Industrial Pharmacy (PHAR441)

Lab Report 1

Granulation and Mixing

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Abstract

The objective of this experiment was to produce acetaminophen granules and to mix them with other substances as to allow for successful compression of this mixture into proper tablets. The granules were produced by low-shear granulation, in which the granules' components were mixed with a liquid binder in a low-shear mixer, then oscillated to one size, and dried in an oven. The granules were then oscillated again to the presumably appropriate size, and mixed with the disintegrants and the lubricant using a cubic mixer. The granules were produced and mixed with the required lubricant and a disintegrant, and are ready for analysis.

1 Introduction

Acetaminophen, known more commonly as paracetamol, is an analgesic and antipyretic drug used for mild to moderate pain like headache, backache, rheumatic pain, and menstrual pain, and to reduce fever. Experts aren't sure about its exact mechanism of action, but suspect it blocks a specific type of cyclooxygenase (COX) enzyme in the brain. Acetaminophen is usually taken as an oral immediate release product, and its recommended dose ranges from 325mg to 1g every 4 to 6 hours. The maximum single dose allowed is 1g, and the maximum daily dose is 4g per 24 hours. Extended release forms of acetaminophen are also available, and their recommended doses are 1300mg every 8 hours or 3900 mg every 24 hours. Acetaminophen products should be stored below 25°C in the original package. [1][2]

Acetaminophen is considered generally safe and well tolerated. The most common side effects include nausea, vomiting, and constipation. Other rare side effects include anaphylaxis or hypersensitivity reactions, rash, pruritus, anemia, and postoperative hemorrhage. Drug-drug interactions of acetaminophen include a serious interaction with sodium fusidate, which can cause very harmful effects, as well as moderate interactions with isoniazid, busulfan, and some anticoagulants. Acetaminophen overdose can cause liver damage on the long term. In case of overdose, patient must refer to a physician or a hospital emergency room immediately, even if no immediate side effects occur. Liver damage may also occur if acetaminophen is taken with 3 or more alcoholic beverages in the same day. [1][2]

Granulation is the process of particle enlargement by agglomeration of particles. It's usually precedes the process of tablet compression in development of tablets to provide a free flowing, easier-to-compress form for tablet compression. [3]

Granules can be prepared by either wet granulation, or dry granulation. [3]

In dry granulation, the powders which are to be formulated into granules are passed through a roller compactor. The roller compactor is composed of two mechanically rotating metal rolls that run counter to each other. When the fine powders pass through these rolls, they are compacted into dense sheets, which are then granulated to a uniform particle size by a mechanical granulator. An alternative dry method is slugging, in which the powders are compressed in a compressing machine into slugs resembling large tablets. The slugs are then granulated into the desired particle size. Dry granulation methods usually leave some powders that have not agglomerated with the rest of the powders. These must be collected and reprocessed. Dry granulation is suitable for materials that are susceptible to damage by moisture or heat drying from moisture. [3]

Wet granulation can be done using three apparatus, low-shear mixers, high-shear mixers, and fluid bed granulator. In low-shear mixers, the intragranular excipients are mixed together to achieve homogenous mixture, then a liquid binder is added to this mixture until granules are formed, with care as to not over wet the mixture. These wet granules are then reduced to one particle size by screening with sieves or milling, and allowed to dry with or without the aid of heat. After drying, the granules are reduced again into a uniform particle size by rescreening or by milling. A disadvantage of this process is open nature of the equipment, the possibility of migration of soluble components during drying, and the lack of in-process control. Variables that affect the process of low-shear wet granulation include the rotation speed of the mixer, the amount of powder loaded into the mixer, the addition rate of the liquid binder, the granulation process time, the characteristics and amount of the binder, and the characteristics of the powders to be granulated including their particle size, solubility, and wettability. [3]

High-shear wet granulation is done using a machine composed of a mix-

ing bowl containing a high-speed main impeller that rotates horizontally to disperse and mix the powders, and a chopper to break granules into a certain size. The intragranular excipients are added to the machine where they are mixed by the impeller at high speed. Then, the impeller is turned to a lower speed for addition of the liquid binder via a port. When a moist mass is formed, the chopper breaks up this mass into granules. When granules are formed successfully, they are passed through a sieve to break up any aggregates, dried, and sieved into a uniform size again. Variables that affect this process are similar to low-shear granulation, with the addition of the properties of the chopper and its rotation speed. [3]

Fluid-bed granulation is an efficient process in which powder mixing, granulation, and drying are all done in a single apparatus. In the apparatus, the powders are fluidized and mixed by blowing heated air through them. Then, the liquid binder is sprayed through a nozzle in the machine for the granulation, and the powders start adhering as they collide. After satisfactory granules are produced, the granules can be dried used the heated air stream. Same variables that affected the two previous wet granulation methods affect fluid bed granulation. In addition, atomization, which is the process of spraying the liquid binder through the nozzle, is also a variable in this case, seeing how the nozzle properties including size and shape, the spray rate, and the spray angle can affect the process. The temperature and humidity of the fluidizing air also affects the process, as well as the fluidization properties of the powders involved. [3]

This experiment uses the low-shear wet granulation method to produce acetaminophen granules suitable for compression into tablets. The intragranular excipients chosen include the API, diluents, and a disintegrant. A liquid binder solution was used for the granulation process. The granules were screened into a smaller size using an oscillator before drying, and then dried and screened into desired size, to get a finished granular product.

The granules then needed to be mixed with the extragranular excipients required, including additional disintegrant, and a superdisintegrant. Superdisintegrants are excipients used to allow for fast disintegration of the tablet. They swell upon interaction with fluids, allowing them to break up the granules from each other. Note that these disintegrants break the granules only from each other, as they are extragranular. Another disintegrant was added

to the granules themselves to allow for their disintegration.

Another extragranular excipient is the lubricant, which is very important to allow for easy flowing of the granules through the tableting machine. The mixing process was done using a cubic mixture, in which the rotation speed and mixing time can be calibrated more efficiently than normal mixers, which is especially important to control especially in lubrication.

2 Experimental

2.1 Procedure

The procedure is the same as the one in the Industrial Pharmacy (PHAR441) Lab Manual, with the following changes and notes:-

1. An additional 5.6g of the PVPK30 were added, after being dissolved in 20g of water.
2. A mesh no. 20 was used for screening initially, but was changed to a mesh no. 16 halfway through (discussed in "Discussion").
3. 80g of sucrose were powdered using a mortar and pestle, and added instead of 64g of croscarmallose sodium (Ac-Di-Sol) (discussed in "Discussion").

2.2 Ingredients

1. Acetaminophen (assay 98.5%):-
    - Quantity: 50mg per tablet, 50g per batch (1000 tablets).
    - Function: API, analgesic and antipyretic.
    - Batch: SEP00315
    - Expiry: 5/2020
    - Doses and considerations about this API are discussed in "Introduction".

2. Starch:-

    - Quantity: 186mg per tablet, 186g per batch.
    - Function: Diluent / Disintegrant.
    - Batch: APR06913
    - Expiry: 5/2020

3. Lactose:-

    - Quantity: 160mg per tablet, 160g per batch.
    - Function: Diluent.
    - Batch: 63-42-3
    - Expiry: 2/2019
    - 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.
    - Batch: 69-65-8
    - Expiry: 8/2021

5. Avicel PH101 (Microcrystalline Cellulose):-

    - Quantity: 144mg per tablet, 144g per batch (in two parts, one intragranular, and one extragranular).
    - Function: Disintegrant.
    - Batch: NOV00813
    - Expiry: 5/2020
    - Avicel PH number is a pharmaceutical classification of Avicel (diffecent from food industry classification RC) which indicates the moisture content and particle size of microcrystalline cellulose. Avicel PH101 and 102 are the most widely used in the pharmaceutical industry. [4]

6. PolyVinylPyrrolidone (Povidone or PVP) K30:-

    - Quantity: 64mg per tablet, 64g per batch. (Theoretically, discussed in "Discussion").
    - Function: Binder.
    - Batch: 004-4
    - Expiry: 8/2021
    - PVP is generally considered safe. Its only serious side effect is pulmonary vascular injury which occurs only if injected intravenously. [5]
    - PVP's K number, specified in the material used in this experiment as 30, refers to its molecular weight.

7. Sucrose:-

    - Quantity: 80mg per tablet, 80g per batch.
    - Function: Disintegrant.

8. Magnesium Stearate:-

    - Quantity: 12mg per tablet, 12g per batch.
    - : Function: Lubricant.
    - Batch: 0798A150
    - Expiry: 10/2020
    - Consuming more than 2500mg/kg of magnesium stearate per day can cause serious side effects. However, this level is too high for the substance to be considered dangerous. [6]

2.3 Machines

Machine Name	Model and/or S/N	Function	Involved Parameters
KitchenAid Artisan Tilt Head Stand Mixer	KSM150	Low-shear mixer	Bowl size, impeller size/shape, impeller rotation speed mixing time
Pharmatest Wet Granulator	WG-30 S/N: 10-00642	Wet granulator, breaks wet agglomerates formed in mixer to granules	Rotation speed, the used sieve's mesh number
Homogenizer Mixer	L5M-A	Mixer, dissolved PVP in water	Rotation speed
OHAUS Moisture Analyzer	MOA011	Determine moisture content of samples	X
Pharmatest Cubic Mixer	S/N: 10.00499	Mix granules with lubricant and disintegrant	Rotation speed, mixing time

Table 1: Machines used in experiment

3 Results and Discussion

3.1 Results

Moisture content of powder mixture before granulation = 4.44%
Moisture content of granules after drying = 5.20%

3.2 Granulation

After the addition of the PVP solution the mixture was still soft and proper granules were not observed, the explanation was "there is some PVP that adhered to the wall of the mixer", so additional 20ml of PVP were added and were sufficient to make the mixture ready for the next steps.

In step two, mesh no. 10 was chosen and there was an obvious variation in the size of granules. After that granules were placed in the oven for 2 days for drying to decrease moisture so that granules become more rigid,

more flowable, do not aggregate with each other, and decrease adherence on the walls of the compression machine. The granules were required to return to the original moisture content of the powder mixture before granulation. However, due to time limitation, their moisture content only reached 5.20%, which was determined to be close enough to the original moisture content. An increase in moisture content can affect the flowability and compressability of the granules.

After drying the granules, and measuring the moisture content, the next step was to oscillate the granules again into a small, uniform particle size. The oscillator with a sieve of mesh no. 20 was first chosen for this step. Initially, an amount of the granules were successfully reduced to size. However, after a while, the process became too slow, and most of the granules added to the machine were dropping from the edges of the sieve into the tray without any reduction in particle size. Upon investigation of the issue, it was found that the sieve was not tight enough as to allow for proper oscillation in the machine, but upon tightening the sieve as much as possible, it was determined that the sieve was too long, and that the remaining amount apparently would not be successfully reduced in size in these conditions. Another sieve of larger size, mesh no. 16, was found to be the only solution available at the time of the experiment. The mesh no. 20 sieve was replaced with the mesh no. 16 sieve for the rest of the operation, and the granules which have dropped through the edges of the sieve were collected and reprocessed. This will definitely cause variation in the particle size of the produced granules, which will probably be shown during particle size analysis by the sieve analyzer.

3.3 Mixing

The mixing operation includes mixing the prepared granules with a lubricant, which is magnesium stearate, as well as Avicel PH101 (microcrystalline cellulose) as a disintegrant, and a superdisintegrant. Choices for a suitable superdisintegrant, which aids in fast disintegration of the tablet by swelling upon interaction with water and breaking up the tablet, included sodium starch glycolate, crosscarmallose sodium, and . However, none of those ingredients were available at the time of the experiment, and the most suitable substitute was to use a normal disintegrant instead. Avicel PH101 was the first choice for a substitute. Its amount would be increased in the formula as to serve the purpose. Powdered sucrose was the second choice. Sucrose

was chosen in the end on the basis that it's more water soluble, and so would interact with water surrounding it to be solubilized and might cause good breaking up of the tablet during this process. The suggested amount of superdisintegrant introduced in the lab manual is 64g per batch, but the amount was increased to 80g of sucrose per batch to accommodate for its inferiority as a disintegrant compared to superdisintegrants. Disintegration test will show if this substitution and increase in amount will result in tablets of good disintegration properities.

4 Conclusion

The objective of this experiment was to produce proper acetaminophen granules, and mix them with the required lubricant (magnesium stearate), and disintegrant. Despite the issues that occurred due to handling of the equipment or availability of substances, the granules were produced and are ready for analysis of particle size, density, and flowability. These tests, along with the tablets produced afterawrds, will show how the different parameters involved in the production of the granules will affect the end product.

5 Questions

1. Longer mixing time of lubricants with granules may result in formation of thicker than required films of lubricants on the granules. Lubricants increase flowability of granules by forming a thin film on the granules, but of this film becomes thicker, it can decrease the hardness of the produced tablets, and increase their disintegration time. [7]

2. To assure homogenetiy of magensium stearate in the mixture. If magnesium stearate isn't homogenous in the mixture, it may lead to some portions being more lubricated than other portions of the mixture. It may also lead to overlubracation of those portions, which will affect the hardness and disintegration of some of the tablets produced. The cubic mixer also allows for more control over the rotation speed and mixing time than the low-shear mixer. [7]

3. Formulating PVP into a solution and then adding assures that the binder will be better distributed over the entire powder mixture, since

the solution with penetrate the mixture better and surround all the particle, thus assuring that all particles are bound.

6 References

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