

**Faculty of Pharmacy, Nursing and Health Professions**

**Program of Doctor of Pharmacy**

**Industrial Pharmacy PHAR 411**

**Lab Report

Granulation and Mixing**
**Experiment No.** :1-2

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**Experiment Date :** 2019/9/ 11-25

**Submission Date** : 2019/10/9

**Students Signature**

**Supervisor Signature**

**Objectives:-**1- To understand the techniques of granulation (Wet).
2- To understand how to use the machines and instruments, and for what they use.

**Abstract:-**Granulation, is process to agglomeration particle in order to produce tablets, in our experiment we applied wet granulation that use a liquid binder to form granules, the benefits from this technique are minimizes segregation dust, and improves flow ability. Our API is Acetaminophen and we have granulate and mix it with excipients. Granule uniformity is important in pharmaceutical manufacturing, as the tablet must contain a uniform distribution of excipients in the product in order to comply with United States Food and Drug Administration (FDA) regulations.

**Introduction:-**

Paracetamol or Acetaminophen are the same thing, is an analgesic drug, common used in our community for headache, menstrual pain. In addition to active ingredients, formulations are complex mixtures of diluents, binders, disintegrants, surface active agents, glidants, lubricants, colorants, coating substances, surfactants and many other raw materials that impart different properties to the final solid dosage product. Granulation is often required to improve the flow of powder mixtures and mechanical properties of tablets.  Granules are usually obtained by adding liquids (binder or solvent solutions). Granulation, a technique of particle enlargement by agglomeration, is one of the most significant unit operations in the production of pharmaceutical dosage forms, mostly tablets and capsules.[1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4401168/#R1) During the granulation process, small fine or coarse particles are converted into large agglomerates called granules. Generally, granulation commences after initial dry mixing of the necessary powder ingredients along with the active pharmaceutical ingredient (API), so that a uniform distribution of each ingredient throughout the powder mixture is achieved. Although granules used in the pharmaceutical industry have particle size in the range of 0.2-4.0 mm, they are primarily produced as an intermediary with a size range of 0.2-0.5 mm to be either packed as a dosage form or be mixed with other excipients before tablet compaction or capsule filling.

**Experimental:-

1- Procedure**

**Granulation:-**
**a-** We weight the actual quantity of each excipient for the experiment.

**b-** We mix the following ingredients using plastic sack and then screen the mixture from sieve mesh:

Table 1: Information about material’s name

| **Material** | Acetaminophen | Starch | Lactose | Mannitol Powder | Acivel PH101 |
| --- | --- | --- | --- | --- | --- |

**c-** We transfer the above mixture to the bowl and mixed for 15 min at impeller speeds (Take sample and measure Moisture contents-1.5g- )

**d-** We prepare the granulation solution by adding the PVP K30 to purified water (28% w/w PVP K30 in P.W.) and mix until the PVP K30 dissolved. (Granulation Liquid)

**e-** Weadd the liquid binder (Granulation Liquid) to the powder by pouring it via a port in the lid of the granulator, while impeller are running at a low speed (40)

**f-** Once a satisfactory granule has been produced, the granular product is discharged, passing through a wire mesh which breaks up any large aggregates.

**g-** Wetransfer the granules on stainless steel trays to the oven and dry until you reach the initial moisture content (Take sample and measure Moisture contents (LOD).

**h-** We discharge the stainless steel trays into plastic bags and transfer them to the storage area.

**Mixing:-**

**1.** Wetransfer the granules from experiment 1 to the Mixing area

**2.** We make sure that the Mixing machine is clean and ready to be used

**3.** We transfer the granules to the bowl or to the cube mixer

**4.** We mix for 5 min

**5.** We add to the bowl the following materials :-

**Table 2: Information about material’s name**

| **Material** | Mannitol | Avicel PH101 |
| --- | --- | --- |

**2- Ingredients:-**

**Table 3: Information about material’s name and Function**

| **Ingredient** | **Function** |
| --- | --- |
| Acetaminophen | API |
| Starch | Diluent, Disintegrant |
| Lactose | Diluent |
| Mannitol | Diluent |
| Avicel PH101 | Flow aid |
| AvicelPH101 | Disintegrant |
| Croscarmellose | Disintegrant |
| PVPK30 | Binder |
| Magnesium stearate | Lubricant |

**3- Machine/ Instrument**

1.Precision Balance KERN kb2000-2N

Serial number W1206981

 A precision balance is needed to obtain an accurate mass of each ingredient being used. The balance had a minimum increment weight of 1 mg, and a maximum weight of 2010 grams. This was suitable for our measurements as the weight of the mixture as a whole was well under this amount and we had no ingredients weighing under 10 mgs. No parameters have to be inserted.



 2. Pharmatest wet granulator

Model: WG-30

Serial number 10-00642

Company: Pharma test

 Operating with an oscillating rotor granulation method and containing a flow through mesh, allowed this wet granulator to be suitable for inserting the granular product and obtaining suitably sized granules. Parameters inserted are the number of rotations per minute (RPM), amount of time required for the process, and the mesh can be replaced based on the size required.



 3. Homogenizer Mixer

 PHDHOM012

 Model: L5M-A

Company: Silverson

This mixer was used to create a homogenous granulating liquid mixture of PVP and water, without being a time consuming or mess inducing process which leads to a loss of materials. Speed and height of mixer can be manually changed before and throughout the mixing process to ensure no spillage and the ability to adjust while mixing.



 4.Moisture Analyzer

 Model: MOA011

 Company: OHAUS

The moisture analyzer works by slowly drying a sample of material and determining the amount of liquid or moisture in it, as well as displaying the sample’s weight and length of the test. It was used to test the moisture content of the mixture or powders before adding the granulating solution, and after drying the granules.



 5. Cubic Mixer

 Serial number 10.00499

Company: Pharma test

 This machine was used to mix the superdisintegrant and direct compression binder at a slow and controlled rate to ensure uniform distribution between the granules. In addition to the slow and short mixing of the lubricant. Parameters added were the RPM and time of mixing.



 7- Pharmatest coating pan

 Company: Pharma test

 Operating with an oscillating rotor granulation method and containing a flow through mesh, allowed this wet granulator to be suitable for inserting the granular product and obtaining suitably sized granules.



**Results and discussion :-**

**Table 4: Information about material’s name and Weight**

| **Ingredient** | **Theoretical weight** | **Actual weight** |
| --- | --- | --- |
| Acetaminophen | 50mg | **50.97 g** |
| Starch | 186mg | **186 g** |
| Lactose  | 160mg | **160 g** |
| Mannitol | 120mg | **120.02 g** |
| Avicel PH101 | 72mg | **72 g** |
| AvicelPH101 | 72mg | **72 g** |
| Croscarmellose | 64mg | **64.5**  |
| PVPK30 | 64mg | **62.11 g** |
| Magnesium stearate  | 12mg | **12 g** |

According to the procedure, the experiment began by weighing the needed amounts of each material and a plastic bag was used to store them for some time, the problem there was getting the bag to stay on the balance in a way that stabilizes the balance reading since it had a relatively big volume.

 While the materials were transferred to the mixer, an insignificant amount of dust was formed even though the bags were opened and their content released at a very low height to reduce dust formation as much as possible. Given that the materials were powder, their flowability profile was bad which meant that while mixing in the low shear mixer, some particles stuck to the bowl and the beater. This problem was solved by stopping the mixing and manually removing the particles from the bowl and the beater and adding them again to the mix while wearing gloves.

 A sample of 1.5 grams was then taken from the mixture to operate a moisture content test on, and the result was a moisture content of 4.26% .

 To calculate the amount of water needed to form the granulating liquid of 28% w/w PVP solution, the following equation was used: 28g PVP/72g water \* 64g PVP, resulting in the theoretical need of 164.8 gram of water While adding the granulating liquid, a certain amount of the solution was dumped, and PVP was lost. This occured as the granules had reached the wanted stage of granulation, that being them sticking together when a small amount of pressure was placed on a handful of them, without requiring the complete amount of solution. This could be fixed by forming a solution of PVP in less than required amount of water and then adding more water to the mixture if needed, or by adding PVP as a powder and then slowly adding the water in.

After the formation of the granulating mass, different mesh sizes were tried to find the most suitable size for the granules. Smaller mesh opening sizes were not used, as the wet mass would stick to them and large masses would clog the pores. Then the drying process started, and the trays were inserted into the oven and left to dry for about a week, using the dry air technique. This was a faulty process as a large amount of trays were inserted at the same time, the trays would be taken out and replaced for hours at a time and the granules mixed every couple of days , and the oven was turned off on two separate days. at the end of the week, the test sample of 1.25 grams gave a result of 5.36%, which is suitable amount, and it is very good because of lsmall difference , and maybe error occurs due to taking our tray from the oven , because we lake sufficient ovens in our lab .

The granules were then taken and put in the wet granulator again, this time, with a mesh size of 24, to form smaller granules with less differences in size. This ensures that no segregation will occur during the next steps and better flowability properties.

 Then the newly sized granules were taken over to the cubic mixer. When the mixing process began, the granules were first mixed together to ensure there was segregation in the granules based on their size. The amounts of Croscarmellose, Avicel, and Magnesium Stearate were adjusted from the original amount in the formula due to a loss of powder and granules during the weighing processes, the mixing, and the granulating. Then the Croscarmellose and the second portion of Avicel were added to the cubic mixer and mixed to ensure their uniform distribution, without the presence of any blades which would damage the granules and break them apart. Finally the Magnesium Stearate was mixed in for a short amount of time, just long enough to ensure its even distribution, but not allow it to form complete films around the granules which would hinder the tableting process, as it would decrease tablet hardness and cause an inability to properly compress them. Avicel PH101 was added in two steps, one was in the low shear mixing, the other was in the cubic mixer. This is due to Avicel’s use for more than one purpose. The first amount it was used as a wet granulation binder, however after the addition of the solvent, PVP and drying another amount was added to aid in the compression part and to work as a direct compression binder, if that amount was added before it would have been mostly aiding in the wet granulation part that is why it was added after drying in the low speed cubic mixer part. The end result was granules of small, but mostly uniform sizes, with little powder left not in the granule form, that have been coated with a disintegrant, a compression binder, and a thin film of lubricant.

**Conclusion :-**

 The process of low shear mixing, wet granulation, and mixing of final materials resulted in evenly sized granules with uniform distribution of the powders. However, the process of adding the granulating liquid should have been corrected as to prevent the loss of PVP, and caution should be taken as to lose less material during the different processes. In conclusion, the granulation and mixing went fairly well and gave good results.

 **Questions :-**

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

Because over mixing of magnesium streatre can cause over lubrication making the particles covered with hydrophobic material that makes it hard to penetrate and dissolve the drug.

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

Slow speed is needed here to prevent the magnesium stearate from over lubrication and the low shear mixer ’s speed is too high and can cause over lubrication, in addition to the risk of the mixer damaging the formed granules 3. Why was the PVP used as a solution and not as a powder? Why was PVP dissolved in water not in alcohol? That is because PVP has better solubility in water than alcohol, despite pvp being freely soluble in in ethanol, and water is cheaper. Water is also safer considering any residues left in thegranules.

**3. Why was PVP used as a solution and not as a powder ? Why was PVP dissolved in water not in alcohol?**

To ensure that the binder will be distributed over the powder mixture. Because Acetaminophen dissolved in alcohol and this will create a problem in our expirement.

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