Mechanisms of granule formation: pharmaceutical industry

For the production of solid oral dosage forms most fine pharmaceutical compounds require granulation to improve their flowability and processing properties prior to tabletting.

http://www. pharmamanufacturing. com/articles/2008/096. html

http://www. scribd. com/doc/6601180/Tablet-Granulation

Tablets are the most common drug dosage form today, and thus granulation, which allows primary powder particles to adhere and form granules, is one of the most important unit operations in drug manufacturing. Understanding granulation grows more complex each year. This article reviews the most current methods and mechanisms of pharmaceutical granulation, including factors that can lead to improved control.

Particle-bonding Mechanisms

a) Adhesion and cohesion forces in immobile films. If sufficient liquid is present in a powder to form a thin, immobile layer, there will be an increase in contact area between particles. The bond strength between particles will increase, as the Van der Waals forces of attraction are proportional to the particle diameter and inversely proportional to the square of the distance of separation [1].

b) Interfacial forces in mobile liquid films. During wet granulation, liquid is added to the powder mix and distributed as films around and between the particles. There are three states of water distribution between particles. At low moisture levels, the pendular state, particles are held together by

surface tension forces of the liquid/air interface and the hydrostatic suction pressure in the liquid bridge.

When all the air has been displaced from between the particles, the capillary state is reached, and the particles are held by capillary suction at the liquid/air interface. The funicular state represents an intermediate stage between the pendular and capillary states. Moist granule tensile strength increases about three times between the pendular and the capillary state. These wet bridges are, however, a prerequisite for the formation of solid bridges formed by adhesives present in the liquid, or by materials that dissolve in the granulating liquid.

Solid bridges can be formed in two ways:

Hardening binders. When an adhesive is included in the granulating solvent it forms liquid bridges, and the adhesive will harden or crystallize on drying to form solid bridges to bind the particles.

Crystallization of dissolved substances. The solvent used to mass the powder during wet granulation may partially dissolve one of the powdered

ingredients. When the granules are dried, crystallization of this material will take place and the dissolved substance then acts as a hardening binder.

c) Attractive forces between solid particles. In the absence of liquids and solid bridges formed by binding agents, there are two types of attractive force that can operate between particles in pharmaceutical systems, electrostatic forces and Van der Waals forces. Van der Waals forces are about four orders of magnitude greater than electrostatic and add to the strength of granules produced by dry granulation.

Mechanisms of Granule Formation

a) Nucleation. Granulation starts with particle-particle contact and adhesion due to liquid bridges. A number of particles will join to form the pendular state. Further agitation densifies the pendular bodies to form the capillary state, and these bodies act as nuclei for further granule growth [2].

b) Transition. Nuclei can grow in two possible ways: either single particles can be added to the nuclei by pendular bridges, or two or more nuclei may combine. The combined nuclei will be reshaped by the agitation of the bed. This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution.

c) Ball Growth. If agitation is continued, granule coalescence will continue and produce an unusable, over-massed system, although this is dependent upon the amount of liquid added and the properties of the material being granulated [1].

There are four possible mechanisms of ball growth, which are illustrated in Figure 1 [3]:

Coalescence. Two or more granules join to form a larger granule.

Breakage. Granules break into fragments which adhere to other granules, forming a layer of material over the surviving granule.

Layering. When a second batch of powder mix is added to a bed of granules, the powder will adhere to the granules, forming a layer over the surface and increasing the granule size.

Abrasion Transfer. Agitation of the granule bed leads to the attrition of material from granules. This abraded material adheres to other granules.

Granulation Methods [4]

Dry Granulation. This requires two pieces of equipment, a machine for compressing the dry powders into compacts or flakes, and a mill for breaking up these intermediate products into granules. The dry method may be used for drugs that do not compress well after wet granulation, or those which are sensitive to moisture.

Wet Granulation. In this method, the wet mass is forced through a sieve to produce wet granules which are then dried. A subsequent screening stage breaks agglomerates of granules. Organic solvents are used when water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required. Because direct compressing is not the best technology for many active substances, wet granulation is still a preferred

method. Even if the active substance is sensitive to hydrolysis, modern equipment (e. g., a fluidized bed) eliminates all problems in wet granulation [2].

http://www. investopedia. com/terms/l/leptokurtic. asp

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Introduction

Granulation can be used to

For the production of solid oral dosage forms most fine pharmaceutical compounds require granulation to improve their flowability and processing properties prior to tabletting.

Method and Materials The experiment was carried out as explained in PY2020A practical booklet, without any amendments. Paracetamol (25g), lactose (265g) and sodium starch glycollate (2. 945g) and PVP solution 15% (30ml) was used. 1 Erweka AR402 oscillating granulator with the finer sieve was used to granulate the drug without too much force with variables of turns (rpm) and time (minutes). The machine had an emergency switch off button and safeguard on top which turns off machine when you put your hand in. Sieve shaker used was Retsch A5 200 basic was used to separate the particles into different sizes by vibration with variables of amplitude and speed. The top sieve was fixed by parallel bars with screws and bottom of sieves contained rubber bands to control any overflow and stability.

Discussion

Modal: Low so most particles are fine. (low) Relate to flow rate. Better flow rate.

Small IQR-data close to each other.

Positive skewness means more particles with finer particles, so flow rate is better.

What Does Leptokurtic Mean?

A description of the kurtosis in a distribution in which the statistical value is positive. Leptokurtic distributions have higher peaks around the mean compared to normal distributions, which leads to thick tails on both sides. These peaks result from the data being highly concentrated around the mean, due to lower variations within observations.

Limitations: 7. 9% MC was lost after 45 minutes in 75oC oven compared to 9. 51% in 130oC heater balance. Tray was exposed to air for different amount of periods each time, errors as tray was allowed to cool down. Not dried properly Granulators normally used for large quantities. If lubricant used, particle size would be higher. Improvements: More repeats, heat for longer and at high temperature.