**Particle size analysis**

* + Knowledge and control of the size, and the size range, of particles is of a profound importance in pharmacy. Thus, the size, and hence the surface area, of a particle can be related in a significant way to the physical, chemical and pharmacological properties of a drug.
  + Clinically, the particle size of a drug can affect its release from dosage forms that are administered orally, parenterally, rectally, and topically.
  + The successful formulation of suspensions, emulsions, and tablets, from the viewpoints of both physical stability and pharmacologic response, also depends on the particle size achieved in the product.
  + In the area of tablets and capsules manufacture, control of the particle size is essential in:
    - Achieving the necessary flow properties, and
    - Proper mixing of granules and powders.

**Methods of particle size analysis:**

1. **sieving method:**
   * This method is the simplest and most widely used method of determining particle size and size distribution.
   * Results are obtained on weight basis.
   * It useful for practical lower limit of 76 μ.
   * This method utilizes a series of standard sieves calibrated by the National Bureau of Standards.
   * According to the method of USP, a definite mass of the sample is placed on the proper sieve in a mechanical shaker. The powder is shaken for a definite period of time, and the material that passes through one sieve and is retained on the next finer sieve is collected and weighed.
2. **optical microscopy method:**
   * According to this method, an emulsion or suspension is mounted on a slide and placed on a mechanical stage. The microscope eye piece is fitted with a micrometer by which the size of the particles may be estimated. The field can be projected onto a screen where the particles are measured more easily, or photograph can be taken from which a slide is prepared and projected on a screen for measurement.
   * ***Disadvantages:***
3. The diameter is obtained only from two dimensions of the particle, length and breadth. No estimation of the depth (thickness) of the particle is ordinarly available.
4. The number of particles that must be counted is from 300 – 500; in order to obtain good estimation of the distribution, and this makes the method somewhat slow and tedious.
5. **sedimentation method:**
   * The analysis is carried out in the following manner: A 1 or 2% suspension of the particles in a medium containing a suitable deflocculating agent is introduced into the Andreasen Apparatus. Then, at various time intervals, a sample of the suspension is taken and analyzed.

**Methods of data presentation:**

1. **Tables:**

The most precise and general method of data presentation is the tabular form, since the data can be expressed explicitly. The table can be a listing of size versus one of the many ways of expressing their distribution, e.g., size frequency or size cummulation.

1. **Graphs:**

*Histograms:*

A histogram is a plot of the frequency of occurrence as a function of the size range. The ordinate, frequency, can represent the weight, surface area, or any other weighing process, in the specific size interval.

*Size frequency curve:*

This is a smooth curve drawn through the mid points of the bars of a histogram.

*Cumulative plots:*

Cumulative plots can be described as those which involve plotting the percent of particles greater than (or less than) a given particle size against the particle size. Thus, the limiting values of the ordinate vary from 0 to 100%. The ordinate can represent different weighing processes.

***Practical:***

**Objectives:**

1. To determine the particle size and size distribution using the sieving method.
2. To get acquainted with the different methods of data presentation and interpretation of the results.

**Determination of particle size by sieving method**

***Procedure:***

1. Weigh accurately 100 g of the supplied powder, then place on the top sieve of the stack of sieves, cover and shake (mechanically) for 15 minutes.
2. Weigh the remaining powder on each sieve.
3. Tabulate your results.
4. Plot the required curves (histogram, normal distribution curve, and cumulative curves).

***Table of results:***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Sieve diameter (particle size), mm** | **Mean particle size (mm)** | **Weight retained on the smaller sieve (g)** | **%weight retained (frequency)** | **Cumulative %** | |
| **Under-size** | **Over-size** |
| **1.7-1.25** |  |  |  |  |  |
| **1.25-0.8** |  |  |  |  |  |
| **0.8-0.6** |  |  |  |  |  |
| **0.6-0.5** |  |  |  |  |  |
| **0.5-0.315** |  |  |  |  |  |
| **0.315-0.25** |  |  |  |  |  |
| **0.25-0.125** |  |  |  |  |  |
|  |  | Σ= |  |  |  |

* Using graph paper, plot the following curves:
  1. Histogram ( frequency vs. p.s. range).
  2. Size distribution curve ( frequency vs. mean p.s.).
  3. % cumulative curve ( % cumulative vs. mean p.s.).

**Particle size analysis by sieving method**

A sample of granules having different particle size was analyzed utilizing a series of standard sieves placed in a mechanical shaker. The sample is shaken for a definite period of time, and the material that passes through one sieve and retained on the next finer sieve was collected and weighed.

The following data were obtained:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Particle size range | Weight retained on the finer sieve (g) |  |  |  | |
|  |  |
| 1.25-1.00 mm | 10.35 |  |  |  |  |
| 1.00mm-800μm | 14.50 |  |  |  |  |
| 800-710μm | 23.71 |  |  |  |  |
| 710-600 μm | 32.62 |  |  |  |  |
| 600-500 μm | 45.61 |  |  |  |  |
| 500-400 μm | 30.21 |  |  |  |  |
| 400-315 μm | 21.62 |  |  |  |  |
| 315-250 μm | 13.92 |  |  |  |  |
| 250-125 μm | 7.40 |  |  |  |  |
|  |  |  |  |  |  |

Show all the necessary calculations required to plot the size-frequency distribution curve and the cumulative percentage over and under a particular size versus particle size.

**Flow properties of powders**

*The flow property of a material results from* many forces that can act between the solid particles, such as: the frictional forces, surface tension forces, mechanical forces caused by interlocking of particles of irregular shapes, and cohesive or Vander Waals forces.

**Importance:**

1. The ability of powder to flow is one of the important factors involved in mixing different materials to form a powder blend. Mixing is an important pharmaceutical operation involved in the preparation of many dosage forms, including tablets and capsules, and in the studying of dusting powders.
2. The internal flow and granule demixing (the tendency of the powder to separate into layers of different sizes), during flow through the hopper contribute to a decrease in tablet weight during the latter portion of the compression period.
3. The flow rate of a tablet granulation increase with an increase in the quantity of fines added to the granulation. Also, an increase in the lubricant added will raise the flow rate.

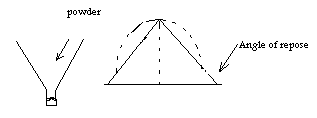
**Factors affecting the flow properties of powders:**

* + 1. Particle size: smaller particles have bad flow because the cohesive forces between the particles are of the same magnitude as gravitational force. So, as particle size increases, the flow is facilitated (improved).
    2. Shape of the particles: flat or elongated particles tend to pack. So, round shape particles are better.
    3. Porosity and density: particles with a high density and low internal porosity tend to possess free-flowing properties.
    4. Texture: surface roughness can lead to poor flow properties due to friction and cohesiveness.
    - To improve flow characteristics of powders, materials termed GLIDANTS are frequently added to granular powders.
    - ***Glidant:*** is a material that improves the flow properties of granulations by reducing the interparticulate friction and eliminating the problems associated with the flow of materials.
    - Examples of commonly used glidants include: magnesium stearate (0.2-2%), starch (2-5%), and talc (0.3-1%).
    - Two of the most common methods to determine the flow properties of powders are:

1. angle of repose method, and
2. Hopper flow rate measurements.

**Dtermination of angle of repose of powders**

**(sodium chloride, lactose, and lactose +2 % talc)**

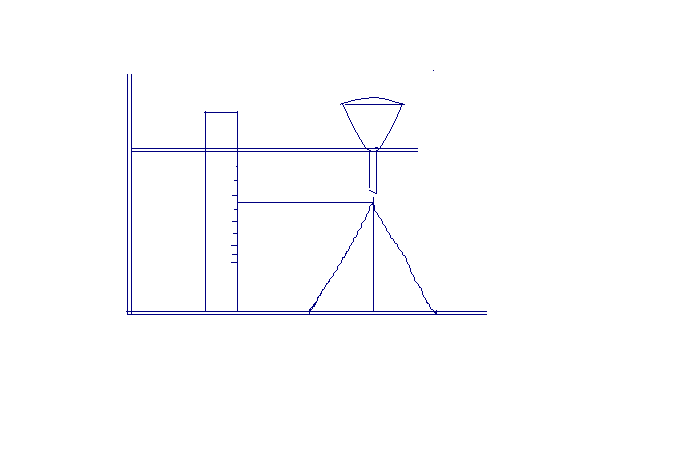
***Angle of repose:*** is the maximum angle between the surface of a pile of powder and the horizontal plane.

**tan θ = h / r** (h: the height, r: the radius)

**then, θ = tan -1 h / r**

As **θ** decreases, the flow property increased.

**Procedure:**

1. A quantity of the supplied powder is allowed to flow **carefully** through a funnel, whose tip is adjusted at 2 cm from a horizontal surface beneath (see the diagram), so that the apex of the heap just touch the lower tip of the funnel.
2. Mark the base of heap. Then remove the powder.
3. Measure the diameter of the formed circle (take the average of two diameters).
4. Repeat the process three times and calculate the average diameter (d). And the radius (r = d / 2).
5. The height of the heap (the distance between the horizontal surface and the lower tip of the funnel) is called (h).
6. Tan the angle of repose θ (tan θ = h / r), get θ (θ = tan -1 h / r), and tabulate your results.
7. Comment on the results.

***Results:***

* Tabulate the results as shown in the table:

|  |  |  |  |
| --- | --- | --- | --- |
| **powder** | **Height (h)** | **Radius (r)** | **Angle of repose (Θ)** |
| Sodium chloride (crystalline) |  |  |  |
| Lactose |  |  |  |
| Lactose + 2 % talc |  |  |  |

* Comment on the results:

**Compressed tablets**

Compressed tablets are solid dosage forms prepared by compaction of a formulation containing the drug and certain excipients selected to aid the processing and improve the properties of the product.

**Tablets excipients:**

* 1. **Fillers (diluents):**

These are used to increase the bulk of the tablet. It is generally not feasible to make tablets with a weight of less than about 70 mg. It is essential that fillers be inert and stable.

Examples:

* 1. Soluble: lactose, sucrose, mannitol, sorbitol.
  2. Insoluble: calcium sulphate, dicalcium phosphate, tricalcium phosphate, calcium carbonate, starch.
  3. **Binders (adhesives):**

The substances that glue the powders together and cause them to form granules are binders or adhesives.

Binders are either sugars or polymeric materials. A list of binders used in wet granulation is shown in the following table:

***Table :*** *some commonly used binders and granulating liquids:*

|  |  |  |
| --- | --- | --- |
| ***Binder*** | ***Strength*** | ***comments*** |
| Water | ----------- | --------------------------------------- |
| Ethanol | ----------- | --------------------------------------- |
| Acacia mucilage | 10-20% | Hard, friable granules |
| Tragacanth nucilage | 10-20% | Same as acacia |
| Gelatin solution | 2-10% | Strong adhesive, use warm. |
| Starch mucilage | 5–10% | One of the best general adhesives, use warm. |
| Glucose syrup | 25-50% | Strongly adhesive, tablets may soften in high humidity. |
| Sucrose syrup | 65-83% | Same as glucose. |
| PVP | 3-15% | ---------------------------------------------- |
| Cellulose derivatives | 3-10% | ----------------------------------------------- |

* 1. **Lubricants, glidants, and anti-adherents:**

Three of the problems associated with tablet manufacture are the flow of granulation, the adhesion of the material to the punches and dies, and the release of the tablet from the press.

1. *Lubricants:*

Are those agents that reduce the friction between the tablet edges and die wall during the ejection cycle, e.g., magnesium stearate.

1. *Glidants:*

Are materials that improve the flow characteristics of granulation, e.g., talc.

1. *Anti-adherents:*

These function to prevent tablet granulation from sticking to the faces of the punches and the die walls, e.g., talc.

* + *Lubricants are added at the very last step before compression, since they must be present on the surface of the granules and in between them and in the parts of the tablet press.*
  1. **Disintegrants:**

Disintegrant is a term applied to substances added to a tablet granulation for the purpose of causing the compressed tablets to break apart when placed into an aqueous environment.

Method of adding disintegrant:

It is better to add it in two portions, one half is added to the powdered components before the wet granulation process and the other remaining portion is added to the finished granulation just prior to compression. This method holds that a disintegrant is required between the granules as well as within them.

Some of the commonly used disintegrants are listed in the table:

***Table:*** *disintegrants: typical amounts used:*

|  |  |
| --- | --- |
| **Disintegrant** | **Concentration (% w/w)** |
| Starch | 5-20% |
| Avicel | 5-20% |
| Algenic acid | 5-10% |
| Veegum | 5-15% |
| Bentonite | 5-15% |

**Methods of manufacture:**

1. **Direct compression method:**

It is the process by which the tablets are compressed directly from powder blends of the active ingredient and suitable excipients (including fillers, disintegrants, and lubricants) which will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blends by wet or dry granulation procedures is necessary.

Successful formulation of direct compression tablets depends upon careful consideration of excipient properties, and optimization of the compressibility, fluidity, and lubricability of powder blends.

***Direct compression vehicles should have:***

* + High fluidity,
  + High compressibility, and
  + Should be inert and compatible with all of the active ingredients.

***Advantages:***

1. Economy (less areas, reduced processing time, reduced labor costs, and fewer manufacturing steps).
2. Elimination of heat and moisture.
3. Stability.

***Limitations:***

* + Drugs characterized by high dose, poor compressibility and poor fluidity (flow) do not lend themselves to direct compression method.

1. **Dry granulation (slugging):**

This refers to the granulation of powder mixture by compression and without the use of heat and solvent. On a relative basis, it is the least desirable of all of the methods of preparing tablet granulation. However, when direct compression is not possible due to the properties and dose of the drug, and wet granulation can not be used because the drug is sensitive to moisture and heat, then dry granulation remains the only method available.

***Advantages:***

1. Suitable for moisture and heat sensitive materials.
2. Results in an improved disintegration, since powder particles are not bonded together by a binder.

***Disadvantages:***

1. Requires a specialized heavy duty tablet press to form slugs.
2. Creates more dust than wet granulation.
3. Does not permit uniform color distribution.
4. **Wet granulation:**

The preparation of granulation for tabletting by wet granulation is the oldest method and still the most widely used.

*Steps of wet granulation:*

1. Milling of drug and excipients.
2. Mixing of the milled powders.
3. Preparation of binder solution.
4. Mixing of binder solution with powder mixture to form wet mass.
5. Course screening of wet mass using 6-12 mesh screen.
6. Drying of moist granules.
7. Screening of dry granules through 20/35 mesh screen.
8. Mixing of screened granules with lubricant and the remaining disintegrant.
9. Tablet compression.

***Advantages:***

1. Improved cohesiveness & compressibility of powders due to added binders.
2. Suitable for high-dosage drugs having poor flow or compressibility properties.
3. Good distribution for low dosage drugs and color additives.

***Disadvantages:***

1. High cost (because of the time, equipments and space requirements).
2. Not suitable for moisture and heat sensitive drugs.

**preparation of acetaminophen tablets (150 mg) by wet granulation methid**

Prepare 500 acetaminophen tablets each containing 150 mg of the drug and the total tablet weight is 225 mg:

***Rx \*F***

Acetaminophen 150 mg (66.67%) 75 g

(binder) Polyvinylpyrrolidone 11.25 mg (5%) 5.625 g

(diluent) Lactose 28.625 mg (12.72%) 14.3125 g

Alcohol Q.S. Q.S.

Starch 21.625 mg (9.61%) 10.8125 g

(glidant) Talc 6.75 mg (3%)

(lubricant) Magnesium stearate 4.5 mg (2%)

***Calculations:***

1. add 20 % excess to compensate for the mechanical loss:

no. of tablets = 500 + (20/100 x500) = 600 tab.

1. F= 600/1 = 600

***Method (wet granulation):***

1. Mix acetaminophen with PVP, lactose, and half the amount of starch. (Mixing is to be made geometrically in a large dish or in a jar by tumbling for 15 minutes).
2. Add alcohol slowly to form a wet mass which retain its shape on handling.
3. Screen the wet mass through a mesh-12 sieve to get the granules.
4. Dry the granules at 50 oC overnight (in an oven).
5. Make size reduction for the dried granules through a mesh-20 sieve (0.8 mm).
6. weigh the granules (W), then add the remaining half of starch, talc and Mg stearate:

Remaining starch = (4.81/100) x W

Talc = (3/100) x W

Mg stearate = (2/100) x W

1. Mix the ingredients in a jar by tumbling for 15 min.
2. Compress.

***Uses:***

Paracetamol is indicated for mild to moderate pain.

**Preparation of aspirin tablets (200 mg) by direct compression method**

Prepare 300 tablets of aspirin, each containing 200 mg of the drug and the total tablet weight is 250 mg:

***Rx \*F***

Aspirin (crystals) 200 mg (80%) 60 g

(directly compressible vehicle) Avicel 30 mg (12%) 9 g

Corn starch 18.12 mg (7.25%) 5.4 g

Mg stearate 1.875 mg (0.75%) 0.562 g

***Calculation:***

1. No. of tablets = 300 + (20/100) x300 = 360 tab.
2. F = 360/1 = 360

***Method (direct compression):***

1. Blend all of the ingredients in cubic mixer for 20 minutes.
2. Compress.

**Preparation of aspirin tablets (150 mg) by dry granulation method**

Prepare 200 tablets of aspirin, each containing 150 mg of the drug and the total tablet weight is 250 mg:

***Rx \*F***

Aspirin (granules) 150 mg (60%) 240 g

(diluent) Lactose 92 mg (36.8%) 22.08 g

(disintegrant) Corn starch 6.25 mg (2.5%) 1.5 g

(lubricant) Mg stearate 1.75 mg (0.75%)

***Calculation:***

1. No. of tablets = 200 + (20/100) x200 = 240 tab.
2. F = 240/1 = 240

***Method (dry granulation):***

1. Mix aspirin, lactose and half amount of disintegrant (starch) in a jar by tumbling for 20 min.
2. Compress into slugs (large, hard tablets).
3. Make size reduction for the slugs using the dry granulator.
4. Screen the granules through mesh-20 sieve.
5. weigh the granules (W), then add the remaining half of starch and Mg stearate:

Remaining starch = (1.25/100) x W

Mg stearate = (0.7/100) x W

1. Mix the ingredients in a jar by tumbling for 15 min.
2. Compress.