture was transferred to cube mixer and mixed for 1 min at speed 150 rpm.

5- A sample of (150 gr) was taken and sieve analysis test was done on 100 gr.

1. **Sieve Analysis Test (Exp 3)**

1-The weight of each empty sieve and the collection pan were recorded.

2-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)

3-100 gm of the powder was weighted and added to the top sieve, and was covered.

4-The nest of sieves were agitated for 10 min at speed of 50.

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

6-Each sieve was reweighted and the weight of material on each sieve was determined.

7-The weight of material in the collecting pan was determined in a similar manner.

1. Ingredients

1. Acetaminophen (assay 98.5%):-

 • Quantity: 50mg per tablet, 50g per batch (1000 tablets).

 • Function: API, analgesic and antipyretic.

2. Starch:-

 • Quantity: 186mg per tablet, 186g per batch.

 • Function: Diluent / Disintegrant.

3. Lactose:-

 • Quantity: 160mg per tablet, 160g per batch.

 • Function: Diluent.

 • Individuals who are sensitive to lactose should be warned of tablets containing lactose.

4. D-Mannitol (C6H22O11):-

 • Quantity: 120mg per tablet, 120g per batch.

 • Function: Diluent.

5. Avicel PH101 (Microcrystalline Cellulose):-

 • Quantity: 72mg per tablet, 72g per batch (in two parts, one intragranular, and one extragranular).

 • Function: Disintegrant.

6. PolyVinylPyrrolidone (Povidone or PVP) K30:-

 • Quantity: 64mg per tablet, 64g per batch.

 • Function: Binder.

 • PVP’s K number, specified in the material used in this experiment as 30, refers to its molecular weight.

7. Magnesium Stearate:-

 • Quantity: 12mg per tablet, 12g per batch.

 • Function: Lubricant.

| **Ingredients** | **Composition PT01** | **Quantity per Tablet (mg)** | **Quantity per Batch (g)** | **Function** |
| --- | --- | --- | --- | --- |
| **Acetaminophen (Paracetamol)** | 6.25% | 50 | 50 | Active IngredientAnalgesic, antipyretic |
| **Starch** | 23.25% | 186 | 186 | Diluent, Disintegrant |
| **Lactose** | 20% | 160 | 160 | Diluent. |
| **Mannitol Powder** | 15% | 120 | 120 | Diluent |
| **Avicel PH101** | 9% | 72 | 72 | Wet granulation Binder, Disintegrant. |
| **PVP K30** | 8% | 64 | 64 | Binder for Granulation |
| **Avicel PH101** | 9% | 72 | 72 | Direct compression binder |
| **Croscarmellose Sodium (Ac-Di-Sol)** | 8% | 64 | 64 | Superdisintegrant |
| **Magnesium Stearate** | 1.5% | 12 | 12 | Lubricant |
| **Total Weight** | 100% | 800 mg | 800 g |  |

1. **Machines**

| **Machine Name** | **Model and/or S/N** | **Function** |
| --- | --- | --- |
| Precision Balance KERN kb2000-2N | W1206981 | It is needed to obtain an accurate mass of each ingredient being used. |
| Pharmatest wet granulator | WG-30S/N10-00642 | Wet granulator, breaks wet agglomerates formed in mixer to granules |
| Homogenizer Mixer | L5M-A | It is used to create a homogenous granulating liquid mixture of PVP and water |
| Moisture Analyzer | MOA011 | It slowly dry a sample of material and determining the amount of liquid or moisture in it**.** |
| Cubic Mixer | S/N 10.00499 | It is used to mix the superdisintegrant and direct compression binder at a slow and controlled rate to ensure uniform distribution between the granules. |
| Retsch Sieve Shaker | AS200 | Particle Size Analysis (Sieve Analysis) works by the principle of vibration |

**Results and discussion:**

| **Ingredient**  | **Theoretical quantity of material(g)**  | **Actual quantity of material (g)** |
| --- | --- | --- |
| Acetaminophen  | 51 g | 51.02 g |
| Starch | 186 g | 186.04 g |
| Lactose | 160 g | 160.05 g |
| Mannitol powder | 120 g | 120.02 g  |
| Avicel PH101 | 72 g | 72.01 g |
| Avicel PH101 | 72 g | 72.03 g |
| Actasol  | 64 g | 64.04 g |
| PVP K30 | 64 g | 64.02 g |
| Magnesium stearate  | 12 g | 12.01 g |

Results of moisture content test?

Moisture content of powder before granulation=4.26%

Moisture content of granules after drying=5.12%

Which is a good percentage, because the granules after drying in the oven remained

Outside for 3 days and that caused moisture absorption from the air.

Mixing:

After weighting the materials, we kept them for a week in the plastic bags. Then, the first five materials (acetaminophen, starch, lactose, mannitol powder and avicel PH101) were added to the low shear mixer and mixed for 15 minutes before adding the granulating liquid, the mixer was on its slowest speed while the mixing and the granulating steps to avoid dustiness. Also, to minimize the material lost, releasing of powder from a low height to avoid dustiness was required. it was necessary to stop the mixer every 5 min to remove and mix the powder that have adhered to the bowel sides because of its low flowability, it is so important to do this step since the PVP may also adhere to the sides and results in over adding of the granulating liquid and very hard granules may result.

Granulation:

In the step of granulating the powder using the granulating liquid PVP and a low shear mixer, all of the granulating liquid was used (64g PVP+164 ml water) although it appeared a little bit too much at the beginning, it showed good results after drying. We determined the end point by obtaining a small quantity of the granules and apply a small amount of pressure on them and see if they stuck together.

Screening:

The granules resulted were passed through a mesh #10 at speed 70 for nearly 3 minutes in the wet granulator, which produced a uniform granules with a little fine powder, this may be because of changing the speed at the middle of the process. Then the drying process started and the trays of granules were put in the oven and left to dry, the oven worked for two days to dry the granules, at the sixth day we’ve transferred the dried granules to a plastic bag and removed the air from it to avoid moisture absorption from the air, we should have put them in the bags much earlier to avoid moisture problems. The next day we screened the dried granules through a mesh#16 at speed 70 for 2 minutes, the resulted granules were smaller and more uniform in size, and less size distribution was observed which will help in preventing segregation, and provide a better flowability and help in the compression.

Then, the avicel PH101 and the actasol were added to the mixture in a plastic bag and mixed manually for almost 10 minutes, the magnesium stearate( as a lubricant) were added after and mixed for not more than 2 minutes to avoid forming complete film around the granules which will hinder the tableting process because it reduces the tablet hardness and hence inability to properly compress them. The mixture was added to the cubic mixture for 1 minute at a speed of 150. And then 100g of the mixture obtained for sieving analysis.

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 |  |

* The original weight of the sample was 100.00 g, there was a little bit lose probably during the weighing step.
* % Loss during sieving = (Initial weight of the sample - Sum of weights retained on sieves)/ Initial weight of sample = 100- 99.84/100\*100= 0.16% lost.
* Calculations :
* Weight Retained on each sieve = (Material + Sieve Weight) - Sieve Weight
* % Weight Retained on each Sieve= (Weight Retained on each sieve/ Total weight) ×100%
* Cumulative % Retained = % Weight Retained on the previous sieves + % Weight Retained on Sieve



Figure1: mass retained on the sieve VS opening size



Figure 2: cumulative% retained on sieves VS opening size

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.

Conclusion:

The whole procedure went well, the acetaminophen granules were produced with the help of many other excipient like the PVP as a granulating liquid. And the resulted granules were evenly sized with almost uniform size distribution after passing it through the meshes in the wet granulator. The in process test sieve analysis was done to measure the size distribution of granules, the result was acceptable with a peak in the middle and distributions around it, a large deviation from it was the peak on the 850 mcm opening size.

**Questions:**

 **Q.1 Why the mixing time after adding Magnesium Stearate is only 3 minutes?**

Because over mixing of magnesium will cause over lubrication, which means that the particles will be covered by a hydrophobic martial that will prevent the dissolution of the drug and decease the hardness of the produced tablets and may hinder their compression.

**Q.2 Why was Magnesium Stearate mixed manually or in cubic mixer, not in the**

**low shear mixer?**

Because low shear mixer will cause over lubrication for magnesium stearate and cubic mixer will protect it from being over lubricating, also to assure homogeneity of magnesium stearate in the mixture and this will affect hardness and disintegration for the tablet.

**Q.3 Why was the PVP used as a solution and not as a powder? Why was PVP**

**dissolved in water not in alcohol?**

PVP is used as a solution to allow complete distribution over the powder particles as much as possible, so it can cover the surfaces of the particles in each granule to allow their agglomeration together. (Which is the main function of a binder)

PVP is dissolved in water rather than alcohol although it is soluble in both of them, because paracetamol is soluble in alcohol while it’s insoluble in water, and we want paracetamol to remain as a powder and not to dissolve in the binder added (PVP in alcohol) instead of the binder acting as an agent to bind powder granules together, that’s why PVP+water was used.