Powders and Granules

Objectives:

After reading this topic, the student will be able to:
Differentiate a powder from a granule.

Explain how a drug's powder particle size influences the pharmaceutical dosage forms which will be used to administer it.

Define micrometrics, the angle of repose, levigation, spatulation, and trituration.

Compare and contrast the various types of medicated powders, e.g., bulk, divided.

Provide examples of medicated powders used in prescription and nonprescription products.

Powder:

Most active and inactive pharmaceutical ingredients occur in the solid state as amorphous powders or as crystals of various morphologic structures.

The term "powder" has more than one meaning in pharmacy.

-It may be used to describe the physical form of a material, that is, a dry substance composed of finely divided particles.

OR

-It may be used to describe a type of pharmaceutical preparation, that is, a medicated powder intended for internal (i.e., oral powder) or external (i.e., topical powder) use.

A powder is defined as a dosage form composed of a solid or mixture of solids reduced to a finely divided state and intended for internal or external use.

Granules which are used as a dosage form consist of powder particles which have been aggregated to form a larger particle which is usually 2-4 mm diameter.

This is much larger than granules prepared as an intermediate for tablet manufacture.

Powders have qualities that make them an attractive dosage form for certain situations:
Unlike a standardized capsule or tablet, powders enable a primary care provider to **easily alter the quantity of medication for each dose**. ➢ Powders can also aid in clinical studies of drug preparations because the dose can be so readily adjusted.

Doses can **be individually weighed and placed in powder papers**, envelopes, or small vials/bottles

Infants and young children who cannot swallow tablets or capsules will accept powders that can be mixed with a formula or sprinkled in applesauce or some other appropriate food.

If a drug is too bulky to be prepared as a capsule or tablet, it may be suitable for a powder dosage form.

Powders provide a rapid onset of action because they are readily dispersed, have a large surface area, and usually require only dissolution, not disintegration, before absorption.

◇ The use of powders:

Although the use of *medicated powders* per se in therapeutics is limited, the use of powdered substances in the preparation of other dosage forms is extensive.

For example, Powdered drugs may be blended with powdered fillers and other pharmaceutical ingredients to fabricate:

-Solid dosage forms as tablets and capsules;

-They may be dissolved or suspended in solvents or liquid vehicles to make various liquid dosage forms;

-They may be incorporated into semisolid bases in the preparation of medicated ointments and creams.

◇ Physicochemical Considerations

Particle Characteristics

Before their use in the preparation of pharmaceutical products, solid materials first are characterized to determine their chemical and physical features, including **:**

-Morphology,
-Purity,
-Solubility,
-Flowability,
-Stability,
-Particle size,
-Uniformity, and
-Compatibility with any other formulation components

Particle Size

The adjustment and control of a drug and other materials powder's particle size; enable both the efficient production of a finished dosage form and the optimum therapeutic efficacy.

The particles of pharmaceutical powders and granules may range from being extremely coarse, about 10 mm (1 cm) in diameter, to extremely fine, approaching colloidal dimensions of 1 µm or less.

In order to characterize the particle size of a given powder, the *United States Pharmacopeia* (USP) uses these descriptive terms:

-Very coarse,
-Coarse,
-Moderately coarse,
-Fine, and
-Very fine

which are related to the proportion of powder that is capable of passing through the openings of standard sieves of varying fineness in a specified period while being shaken, generally in a mechanical sieve shaker.

Sieves can be referred to either by their aperture size or by their mesh size (or sieve number). The mesh size is the number of wires per linear inch. The **sieve number** denotes the **number** of holes present in the **sieve** within one-inch length of the **sieve** mesh.

OPENING OF STANDARD SIEVES

	SIEVE NUMBER	SIEVE OPENING			SIEVE NUMBER	SIEVE OPENING
Very coarse	2.0	9.50 mm			70.0	212.00 µm
Coarse	3.5	5.60 mm			80.0	180.00 µm
coars	4.0	4.75 mm	4-12		100.0	150.00 µm
	8.0	2.36 mm	Granules		120.0	125.00 µm
Fine	10.0	2.00 mm		Very fine	200.0	75.00 µm
			12-20			
	20.0	850.00 µm	Tableting		230.0	63.00 µm
Moder ately	30.0	600.00 µm			270.0	53.00 µm
	40.0	425.00 µm			325.0	45.00 µm
	50.0	300.00 µm			400.0	38.00 µm
	60.0	250.00 µm				

Source: USP 31-NF 26.

-Very coarse (No. 8): All particles pass through a No. 8 sieve, and not more than 20% pass through a No. 60 sieve.

-Coarse (No. 20): All particles pass through a No. 20 sieve, and not more than 40% pass through a No. 60 sieve.

-Moderately coarse (No. 40): All particles pass through a No. 40 sieve, and not more than 40% pass through a No. 80 sieve.

-Fine (No. 60): All particles pass through a No. 60 sieve, and not more than 40% pass through a No. 100 sieve.

-Very fine (No. 80): All particles pass through a No. 80 sieve. There is no limit to greater fineness.

Particle size can influence a variety of factors:

1-Dissolution rate of particles intended to dissolve; **drug micronization can increase the rate of drug dissolution and its bioavailability.**

2-Suspendability of particles intended to remain undissolved but uniformly dispersed in a liquid vehicle (e.g., fine dispersions have particles ~0.5 to 10 µm)

3-Uniform distribution of a drug substance in a powder mixture or solid dosage form **to ensure dose-to-dose content uniformity**

4-Penetrability of particles intended to be inhaled for deposition deep in the respiratory tract (e.g., 1 to 5 µm)

5-Lack of grittiness of solid particles in dermal ointments, creams, and ophthalmic preparations (e.g., fine powders may be 50 to 100 µm in size)

Micromeritics

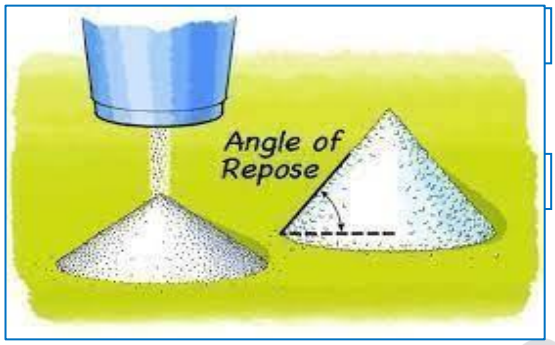
Micromeritics is the science of small particles; a particle is any unit of matter having defined physical dimensions. Micromeritics is the study of a number of characteristics, including:

a-particle size and
b-size distribution,
c-shape,
d-angle of repose,
e-porosity,
f-true volume,
g-bulk volume,
h-apparent density, and
i-bulkiness

Angle of Repose

The angle of repose is a relatively simple technique for estimating the flow properties of a powder.

It can easily be determined by allowing a powder to flow through a funnel and fall freely onto a surface. The height and diameter of the resulting cone are measured, and the angle of repose is calculated from this equation:



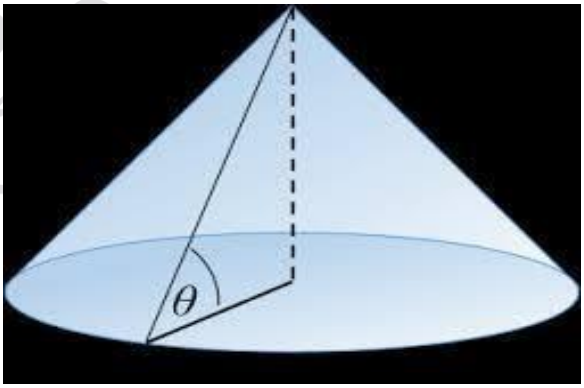
$$\tan \theta = h/r$$

Where **h** is the height of the powder cone and **r** is the radius of the powder cone.

Example*:* A powder was poured through the funnel and formed a cone 3.3 cm high and 9 cm in diameter. What is the angle of repose?

$$\tan \theta = h/r = 3.3/4.5 = 0.73$$

$$\text{arc tan } 0.73 = 36.25^\circ$$



Powders with a low angle of repose flow freely, and powders with a high angle of repose flow poorly.

Angle of repose as an indication of powder flow properties	
Angle of repose (degrees)	**Types of flow**
< 20	Excellent
20 – 30	Good
30 – 34	passable
> 40	Very poor

Flowability:

A number of factors determine the flow properties of powders, including:

-Shape : Spherical particles flow better than needles.

-Size : Very fine particles do not flow as freely as large particles.

In general, particles in the size range of 250 to 2,000µm flow freely if the shape is amen7uable.

Particles in the size range of 75 to 250 µm may flow freely or cause problems, depending on shape and other factors.

With most particles smaller than 100 µm, flow is a problem.

◇ Particle Size Reduction

Comminution, reduction of the particle size of a solid substance to a finer state, is used to facilitate:

-Crude drug extraction,

-Increase the dissolution rates of a drug,

-Aid in the formulation of pharmaceutically acceptable dosage forms, and ➢ Enhance the absorption of drugs.

The reduction in the particle size of a solid is accompanied by a great increase in the specific surface area of that substance.

◇ Comminution of drugs

-On a small scale, the pharmacist reduces the size of chemical substances by grinding with a mortar and pestle.

A finer grinding action is accomplished by using a mortar with a rough surface (as a porcelain mortar) than one with a smooth surface (as a glass mortar).

Grinding a drug in a mortar to reduce its particle size is termed ***trituration*** *or* ***comminution*****.**

-On a large scale, various types of mills and pulverizers may be used to reduce particle size.

Manual methods include

1-Trituration It is the principle method of comminution in pharmacy.

It is the process of reduction of particle size by rubbing in mortar and pestle. The size reduction is the result of both pressure and attrition as the pestle is firmly pressed down and given a circular motion over the inner surface of the mortar. Care must be taken to scraping the side down with spatula frequently

2-Levigation is commonly used in small-scale preparation of ointments and suspensions to reduce the particle size and grittiness of the added powders.

A mortar and pestle or an ointment tile may be used.

A paste is formed by combining the powder and a small amount of liquid (the levigating agent) in which the powder is insoluble.

The paste is then triturated, reducing the particle size.

The levigated paste may then be added to the ointment base and the mixture made uniform and smooth by rubbing them together with a spatula on the ointment tile.

Mineral oil and glycerin are commonly used levigating agents.

3. Pulverazation by intervention: This method includes reduction of particle size with the aid of a second agent, which can readily remove from the pulverized product.

This method usually used to reduce the particle size of camphour which otherwise difficult to triturate. When a few drops of alcohol or other volatile solvent are added, a camphour is readily triturated and the pulverized camphor is readily recovered as soon as solvent evaporated.

On a large scale, various types of mills and pulverizers may be used to reduce particle size.

Fitz Mill comminuting machine with a product containment system. Through the grinding action of rapidly moving blades in the comminuting chamber, particles are reduced in size and passed through a screen of desired dimension to the collection container.

The collection and containment system have the following advantages:

-Protects the environment from chemical dust,
-Reduces product loss, and
-Prevents product contamination.

Special processes of particle size reduction

These processes may be used to prepare powders for dosage forms include freeze-drying and spray drying.

Freeze Drying :(Drying by sublimation, lyophillization): It refers to the removal of water by sublimation from frozen products at low temperatures. Freeze drying is usually carried out in temperature range of –10 to – 40ºC. It is used to dry biological products such as blood serum, plasma, certain antibiotics such as penicillin, and other substances that are heat-labile and cannot be dried by the usual application of heat.

Spray drying: Is a process for converting solution or suspensions into dry, free-flowing powders in a single drying step. The solution or suspension is atomized or sprayed into an enclosed chamber into which heated air is also introduced.

The atomization process produces very fine, generally spherical droplets with large surface areas that dry almost instantaneously.

◇ Blending Powders

When two or more powdered substances are to be combined to form a uniform mixture, it is best to reduce the particle size of each powder individually before weighing and blending.

Depending on the nature of the ingredients, the amount of powder, and the equipment, powders may be blended by :

-Spatulation,
-Trituration,
-Sifting, and
-Tumbling

Spatulation

-Spatulation is blending small amounts of powders by movement of a spatula through them on a sheet of paper or an ointment tile.

-It is not suitable for large quantities of powders or for powders containing potent substances, because homogeneous blending is not as certain as other methods.

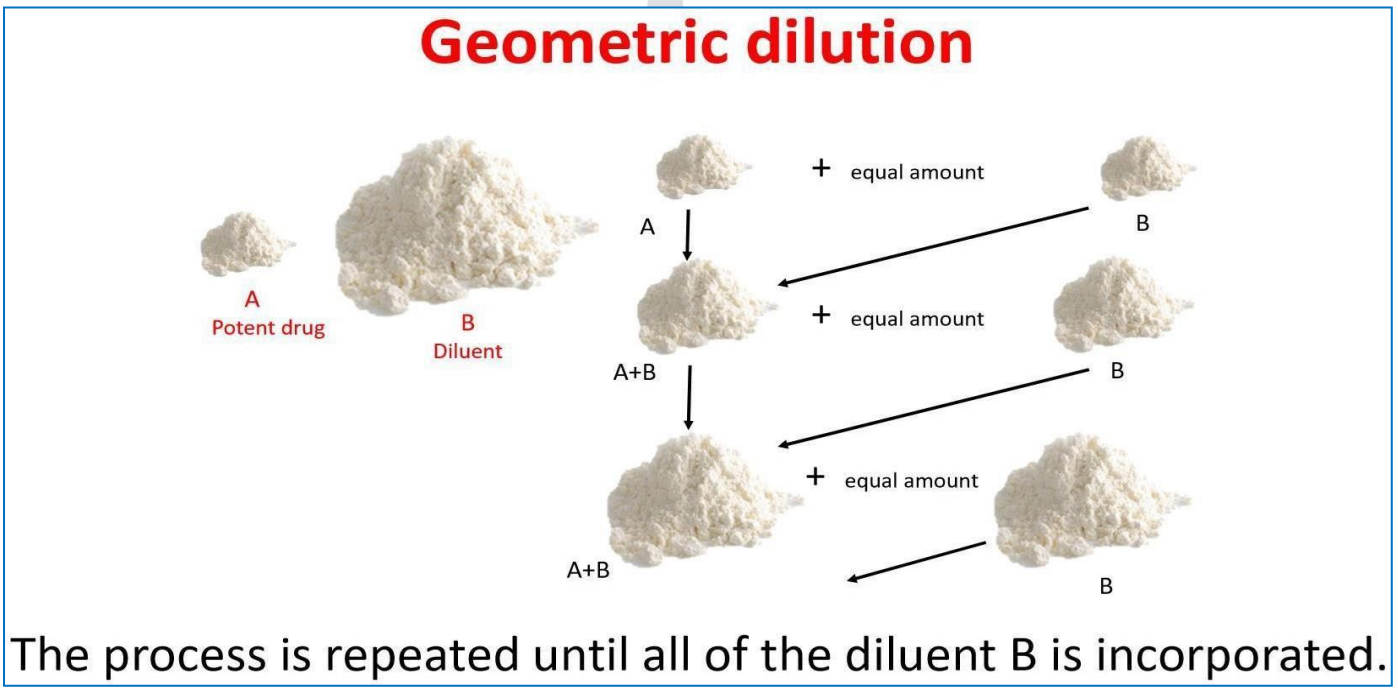
-Very little compression or compacting of the powder results from spatulation, which is especially suited to mixing solid substances that form eutectic mixtures (or liquefy) when in close and prolonged contact with one another.

-Substances that form eutectic mixtures when combined include phenol, camphor, menthol, thymol, aspirin, phenyl salicylate, and other similar chemicals. To diminish contact, a powder prepared from such substances is commonly mixed in the presence of an inert diluent, such as light magnesium oxide or magnesium carbonate, to separate the troublesome agents physically.

Trituration

-Trituration may be employed both to triturate and to mix powders. If simple mixing is desired without comminution, the glass mortar is usually preferred.

-When a small amount of a potent substance is to be mixed with a large amount of diluent, the geometric dilution is used to ensure the uniform distribution of the potent drug.



This method is especially indicated when the potent substance and other ingredients are the same color and a visible sign of mixing is lacking.

-By this method, the potent drug is placed with an approximately equal volume of the diluent in a mortar and is mixed thoroughly by trituration. Then, a second portion of diluent equal in volume to the mixture is added and the trituration repeated.

This process is continued by adding an equal volume of diluent to the powder mixture and repeating this until all of the diluent is incorporated.

-Some pharmacists add an inert colored powder to the diluent before mixing to permit visual inspection of the mixing process. (to ensure uniform distribution)

Sifting (sieving)

-Powders may also be mixed by passing them through sifters like those used in the kitchen to sift flour.

-Sifting results in a light, fluffy product. This process is not acceptable for the incorporation of potent drugs into a diluent powder.

Tumbling

-Another method of mixing powders is tumbling the powder in a rotating chamber.

-Special small-scale and large-scale motorized powder blenders mix powders by tumbling them

-Mixing by this process is thorough but time consuming.

-Such blenders are widely employed in industry, as are mixers that use motorized blades to blend powders in a large vessel.

Problems associated with particle size reduction

-Segregation: is an undesirable separation of the different components of the powder mixture (blend) due to differences in density and size.

-Segregation may occur by:

-Sifting or percolation

Fine particles tend to sift or percolate through coarse particles and end up at the bottom of the container and actually "lift" the larger particles to the surface.

-Air entrapment (fluidization),

Fine, aerated powders with differences in particle size or density may result in a striation pattern and may occur during powder transfer.

-Particle entrapment (dusting).

Dusting occurs when the finer, lighter particles remain suspended in air longer and do not settle as quickly as the larger or denser particles.

General guidelines to minimize or prevent segregation include :

(a) Minimum number of transfer steps and drop heights;
(b) Control of dust generation;
(c) Control of fluidization of the powder;
(d) Slow fill/transfer rate;
(e) Appropriate venting;
(f) Use of a deflector, vane, or distributor; and
(g) Proper hopper design and operating valves (if present).

Medicated Powders

-Some medicated powders are intended to be used **internally** and others, **externally**.

A. Internal powders

• Most powders for internal use are taken **orally** after mixing with water or in the case of infants in their infant formulas. Some powders are intended to **be inhaled** for local and systemic effects.

Other dry powders are commercially packaged for **constitution with a liquid solvent or vehicle**, some for administration **orally**, others for use as an **injection**, and still others for use as a **vaginal douche**.

1-Medicated powders for oral use

• Medicated powders for oral use may be intended for **local effects** (e.g., laxatives) or **systemic effects** (e.g., analgesics)

-and may be preferred to counterpart tablets and capsules by patients who have **difficulty swallowing solid dosage forms.**

-The doses of some drugs are **too bulky to be formed** into tablets or capsules of convenient size, so they may be administered as powders. For administration, they can be mixed with a liquid or soft food.

-Powders taken orally for systemic use may be **expected to result in faster rates of dissolution and absorption than solid dosage forms**, because there is immediate contact with the gastric fluids; however, the actual advantage in terms of therapeutic response may be negligible or only minimal, depending on the drug release characteristics of the counterpart products.

-A **primary disadvantage** of the use of oral powders is the undesirable taste of the drug.

-Some medications, notably antibiotics for children, are intended for oral administration as liquids but are **relatively unstable** in liquid form.

-They are provided to the pharmacist by the manufacturer as a **dry powder or granule for constitution** with a specified quantity of purified water **at the time of dispensing**.

-Under labeled conditions of storage, the resultant product remains stable for the prescribed period of use, generally up to 2 weeks

-Oral powders are formulations composed of solid, loose, dry particles of varying degrees of fine particle size. They contain one or more active substances with or without excipients and if necessary, approved colouring matter and flavouring.

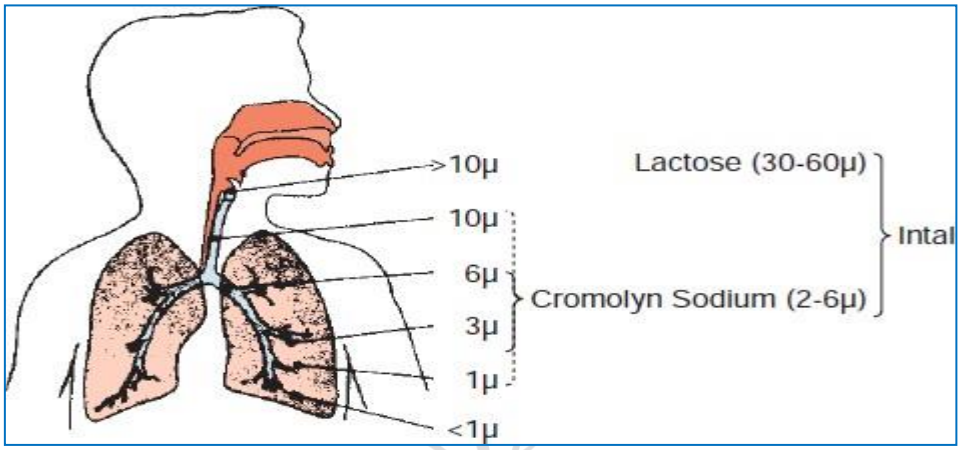
-They are generally administered with water or another suitable liquid, or they may also be swallowed directly.

-All powders and granules should be stored in a dry place **to prevent deterioration due to ingress of moisture. Even if hydrolytic decomposition of susceptible ingredients does not occur, the particles will adhere and cake, producing an inelegant, often unusable product.**

2-Aerosol powders

Some medicated powders are administered by inhalation with the aid of dry powder inhalers (DPIs), which deliver micronized particles of medication in metered quantities.

A DPI is a device used to administer an inhalation powder in a finely divided state suitable for oral inhalation by the patient. An inhalation powder is one used with a device that aerosolizes and delivers an accurately metered amount.
Most of these products are used in the treatment of asthma and other bronchial disorders that require distribution of medication deep in the lungs. To accomplish this, the particle size of the micronized medication is prepared in the range of 1 to 6 µm in diameter.



In addition to the therapeutic agent, these products contain **inert propellants** and **pharmaceutical diluents**, such as crystalline alpha- lactose monohydrate, to **aid the formulation's flow properties** and **metering uniformity** and **to protect the powder from humidity**.

They administered in a metered- valve container that apply a specific dose (Each dose is delivered through the mouthpiece upon activation of the aerosol unit's valve) or can use a powder blowers or insufflators

---

3-Nasal powder

They are medicated powders intended for inhalation into the nasal cavity by means of a suitable device. Some potent drugs are presented in this way because they are rapidly absorbed when administered as a fine powder via the nose.

-Delivery devices have been developed:

-To enhance convenience.

-To ensure that a uniform dose is delivered on each occasion.

-Sufficient drug for one dose may be presented in a hard gelatin capsule diluted with an inert, soluble diluent such as lactose. The capsule is placed in the body of the nasal delivery device and is broken when the device is assembled. The drug is inhaled, via the nose, by the patient as a fine powder.

B. External powders

Medicated powders for external use are dusted on the affected area from a sifter-type container or applied from a powder aerosol. Powders intended for external use should bear a label marked EXTERNAL USE ONLY or a similar label.

Powders for cutaneous application are presented as single-dose powders or multidose powders. They should be free from grittiness. Powders specifically intended for use on large open wounds or on severely injured skin must be sterile.

-Dusting powders contain ingredients used for therapeutic, prophylactic or lubricant purposes and are intended for external use.

Aerosol Dispensing of Powders

Bulk and Divided Powders

Medicated powders may be provided to the patient in bulk or may be divided into unit-of-use packages.

Some powders are packaged by manufacturers, whereas others are prepared and packaged by the pharmacist.

A-Bulk Powders

Among the bulk powders available in pre-packaged amounts are:

a-Antacids (e.g., sodium bicarbonate) and laxatives (e.g., psyllium (Metamucil]), which the patient takes by mixing with water or other beverage before swallowing;

b-Douche powders (e.g., Massengill Powder), dissolved in warm water by the patient for vaginal use;

c-Medicated powders for external application to the skin, usually topical anti-infective (e.g., bacitracin zinc and polymyxin B sulfate) or antifungal (e.g., tolnaftate)

d-Brewer's yeast powder containing B-complex vitamins and other nutritional supplements.

In some cases, a small measuring scoop, spoon, or other device is dispensed with the powder for measuring the dose of the drug.

Dispensing powder medication in bulk quantities is limited to non-potent substances.

-Patients should be educated about appropriate handling, storage, measurement, and preparation of bulk powder prescription and nonprescription products in addition to the customary counseling at the time of dispensing or purchase.

Generally, these products are stored at room temperature in a clean, dry place. These products should be kept out of the reach of children.

-Patients should be instructed how to measure the appropriate amount of the powder and be told the type and volume of liquid or vehicle to use to deliver the medication consistent with package and/or physician instructions.

◇ B-Divided powder

After a powder has been properly blended (using the geometric dilution method for potent substances), it may be divided into individual dosing units based on the amount to be taken or used at a single time.

Each divided portion of powder may be placed on a small piece of paper (Latin chartula; abbrev. chart; powder paper) that is folded to enclose the medication. A number of commercially prepared premeasured products are available in folded papers or packets, including

-Headache powders (e.g., Aspegic powders),

-Powdered laxatives (e.g., psyllium mucilloid, Fybrogel),

-Douche powders (e.g., Massengill powder packets).

Divided powders may be prepared by the pharmacist

Depending on the potency of the drug substance, the pharmacist decides whether to Weighing method: weigh each portion of powder separately before enfolding in a paper (for potent drugs) (The smallest amount of powders in a packet is 130mg).

block-and-divide method: approximate each portion by using the block-anddivide method, used only for non-potent drugs, the pharmacist places the entire amount of the prepared powder on a flat surface such as a porcelain or glass plate, pill tile, or large sheet of paper and, with a large spatula, forms a rectangular or square block of the powder having a uniform depth.

Then, using the spatula, the pharmacist cuts into the powder lengthwise and crosswise to delineate the appropriate number of smaller, uniform blocks, each representing a dose or unit of medication. Each of the smaller blocks is separated from the main block with the spatula, transferred to a powder paper, and wrapped.

Powder paper

The powder papers may be of any size convenient to hold the amount of powder required, but the most popular commercially available sizes are 2.75 × 3.75 in., 3 × 4.5 in., 3.75 × 5 in., and 4.5 × 6 in.

The papers may be :

a-Simple bond paper;
b-Vegetable parchment, a thin, semi-opaque paper with limited moisture resistance;
c-Glassine, a glazed, transparent paper, also with limited moisture resistance; and
d-Waxed paper, a transparent waterproof paper.

The selection of the type of paper is based primarily on the nature of the powder. If the powder contains hygroscopic or deliquescent materials, waterproof or waxed paper should be used.

-For convenience and uniformity of appearance, pharmacists may use commercially available small cellophane or plastic envelopes to enclose individual doses or units of use rather than folding individual powder papers. These envelopes are usually moisture resistant, and their use results in uniform packaging.

-Today, compounded powder papers are rarely used on an outpatient, community practice basis. Their use is usually limited to institutional and research practice

---

Granules Dosage Forms

One disadvantage of bulk powders is that, because of particle size differences, the ingredients may segregate, either on storage in the final container or in the hoppers of packaging machines.

If this happens the product will be nonuniform and the patient will not receive the same dose of the ingredients on each occasion. This can be prevented by granulating the mixed powders.

Granules are aggregates of a group of particles to form larger particles sufficiently robust to withstand handling.

They are irregular or spherical in shape.

They are usually in the 4-12-mesh size range, although granules of various mesh sizes may be prepared depending upon their application.

Advantage of granulation

1-Granules **flow better** than powders. The easy flow characteristics are important in supplying drug materials from the hopper or feeding container into the tableting presses. For this reason powder mixtures are usually granulated if they are intended to be compressed into tablets. Granules also eliminate or control dust.

2-Granules increase compressibility.

3-Granules have **smaller surface area** than a comparable volume of powders. This makes granules **more stable** physically and chemically than the corresponding powders. Granules are less likely to cake or harden upon standing than are powders.

4-Granules are **more easily wetted** by a solvent than are certain powders (which tend to float on the surface), so that granules are also preferred in making solutions. Example: Principen® (ampicillin) for Oral Suspension (Squibb).

Ampicillin is unstable in aqueous solution, so it is usually prepared as granules and reconstituted by a pharmacist with purified water just prior to dispensing.

The granules also contain colorants, flavorants, and other pharmaceutical ingredients, so the resulting solution or suspension has all the desired medicinal and pharmaceutical features of a liquid pharmaceutical.

5-Granules produce particle-size uniformity, thus content **uniformity**.

◇ Examples of granules

A number of commercial products containing antibiotic drugs that are unstable in aqueous solution are prepared as small granules for constitution by the pharmacist with purified water just prior to dispensing.

Examples include:

-KLACID granules for oral suspension (clarithromycin, Abbot),

-Augmentin ES-600 (amoxicillin/ clavulanate potassium, GSK) Uricol granules.

The granules are prepared to contain not only the medicinal agent but also colorants, flavorants, and other pharmaceutical ingredients.

The granules are measured and mixed with water or other beverages, sprinkled on food, or eaten plain.

Granulations of effervescent products may be compressed into tablet form, as Zantac EFFER dose tablets (Glaxo Wellcome). Also (Multivitamins) effervescent granules and tablets are dissolved in water before use.

Preparation of granules

Granules are prepared by wet methods and dry methods.

Wet method:

1-Moisten the powder or powder mixture with a fluid (with or without a binder).

2-Pass the resulting paste through a screen of the mesh size to produce the desired size of granules.

3-The resultant granules are placed on drying trays and are dried by air or under heat. The granules are periodically moved about on the drying trays to prevent adhesion into a large mass.

4-Screening stage.

Another type of wet method is fluid bed processing, in which particles are placed in a conical piece of equipment and are vigorously dispersed and suspended while a liquid excipient is sprayed on the particles and the product dried, forming granules or pellets of defined particle size

---

Dry method:

The dry granulation method may be performed in a couple of ways. By one method, the dry powder is passed through a roll compactor and then through a granulating machine.

An alternative dry method, termed slugging, is the compression of a powder or powder mixture into large tablets or slugs on a compressing machine under 8,000 to 12,000 lb of pressure, depending on the physical characteristics of the powder.

The slugs are generally flat- faced and are about 2.5 cm (1 in.) in diameter . The slugs are granulated into the desired particle size, generally for use in the production of tablets.

• The dry process often results in the production of fines, that is, powder that has not agglomerated into granules. These fines are separated, collected, and reprocessed

---

◇ Effervescent granulated salts:

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 undesirable taste of any medicinal agent.

Using granules or coarse particles of the mixed powders rather than small powder particles decreases the rate of solution and prevents violent and uncontrollable effervescence.

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

Using a combination of citric and tartaric acids rather than either acid alone avoids certain difficulties. When tartaric acid is used as the sole acid, the resulting granules readily lose their firmness and crumble. Citric acid alone results in a sticky mixture difficult to granulate.

Effervescence

-A good effervescent blend consists of both citric acid and tartaric acid (1:2 ratio).

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

Effervescent granules are prepared by two general methods: (a) the dry or fusion method and (b) the wet method

---

Fusion or dry method

In the fusion method, the one molecule of water present in each molecule of citric acid acts as the binding agent for the powder mixture.

Before mixing the powders, the citric acid crystals are powdered and then mixed with the other powders of the same sieve size to ensure uniformity of the mixture.

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 to avoid absorption of moisture and a premature chemical reaction.

After mixing, the powder is placed on a suitable dish in an oven at **34°C to 40°C**. During the heating process, an acid-resistant spatula is used to turn the powder.

The heat releases the water of crystallization from the citric acid, which in turn dissolves a portion of the powder mixture, setting the chemical reaction and consequently releasing some carbon dioxide.

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.

-A no. 4 sieve produces large granules,

-A no. 8 sieve prepares medium size granules, and ➢ A no. 10 sieve prepares small granules.

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

◇ Wet Method

The wet method differs from the fusion method in that the source of binding agent is not the water of crystallization from the citric acid but the water added to alcohol as the moistening agent, forming the pliable mass for granulation.

In this method, all of the powders may be anhydrous as long as water is added to the moistening liquid. Just enough liquid is added (in portions) to prepare a mass of proper consistency; then the granules are prepared and dried in the same manner as described.