Powders, Granules and Spheres

Larry Augsburger
University of Maryland
School of Pharmacy
Powder

- As a dosage form, a powder [Latin, *pulvis*] is a mixture of finely divided drugs and excipients in dry form.
- May be intended for internal use or external use, but *most frequent use is external*. 
- Should be differentiated from the general use of the term “powder” or “powdered” which is commonly used to describe a physical state of matter.
- Use as a dosage form is limited, but use in preparation of other dosage forms is extensive.
Bulk Powders for External Use

• Powders dispensed in bulk intended for topical application are called dusting powders
  – Common diluents are starch and talc

• More easily applied when dispensed in sifter-top shaker containers
  – Most sifter-top containers are not “tight containers”
  – May not be suitable if contains volatile components or if must be protected from atmospheric moisture

• Examples include:
  – Methylbenzethonium Chloride Powder, USP
  – Nystatin Topical Powder, USP
NAME: Patty O’furniture
DATE: 2/25/03
ADDRESS: 20 N. Pine St.

Rx

Zinc oxide

Talc

Starch aa 5 g

Nystatin Topical Powder 1:10 with above (100,000 units per g)
Mix and Make Pulv.

Sig. Apply to area with each diaper change

Dispense in sifter-top container.
Powders for Internal Use

• **Advantages and Disadvantages**
  - Can generally administer fairly large quantities (e.g. pour directly onto back of tongue, stir in beverage, mix with apple sauce etc.)
    - May be preferred by some patients who have trouble swallowing “objects,” such as tablets or capsules.
  - Taste may be a problem

• **Powders for internal use may be dispensed in bulk or in divided, individually packaged portions [doses], depending mainly on the potency of the powder.**
  - Bulk powders for internal (oral) use are usually granulated.
NAME: Lynne Oleum                  DATE: 2/25/03
ADDRESS: 20 N. Pine St.

Rx

<table>
<thead>
<tr>
<th>Drug</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum hydroxide</td>
<td>3.75 g</td>
</tr>
<tr>
<td>Magnesium trisilicate</td>
<td>3.75 g</td>
</tr>
<tr>
<td>Peppermint Oil</td>
<td>10 drops</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>q.s. 15.0 g</td>
</tr>
<tr>
<td>M &amp; Ft Pulv.</td>
<td>7.5 g</td>
</tr>
</tbody>
</table>

Sig. One level tsp in water t.I.d. PC

Package in wide mouth ‘tight container’ (glass jar)
Divided Powders

- Latin *chartulae* (pl.); Abbreviation: *charts*.
- Aka ‘Powder Papers’
- After mixing, the powder blend is divided into individual units based upon the dose to be administered.
- The divided portions are each placed on a small piece of paper, which is then folded to enclose the medication (powder papers).
- Traditionally, the powder packets are dispensed in a cardboard “Powder Box.”
Divided Powders

Hinged lids preferred

Powder Papers Dispensed in Powder Box

Label either on top of lid or on inner surface of lid

University of Maryland
School of Pharmacy
Divided Powders

• Difficult to protect from atmospheric moisture or oxygen
  • Large specific surface area
  • Traditional packaging of divided powders provides little protection from atmosphere (consider “baggies”).
Divided Powders

• Have generally fallen into disuse because of the ready availability of tablets and capsules.

• Some commercial OTC products are packaged in similar unit-dose packets:
  – BC Headache Powders
  – Stanback Analgesic Powders
NAME: Mary Land

ADDRESS: 20 N. Pine St.

DATE: 2/25/03

Age: 11 yrs (88 lbs)

Rx

Hydralazine 0.75mg/Kg/day in 4 divided doses

M & Ft charts. # 8

Sig. Contents of one on Cool Whip or pudding q.I.d.
Calculation of dose:

\[
\frac{88 \text{lbs}}{2.2 \text{lb / Kg}} = 40 \text{Kg}
\]

\[
\frac{0.75 \text{mg}}{\text{kg / day}} \times \frac{40 \text{kg}}{\text{day}} \times \frac{\text{day}}{4 \text{doses}} = 7.5 \text{mg / dose}
\]

How many Hydralazine tabs (25mg) are needed?

Assuming each tablet weighs 200 mg and calculating for 9 doses (1 extra) to account for losses:

\[
\frac{7.5 \text{mg}}{\text{dose}} \times 9 = 67.5 \text{mg}
\]

\[
\frac{25 \text{mg}}{200 \text{mg}} = \frac{67.5 \text{mg}}{X \text{mg}}; \ X = 540 \text{mg}
\]

Hydralazine required Crushed tab powder required to supply

If you wish the content of each powder to weigh 250 mg, add 1710 mg lactose to the 540 mg crushed tablet powder:

\[
250 \text{mg} \times 9 = 2250 \text{mg} - 540 \text{mg} = 1710 \text{mg}
\]
Insufflations

• An insufflation is a powder intended to be blown or aerated into a body cavity such as the nose, tooth socket or the vagina.
  – Example: Compound Clioquin Powder, USP
    • Used by vaginal insufflation as an antitrichomonal
Granules

- Prepared by agglomeration of small particles.
- Generally irregular in shape, as opposed to **spherical**.
- Often in 4 to 12 mesh size, but size can vary greatly depending on the application.
  - May be dispensed in bulk as a dosage form for oral administration, e.g. as antacid, dietary supplement etc.
  - Widely used as an intermediate for making compressed tablets. Powders may also be granulated prior to filling into capsules.
Why granules?

- Flow better than powders (granulation is a *size enlargement* process) and have better compactibility than powders (*binders*)
  - advantage in making tablets or filling capsules (feeding of high-speed equipment)
- Less surface area per unit weight than powders
  - More stable to atmospheric moisture/oxygen
  - Less likely to cake in the container than powders.
Why granules?

• “Wet” granulation provides for the addition of liquid phase suited to dispersion of low dose drugs in solution to ensure content uniformity.
  – Permits handling of powders without loss of blend quality (i.e., drug is locked in granules…a form of ordered mixing)
  – When used as an intermediate for tablets or capsules, this feature is particularly important as a way to achieve content uniformity for low dose drugs.
Why granules?

• “Wet” granulation may improve drug dissolution (e.g. from a tablet) by enhancing wettability through *hydrophilization*.
  – The hydrophilic binder, which covers particle surfaces and is intimately dispersed throughout the matrix of the granules, attracts water and can enhance the ability of hydrophobic, poorly soluble drugs to be wetted by dissolution fluids.
\[ \frac{dw}{dt} = KS \]

**Special Case of the Noyes-Whitney Equat.**

*(Sink Conditions)*

- \( dw/dt \) = dissolution rate (e.g. g/sec)
- \( K \) = constant (for a given set of experimental conditions)
- \( S \) = total surface area of drug accessible to solvent

For drugs that are relatively hydrophobic, hydrophilization may increase the *effective* surface area, \( S \).
Examples of Granules as a Dosage Forms

- Reconstituted antibiotics
- Bulk laxatives, e.g. Senokot Granules [granules contain standardized senna concentrate]
- Bulk analgesics, e.g., effervescent granules such as Bromo Seltzer
# Selected Binders for Wet Granulation

<table>
<thead>
<tr>
<th>BINDER</th>
<th>% OF FORMUL</th>
<th>% IN BINDER SOLUTION</th>
<th>SOLVENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREGELAT. STARCH</td>
<td>2-5</td>
<td>10-15</td>
<td>WATER</td>
</tr>
<tr>
<td>STARCH</td>
<td>2-5</td>
<td>5-25</td>
<td>WATER</td>
</tr>
<tr>
<td>GELATIN</td>
<td>1-3</td>
<td>5-10</td>
<td>WATER</td>
</tr>
<tr>
<td>PVP (polyvinylpyrrolidone)</td>
<td>0.5-5</td>
<td>5-10</td>
<td>WATER OR HYDRO-ALCOHOLIC</td>
</tr>
<tr>
<td>HPMC (hydroxypropylmethyl cellulose)</td>
<td>2-5</td>
<td>5-10</td>
<td>WATER OR HYDRO-ALCOHOLIC</td>
</tr>
</tbody>
</table>
Manufacture of Granules

• Traditional Wet Method

1. Blend powders
2. Add Binder Solution
3. Moist Mass
4. Pass through screen
5. Moist Agglomerates
6. Dry
7. Pass through screen
8. Properly sized dry granules
9. Dried Granules
Low Shear Granulator
(Planetary Mixer)

Mixing arm rotates on its own axis and revolves (i.e., “planetary” motion)
High Shear Granulator
(Collette Gral Type)

- Bowl
- Impeller 200-600 RPM
- High speed Chopper (1500-4000 RPM)
Fluid Bed Granulation

- Exhaust Filter
- Spray Nozzle
- Product Container
Fluid Bed Granulation

• Requires proper balance of inlet air temperature and feed rate.
  – For a given feed rate:
    • Higher inlet air temperatures cause rapid evaporation of the binder solution and results in smaller, friable granules.
    • At lower inlet temperatures, drying is slower (particles stay wetter longer); produces larger, denser, stronger granules.
  – For a given inlet temperature
    • Higher feed rates increases the ‘evaporative load’ and slows drying; tends to produce larger, denser and stronger granules
    • Lower feed rates tend to produce smaller, friable granules
Wet granulation is not practical for drugs sensitive to water or heat...
Dry Granulation

• Slugging (Older Process)
  – Mix with dry binders
  – Compress into large crude tablets (slugs) on a special heavy duty "slugging press"
  – Mill the slugs to form granules
  – Slugging is slow and may require double lubrication (could slow drug dissolution)

• Roller Compaction
  – Powder blend force between rollers to form a cake ("ribbon")
  – Cake milled to form granules
Roll Compactor

Screw Auger

Compacted Cake → Milled ("Ribbon")
Dry Granulation

- Compact formation facilitated by
  - Increased time under pressure facilitates bonding between particles
  - Use of highly compactible excipients that can effectively function as *dry binders*.
    - Microcrystalline cellulose
Effervescent Granulated Salts
“Effervescent Salts”

- Effervescent granules contain medicinal substance usually in combination with sodium bicarbonate, citric acid and tartaric acid.
- Carbon dioxide forms with placed in water.
- Carbonation helps mask the unpleasant taste of drugs.
- Granular form (as opposed to power form)
  - Dissolves more slowly and provides a more controlled reaction
  - More stable to atmosphere
Manufacture of Effervescent Granules

- Wet method - moisten with “non-solvent,” e.g. 95% alcohol. Just enough water to granulate without causing effervescence.
- Dry (fusion) method - Requires use of citric acid monohydrate. Under carefully controlled conditions, heat to 93-104°F to liberate the water of crystallization from CA which then serves to moisten the powders for granulation.
Pharmaceutical Pellets

• The terms "pellet" and "bead" are often used interchangeably to describe spherical or nearly spherical particles, typically in the 0.5 to 1.5 mm size range

• Two main methods of manufacture:
  – Extrusion/Spheronization: A type of granulation process which produces spherical "granules."
    • Generally involves the same fillers and binders as are used as in conventional granulation.
    • Drug becomes integral part of the pellet
  – Layering drug onto the surface of preformed sugar-starch beads (non-pareils)

• Pellets of either type are usually coated with a functional coating to provide modified drug release.
Section Through a Layered Pellet
Modified Release Dosage Forms

• Dosage forms whose drug-release characteristics of time-course and/or location are modified:
  – Delayed Release
  – Extended (Sustained) Release
Delayed Release

• Release of a drug (or drugs) at a time other than immediately following oral administration, e.g.
  – Enteric Coated
    • Prevents release of drug in stomach; releases after passing pyloric sphincter
  – Pulsatile Drug delivery
    • programmable to release drug at predetermined time or place.
Extended (Sustained) Release

- Any product formulated to make the contained medicament available over an extended period of time after ingestion, thus providing for a reduction in dosing frequency as compared to the same drug presented in a conventional IR dosage form.
  - Controlled Release (Ideal zero order)
  - Prolonged Release
Differences in Definitions

- Immediate Release
- Delayed Release
- Controlled Release (Zero-order)
- Prolonged Release

Therapeutic Range

Plasma Concentration vs. Time
Functional Coatings are Coatings that Modify Drug Release

- An *Extended Release* formulation may consist of uncoated pellets that provide the priming dose and perhaps three groups of coated pellets each with coatings of different thickness to provide the extended release.
- *Enteric coated* delayed release beads are coated to prevent release in the stomach.
Dissolution Controlled Systems

• Coat drug laden pellets with a slowly dissolving/eroding polymeric material – once the coating is gone, all drug inside membrane is immediately available for dissolution/absorption.

• Drug release controlled by thickness of coating – drug will be released at different predetermined times (“pulses”) from batches having different membrane thicknesses.

• Mixing batches that have different membrane thicknesses provides more or less uniform sustained release.

• Spansule®
Diffusion Controlled Systems
(Reservoir Systems)

• Also known as "Membrane Modulated Controlled Release Systems"
• Coating forms an insoluble, permeable membrane.
  – Examples: Nitro-BID, Nitrospan, Measurin
Pelletted Drug Delivery Systems

Inderal LA
Pelleted Systems Provide...

- **Ideal Shape**
  - Easier to have uniform thickness compared to irregular shapes
  - High flowability

- **Flexibility in Design of Drug Delivery Systems**
  - Modified Release
  - Delivery to Special Populations
    - "Sprinkle Concept" [Theo-Dur Sprinkle]
  - Combined Delivery of Two or More AIs in same DF
    - May or may not be compatible
    - Different release rates based on PK of each drug
Pelleted Systems Provide...  
(continued)

– Usually filled into capsules, but also may be tableted.

• Requires **special** consideration – need to avoid damage or destruction of any controlled release coatings.

![Toprol XL 50 Beads](image)
Extrusion and Spheronization

• Spheronization
  – Process of preparing spherical pellets from cylindrical (more or less) extrudate strands by high speed rotation over a friction plate in a spheronizer.

• Extrudate
  – Formed by forcing a moist drug-excipient mixture (wet granulation) through a "pasta machine."

• Marumerization
  – Spheronization as referred to by the trademark granted to the originator, Nabuo Nakahara, of the Fuji Denkyo Co., Japan
Extrusion and Spheronization

Blend drug + filler → Wet granulate → Pass through Extruder → Spheronize → Dry → Coat → Tablet

Fill into Capsules
Typical Extruder

Feed

Extrudate
(Short pieces of “spaghetti-like” strands)
View of Actual Extruder
Spheronizer

Surface of Disc
SPHERONIZATION

• Rotational speeds of 100 - 1000 RPM
• Very rapid process
  – May be completed in a little as 2 minutes and typically requires no more than 15 minutes.
• Greater deformation and rounding at higher speeds that provide more forceful impacts
  – Extrudate must have the correct degree of plasticity to form spheres – must not be too “stiff”
  • Yield strength of extrudate is mostly dependent on having optimal moisture content
Formation of Spheres

Shape Factor

Time (min.)

Cylinders
Cylinders with rounded ends
Dumbell
Ellipsoid
Spheroid