Powders & Granules

Powders

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.

Composition

Properly prepared, powders have a uniform, small particle size that has an elegant appearance. In general, powders are more stable than are liquid dosage forms and are rapidly soluble, enabling the drug to be absorbed quickly.

The properties of powders are related to the size and surface area of the particles. For example, large particles that are denser tend to settle more rapidly than do small particles; particles that are more bulky will settle more slowly. This characteristic must be considered in mixing or storing and shipping, when powders of different particle size may become segregated.

Another concern stems from the fact that powder dosage forms have a large surface area that is exposed to atmospheric conditions. Thus, powders should be dispensed in tight containers. Further, because powders of small particle size present a greater surface area to the atmosphere, they are more reactive in nature and can adsorb larger quantities of gases, such as carbon dioxide.

However, if the powder has a smaller particle size, it can dissolve at a more rapid rate, unless adsorbed gases prevent the water from surrounding the individual particles and wetting them, thereby decreasing their wetting properties.

Topical Powders

Topical powders should have a uniform, small particle size that will not irritate the skin when applied. They should be impalpable and free flowing, should easily adhere to the skin, and should be passed through at least a No. 100-mesh sieve to minimize skin irritation. The powder should be prepared so that it adheres to the skin.

The powder should be prepared so that it adheres to the skin. Highly sorptive powders should not be used for topical powders that are to be applied to oozing wounds, as a hard crust may form. A more hydrophobic, water repellent powder will prevent loss of water from the skin and will not cake on the oozing surfaces. Talc, or any other naturally derived product that is to be used on open wounds, should first be sterilized to avoid an infection in the area.

Topical powders usually consist of a base or vehicle, such as cornstarch or talc; an adherent, such as magnesium stearate, calcium stearate, or zinc stearate; and possibly an active ingredient, along with an aromatic material. The powder should provide a large surface area, flow easily, and spread uniformly. The large surface area will aid in absorbing perspiration and give a cooling sensation to the skin.

Insufflated Powders

Insufflated powders are finely divided powders that are intended to be applied in a body cavity, such as the ears, nose, vagina, tooth socket, or throat. When using an insufflator, or "puffer," the patient simply "puffs" the desired quantity of powder onto the affected area or into the cavity. This device is particularly appropriate for anti-infectives.

Physicochemical Considerations

Before the use of powders 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.

Drug and other materials commonly require chemical or pharmaceutical processing to enable both the efficient production of a finished dosage form and the optimum therapeutic efficacy. This usually includes the adjustment and control of a powder's particle size.

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.

Granules typically fall within the range of 4- to 12-sieve size

Very coarse →

Coarse →

Moderately coarse →

Fine →

Very fine →

SIEVE NUMBER	SIEVE OPENING
2.0	9.50 mm
3.5	5.60 mm
4.0	4.75 mm
8.0	2.36 mm
10.0	2.00 mm
20.0	850.00 μm
30.0	600.00 μm
40.0	425.00 μm
50.0	300.00 μm
60.0	250.00 μm
70.0	212.00 μm
80.0	180.00 μm
100.0	150.00 μm
120.0	125.00 μm
200.0	75.00 μm
230.0	63.00 μm
270.0	53.00 μm
325.0	45.00 μm
400.0	38.00 μm

- Dissolution rate of particles intended to dissolve; drug micronization can increase the rate of drug dissolution and its bioavailability.
- 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).
- Uniform distribution of a drug substance in a powder mixture or solid dosage form to ensure dose-to-dose content uniformity.
- Penetrability of particles intended to be inhaled for deposition deep in the respiratory tract (e.g., 1 to 5 µm).
- 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)

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.

Levigation is the process of reducing the particle size of a solid by first forming a mass of the solid with a liquid and then grinding the mixture in a mortar with a pestle or on a slab with a spatula.

Levigation is convenient for the comminution of medicinal agents which are to be incorporated into fatty bases for the preparation of semisolids.

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** is blending small amounts of powders by movement of a spatula through them on a sheet of paper or an ointment slab. 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. 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 them physically.

- **Trituration** may be employed both to comminute and to mix powders. If simple admixture is desired without the special need for 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 method is used to ensure the uniform distribution of the potent drug. This method is especially indicated when the potent substance and other ingredients are of the same color and a visible sign of mixing is lacking.
- **Sifting** by passing the powders 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.
- 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.

Medicated Powders

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

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**".

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.
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.

Sterile dry powders intended to be constituted with sterile water of injection prior to administration by injection.

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.

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.

Dispensing of Powders

Medicated powders may be provided to the patient as **bulk powders** or as **divided powders**.

Bulk Powders

These are limited to those powders which are non-toxic and can be measured safely in a spoon by the patient as well as for the dusting powders.

Among the bulk powders available are:

a) Antacids (e.g., sodium bicarbonate) and laxatives (e.g., Metamucil) which the patient takes by mixing with water or another beverages 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-infectives (e.g., bacitracin zinc and polymyxin B sulfate) or antifungals (e.g., tolnaftate); and
d) Multivitamins and nutritional supplements powders.

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. Powders containing substances that should be administered in controlled dosage are supplied to the patient in divided amounts in folded papers or packets.

Divided Powders

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.

Depending on the potency of the drug, the pharmacist decides whether to use weighing method or blocking and dividing method.

Several kinds of papers may be used:

a) Simple bond paper;
b) Vegetable parchment, a thin, semiopaque 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.

Powders containing volatile components should be wrapped in waxed or glassine papers. Powders containing neither volatile components nor ingredients adversely affected by air or moisture are usually wrapped in a white bond paper.

Problems associated with powder dosage form

Eutectics

Some powders may become sticky or pasty, or they may liquefy when mixed together, such as acetanilide, aspirin, camphor and chloral hydrate.

To keep the powders dry, one can mix them with a bulky powder adsorbent such as light magnesium oxide or magnesium carbonate. Also, these powders should be triturated very lightly by using a spatula for mixing rather than a mortar and pestle. The latter will cause compression and make the problem worse. It may also be advisable to double wrap the papers.

Hygroscopic and deliquescent powders

Hygroscopic powders will absorb moisture from the air. Deliquescent powders will absorb moisture from the air to the extent that they will partially or wholly liquefy. These problems must be overcome for the powder to be acceptable to the patient and usable.

The best approach is to dispense the ingredients in tight containers and incorporate a desiccant packet when necessary. The patient should be instructed to store the powder in a dry place in a tightly closed container.

To lessen the extent of the problem, the compounding pharmacist can in some situations dilute the powder with an inert drying powder to reduce the amount of surface area exposed to the moisture. Examples for hygroscopic and deliquescent powders are ammonium bromide, calcium bromide, hyoscyamine hydrobromide and hyoscyamine sulfate.

Efflorescent powders

An efflorescent powder like alums, atropine sulfate, caffeine, citric acid and codeine is a crystalline powder that contains water of hydration or crystallization. This water can be liberated either during manipulations or on exposure to a low-humidity environment. If this occurs, the powder will become sticky and pasty, or it may even liquefy.

One approach is to use an anhydrous salt form of the drug, keeping in mind the potency differential between its anhydrous form and it's hydrated form. Another method is to include a drying bulky powder and to use a light, noncompacting method of mixing the powders.

Explosive Mixtures

Some combinations of powders like bromine & alcohol, chlorates & bisulfites as well as chloric acid & bromides may react violently when mixed together. Special precautions must be taken if it is necessary to prepare a formulation containing these mixtures.

Incorporation of liquids

A liquid that is to be incorporated into a dry powder can be adsorbed onto an inert material (carrier) such as lactose or starch and then geometrically introduced into the bulk of the powder. Pasty material can be added to dry powder by mixing it with increasing quantities of the powder, which will dry out the paste.

It is best to add some materials by preparing an alcoholic solution and spraying it evenly on the powder, which has been spread out on a pill tile. The alcohol, or another suitable solvent, should then be allowed to evaporate, leaving the ingredient uniformly dispersed. This method may be especially suitable for high-potency drugs or flavoring agents because it minimizes the possibility that clumps of active drug will develop in the powder blend.

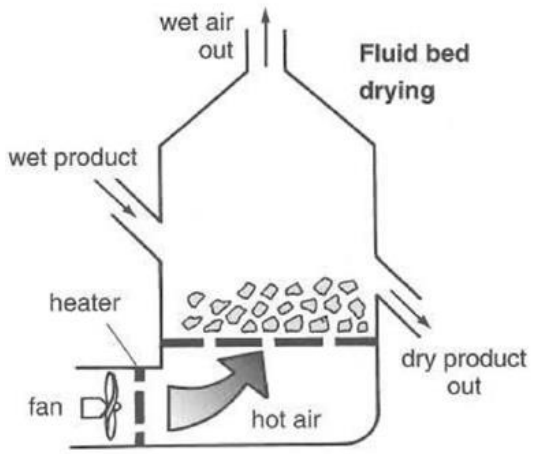
Granules

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.

Granules are frequently compacted into tablets or filled into capsules, with or without additional ingredients.

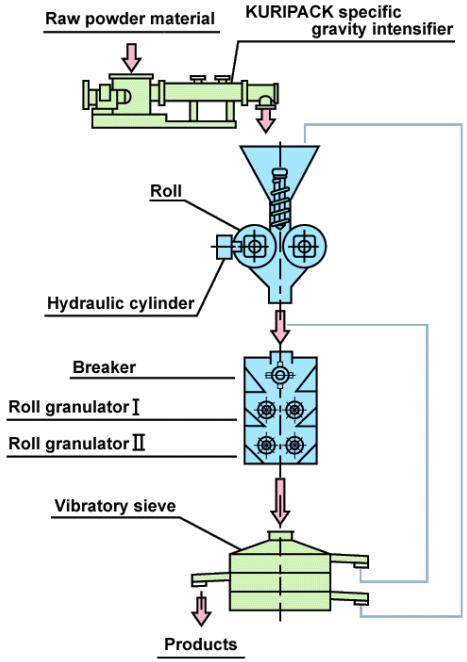
As indicated previously, granules are prepared agglomerates of smaller particles of powder. They are irregularly shaped but may be prepared to be spherical. They are usually in the 4- to 12-mesh sieve size range, although granules of various mesh sizes may be prepared depending upon their application.

Granules are prepared by wet methods and dry methods. One basic wet method is to moisten the powder or powder mixture and then pass the resulting paste through a screen of the mesh size to produce the desired size of granules. The 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. Another type of wet method is fluid bed processing.



Fluidized bed dryer

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



Roller Compactor

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 high pressure, depending on the physical characteristics of the powder. The slugs are generally flat-faced and are about 2.5 cm (1 inch) 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.

Granules flow well compared to powders. Because of their flow properties, granulations are commonly used in tablet making to facilitate the free flow of material from the feeding container (or hopper) into the tablet presses. Granules have other important characteristics. Because their surface area is less than that of a comparable volume of powder, granules are usually more stable to the effects of atmospheric humidity and are less likely to cake or harden upon standing. Granules also are more easily wetted by liquids than are certain light and fluffy powders (which tend to float on the surface) and are often preferred for dry products intended to be constituted into solutions or suspensions.

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.

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

a) Dry or Fusion 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. 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.

b) 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 alcohol used as the moistening agent, forming the pliable mass for granulation.

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 previously described.