Lab. 2 Industrial Pharmacy

preparation of effervescent granules

By

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Granule dosage form

- Granulation is the process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules with a typical size of (0.2 to 0.5) mm.

- Granules are defined as a dosage form composed of dry aggregates of powder particles that may contain one or more APIs, with or without other ingredients.
- They may be swallowed as such, dispersed in food, or dissolved in water.

- They are irregularly shaped but may be prepared to be spherical.
- They are usually small in the 4- to 12-mesh sieve size range

Reasons for granulation

1. To prevent segregation of the constituents of powder Mix

2. To improve the flow properties of the powder mixture

3. To improve the compaction and compressibility characteristics of the powder mix

4. The granulation of toxic materials will reduce the hazard of the generation of toxic dust, which may arise during the handling of the powders.

5. Materials, which are slightly hygroscope, may adhere & and form a cake if stored as a powder.

Effervescent granules

- An effervescent dosage form, frequently tablets or granules, contains ingredients that, when in contact with water, rapidly release carbon dioxide.
- The dosage form is dissolved or dispersed in water to initiate the effervescence prior to ingestion.

- Effervescent salts are granules or coarse to very coarse powders containing a medicinal agent in a dry mixture usually composed of sodium bicarbonate, citric acid, and tartaric acid.
- When added to water, the acids and the base react to liberate carbon dioxide, resulting in effervescence. The resulting carbonated solution masks the undesirable taste of any medicinal agent.

Important notes for using granules:

- 1- By using granules or coarse particles of mixed powders rather than small powder particles rate of solution is decreased and uncontrollable effervescence is prevented.

- 2- Sudden and rapid effervescence could overflow the glass and leave little residual carbonation in the solution.

- 3- Combination of citric acid and tartaric acids rather than either acid alone to avoid certain difficulties. ??

Advantages:

1. Rapid onset of action
2. Pleasant taste
3. Psychological effect, patient comfort to it.
4. Provide alkaline solution, neutralization of a acidic drugs as aspirin (alkalinization of urine and increase excretion of drug which is acidic).

Disadvantages:

1. Unstable (absorb the water [moisture] from the atmosphere).
2. Not accurate dose estimation because the one who estimate the dose is the patient himself.
3. Sodium overload (these granules are not suitable for hypertensive patients)
4. Have many drug-drug interactions.

Method of effervescent granules preparation

- **1. dry or fusion method**
- **2. Wet granulation method**

- **The choice of granulation method depends on???**

Steps of Dry or fusion method

Principle: The one molecule of water present in each molecule of citric acid acts as the binding agent for the powder mixture.
This molecule of water is liberated by using heat. Therefore, this method is called the fusion method.

1. Grinding and mixing the powders

- Before mixing the powders, the citric acid crystals are powdered and then mixed with the other powders of the same sieve size.
- The sieves and the mixing equipment should be made of stainless steel or other material resistant to the effect of the acids.
- The mixing of the powders is performed as rapidly as is practical, preferably in an environment of low humidity. WHY?

2. After mixing, the powder is placed on a suitable dish in an oven at 34°C to 40°C.

The heat releases the water of crystallization from the citric acid

3. The released water in turn dissolves a portion of the powder mixture, setting the chemical reaction and consequently releasing some carbon dioxide

4. This causes the softened mass of powder to become somewhat spongy, and when it has reached the proper consistency (as bread dough), it is removed from the oven and rubbed through a sieve to produce granules of the desired size.

5. The granules are dried at a temperature not exceeding 54°C and are immediately placed in containers and tightly sealed.

Packaging and storage (cool and dry place): Stored in a wide-mouth bottle with colored glass, tightly closed and sealed to exclude air, and kept in a cool dry place.

Effervescent granules (and tablets) are to be labeled to indicate they are not to be swallowed directly.

Reconstitution of granules must ensure complete wetting of all ingredients and sufficient time and agitation to allow the soluble components to dissolve.

Experimental work

- R_x

paracetamol 500mg/5gm

effervescent granules qs 120gm

sig: Dissolve 1 tsp in one-half glass of cool water, and drink. Repeat this every 8 hours

The required amount of each ingredient:

❑Paracetamol:

- $\frac{0.5gm(\ of\ paracetamol\ )}{xgm(total\ paracetamol\ in\ the\ entire\ formula)} = \frac{5gm}{120gm}$

- X=$\frac{0.5gm*120gm}{5\ gm}$= 12 gm

❑Effervescent vehicle=120gm-12gm=108 gm of effervescent base

- Effervescent base consist of :
  - (1 PART) citric acid : (2 PARTS) tartaric acid

Citric acid

- 1 g (MW = 210) of citric acid reacts with 1.2 g (MW = 84) of sodium bicarbonate as obtained from the following:

- $3NaHCO3 + C6H8O7.H2O \rightarrow 4\ H2O + 3\ CO2 + Na3C6H5O7$

  3×84 210

$$\frac{1}{210} = \frac{x}{3 \times 84}$$

$$x = 1.2\,g$$

Tartaric acid

- Since it is desired to use a 1:2 ratio of citric acid to tartaric acid, 2 g (MW = 150) of tartaric acid reacts with sodium 2.24 g of bicarbonate according to the following calculation:
- $2\ NaHCO3 + C4H6O6 \rightarrow 2\ H2O + 2CO2 + Na2C4H4O6$

  (2×84) (150)

- $\frac{2}{150} = \frac{x}{2*84}$ ➔ x=2.24 gm
- Therefore, 1.2 g and 2.24 g of sodium bicarbonate are required to react with 1 + 2 g of the combination of citric acid and tartaric acid.
- Since it is desired to leave a small amount of the acids unreacted to enhance palatability and taste, of the required 3.44 g (2.24 g + 1.2 g), only 3.4 g of sodium bicarbonate will be used.

Sodium bicarbonate

- Therefore, the ratio of the effervescent ingredients is **1:2:3.4** for the citric acid: tartaric acid: sodium bicarbonate.

- Since the prescription requires 108 g of the effervescent mix, the quantity of each ingredient can be calculated as follows:

- 1 + 2 + 3.4 = 6.4 total parts
- (1/6.4) × 108 g = 16.875 g of citric acid
- (2/6.4) × 108 g = 33.750 g of tartaric acid
- (3.4/6.4)× 108 g = 57.375 g of sodium bicarbonate
- Total = 108 g

- The prescription will require 12 g of the active drug and 108 g of this effervescent vehicle.

procedure

Wet method

1.Weigh the required amount of all ingredients (sod., citric, tartaric) to prepare the required amount of formulation

2. grind the powder in mortar to finely ground powder then pass through sieve no. 30

3. **Mix all ingredient powders homogeneously in a porcelain mortar, then add a wetting agent (alcohol 95 %) to form a coherent mass(EXAMINE WITH BALL TEST)**

4.The coherent mass passed through sieve no 8, By pressing in one direction the collected granules are dried in a hot oven at 40° C for 10 minutes.

5.Sieve with 8 mesh size sieve

6. Pack the final product in a well-tight container

- **ball test:**
  - Add liquid drop by drop until you get a proper dough-like mass consistency by examining using your thumb and hand.

  - If you still see too many cracks after compressing your finger into the ball of material, the mass still needs some binder.
  - If 2-4 cracks are seen, the amount of binder is optimum.
  - If the mass is sticky, more dry mixture is required because the binder is present in excess.