SOLID DOSAGE FORMS

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Reference: A. J. Hickey & D. Ganderton, Pharmaceutical Process Engineering, Chapter 14, 2nd edition, Informa Healthcare. 2010

DOSAGE FORMS

- **Dosage forms** are essentially pharmaceutical products in the form which involves a mixture of active drug components and inactive nondrug components (excipients).
- Depending on the method/route of administration, dosage forms come in several types:
  - Liquid dosage forms
  - Solid dosage forms
  - Semisolid dosage forms

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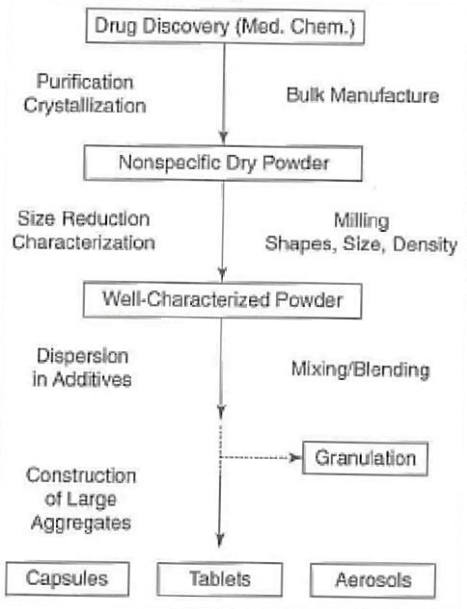
Solid Dosage Forms Introduction

- In previous topic, the subject of powders was addressed from a physicochemical standpoint.
- The *unit processes* involved in incorporating powders in solid dosage forms must also be considered.
- Solid dosage forms can be divided into **granules**, **capsules**, **tablets** for oral delivery, and **inhalation products**.
- Note that solid particulates might also play a role in certain parenterals in the form of reconstitutable products.

Solid Dosage Forms Introduction

- Solid dosage forms are the most desirable final products of a development process that begins with drug discovery and proceeds through bulk product manufacturing, preformulation, and formulation characterization to one of the products mentioned.

Solid Dosage Forms



Solid Dosage Forms
Introduction

- Most solid dosage forms are intended for oral ingestion.
  - The drug released from the dosage form is available at the site of absorption or action within the gastrointestinal tract.
- Preformulation studies are required before a formulation is developed.
  - By studying the properties of the drug, it is possible to delineate a course of action for composing the formulation.

Solid Dosage Forms
Drug Properties

- organoleptic properties
- purity
- particle size, shape, and surface area
- solubility
- dissolution
- parameters affecting absorption (dissociation constant, partition coefficient)
- crystal properties and polymorphism
- stability (chemical and physical)
- compatibility (with excipients and potential packaging materials)
- miscellaneous physicochemical properties like
  - density
  - hygroscopicity
  - flowability
  - compressibility
  - wettability

Solid Dosage Forms
Introduction

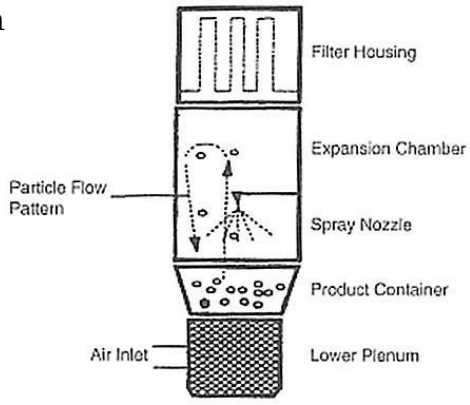
- Problem solving in service of formulation development can be derived from knowledge of these properties.
- The additives employed in solid dosage forms are categorized as **diluent**, **glidant**, **lubricant**, **disintegrant**, and **binder**.
  - Several candidates from each category may be considered as components of a possible dosage form.
  - Lubricants and disintegrants play a more substantial role in compressed tablet dosage forms than they do in granules or capsules.

Solid Dosage Forms
Granulation

- The simplest form of solid dosage form employs granules prepared from the drug and other components in stable aggregates in sizes large enough to facilitate accurate manipulation and dispensing in bulk and at the level of the unit dose.
- Following particle size reduction and blending, the formulation may be granulated, which provides homogeneity of drug distribution in the blend.
- In addition, it may help flow properties and powder compression characteristics.

Solid Dosage Forms
Granulation

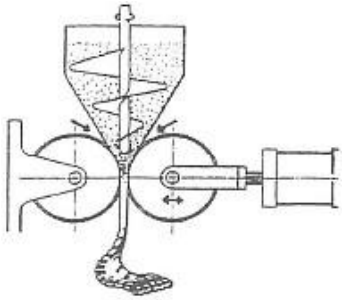
- Large granules can be prepared from primary particles by drying from a slurry or by spraying with granulation solution.



Top-spray granulator

Solid Dosage Forms
Granulation

- An alternative method employs an auger to force the blend between rollers, thereby forming a compressed solid that disintegrates into large aggregates.



Granulator with an auger to force the blend between rollers

Solid Dosage Forms
Granulation Steps

1. Granulation begins with transferring powders to a mixer and blending the product.
2. The granulation solution can be added, and coarse milling or wet granulation begins.
3. Finally, the product is dried and milled to an appropriate size.

Solid Dosage Forms
Granulation

- If the powder is *unstable in the presence of polar solvents*, it may be compressed directly.
- Granulation **increases the uniformity** of drug distribution in the product, **improves the powder flow rate and uniformity of flow**, and, if used as an aid to tableting, **assists in compression and bonding**.

Solid Dosage Forms
Granulation

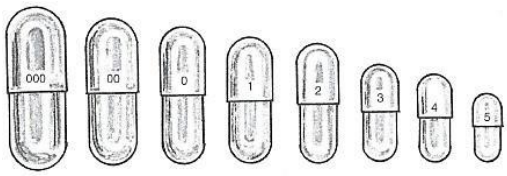
- More sophisticated approaches to combining the drug and excipients into a free-flowing large particle size to improve homogeneity, handling, and drug release characteristics include spray drying, fluid bed drying, extrusion spheronization, and microsphere or microcapsule formulation.
- All of these processes are governed to some degree by fundamental fluid flow, heat, and mass transfer phenomena.

Solid Dosage Forms
Hard Capsules

- Hard capsules have traditionally been manufactured from gelatin.
- The gelatin is obtained from bone or skin (calf or pig) acid or alkali treatment over a period of weeks, in some cases as long as 30 weeks (pork skin, 1-5% HCI).
- The product pH is adjusted, and a hot water extraction is followed by filtration, concentration, and solidification.
- The final product is milled to size.

Solid Dosage Forms
Hard Capsules

- Capsule shells are prepared by dipping manganese bronze pins into a bath of molten gelatin. Once removed from the bath, the gelatin solidifies on the pins.
- The caps and bodies are then dried and trimmed.
- Colorant or titanium dioxide (for opacity) is added as part of this process.



Solid Dosage Forms
Hard Capsules

- Not all capsules are made from gelatin, and alternatives are needed, why?
  - The need for capsules with different physicochemical properties, to aid in stability for example, has promoted a search for alternative materials.
  - In addition, individuals who, for strict religious or health reasons, cannot ingest gelatin, need alternative products.
- In this regard, starch and hydroxypropylmethyl cellulose (HPMC) have been developed.
- There is no reason to believe that other film-forming polymers might not be useful in this regard.

Solid Dosage Forms
Hard Capsules

- One significant issue that must be considered is the **moisture content of the capsule**.
- Gelatin is known to *optimally* contain 5% to 15% moisture.
  - Below 5%, the shell becomes brittle and may shatter.
  - Above 15% the gelatin distorts, and the shape of dosage form, if not its integrity, is challenged.
- The presence of a nutrient-rich environment and moisture may offer an ideal situation for *microbial growth* and *enzyme action*.
- **Control of microbial growth** is, therefore, a serious consideration in the preparation of capsule products.

Solid Dosage Forms

Hard Capsules Sizes

- Various capsule sizes are manufactured
- There are no strict rules for predicting required capsule size.
- Capsules are selected on the basis of their capacity and the nature of the formulation to be added.
- The **bulk density** and **compressibility** of the drug product (drug and excipients) dictate the quantity of drug that can be placed within a capsule of known volume.
- Since the drug dose required to achieve a therapeutic effect can be estimated for new compounds and is known for existing compounds, this information can be used in conjunction with the capsule volume to select an appropriate size.

Solid Dosage Forms

Hard Capsules Production

- The requirements for capsule production depend on the scale of manufacturing.
- Extemporaneous preparation (6-12 capsules) usually employs enough of the product formula to fill one more capsule than required, to account for loss of fill in manipulation.
- Special consideration should be given to controlled substances where all of the drug must be accounted for.
- Industrially (thousands), the amount necessary to fill the desired number can be prepared because the error will be small on such a large scale.

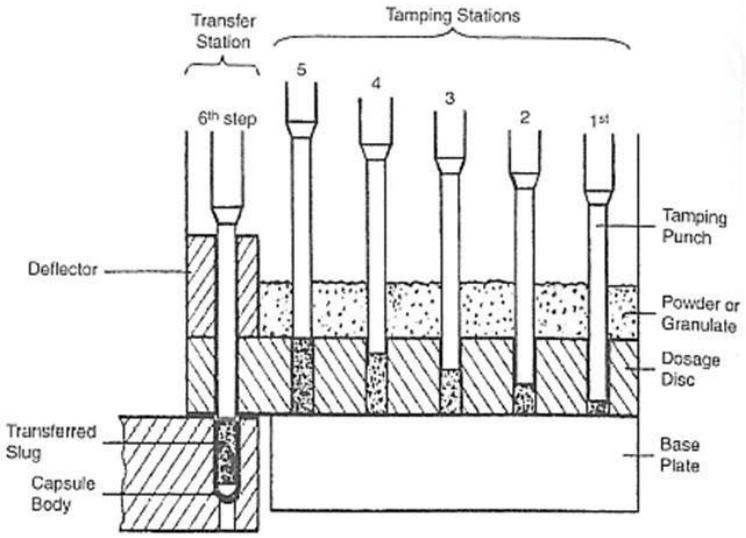
Solid Dosage Forms
Hard Capsules Production

- The operations involved in large- or small-scale capsule filling are the same.
- The capsules as supplied in random orientation must be rectified into a bodies-down, caps-up orientation.
- The two shells are then separated, and the capsule is filled with product formulation.

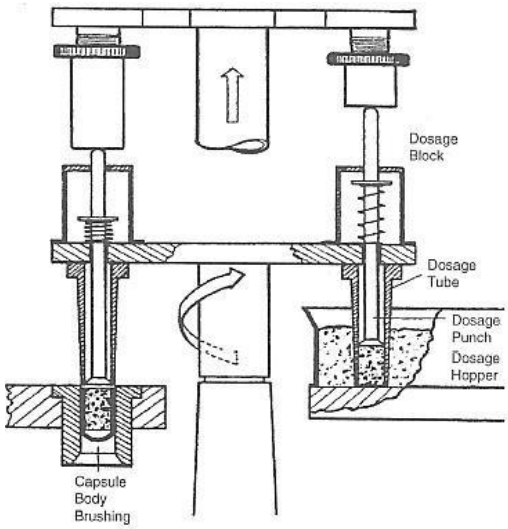
Solid Dosage Forms
Hard Capsules Production

- Various methods are available to fill the capsules.
  - For small-scale production, a plate or single capsule filling method is employed.
  - On a larger scale, tamping, intermittent compression, continuous compression vacuum, or auger filling may be employed.
- The shells are then joined and sealed, and the completed product is discharged.

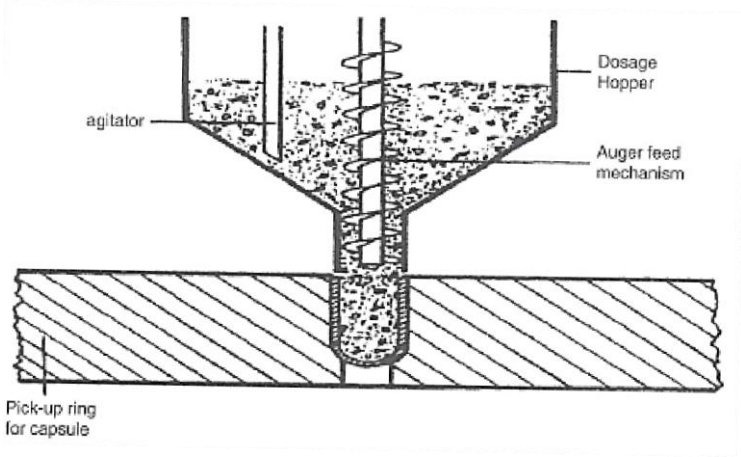
CAPSULE FILLING BY TAMPING



CAPSULE FILLING BY COMPRESSION



Capsule Filling by Auger Filling



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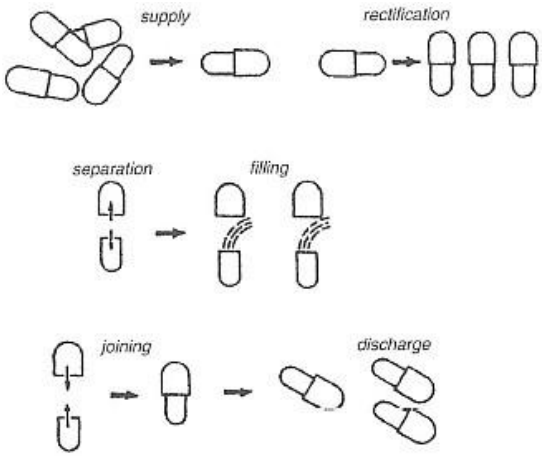
Solid Dosage Forms

Hard Capsules Production

- The shells are then joined and sealed, and the completed product is discharged.



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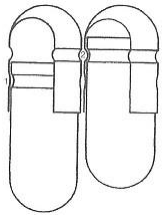
Solid Dosage Forms
Hard Capsules Production

- Different locking mechanisms have been developed for capsules.



- A cleaning and polishing step also follows the manufacturing procedure to improve product appearance.

Solid Dosage Forms
Hard Capsules Packaging

- The product is visually inspected following production, its potency and uniformity are evaluated, and it is transferred hygienically to the final packaging.
- If the product is hygroscopic, it may be necessary to package capsules with desiccant to avoid moisture uptake.
- Alternatively, impervious packaging materials, such as aluminum blisters, may be used.

Solid Dosage Forms
Hard Capsules Advantages

- Capsules are easier to prepare than tablets.
- Capsules are quite flexible with respect to dose
- Capsules are easily combined with other solid dosage forms since other capsules or tablets can be incorporated into larger capsules.

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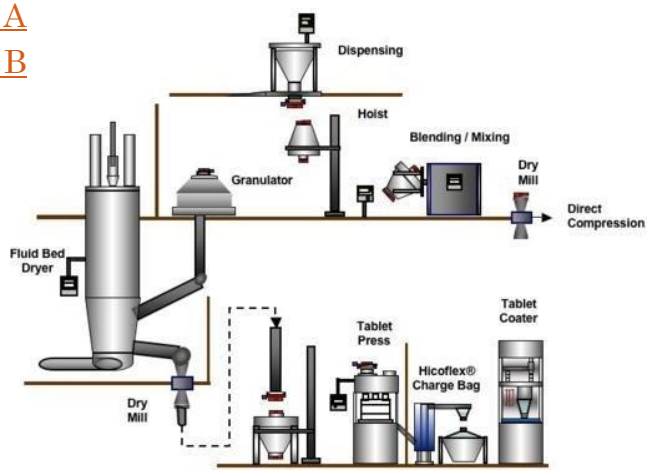
Solid Dosage Forms
Tablets

- **Tablet Manufacturing Process Video**
  - Part A
  - Part B



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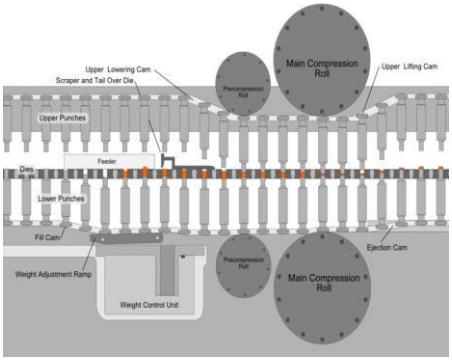
Solid Dosage Forms
Tablets

- Additional processes are required for tablet production beyond those described previously.
- Compressed solids, tablets, or caplets are prepared by placing the blend of component additives in a cylinder or die, above a movable piston or punch.

Solid Dosage Forms
Tablets

- An upper punch is brought into the top of the piston, and pressure applied to the distal ends of the punches forces the powder into a compact.
- Tablet manufacture depicting the three steps of filling, compression, and ejection →



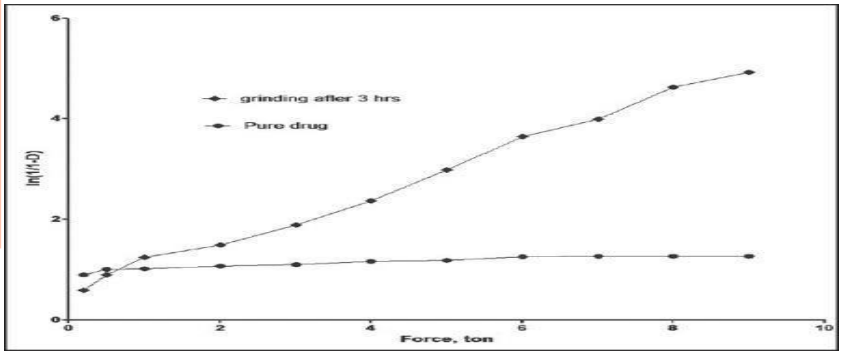
Solid Dosage Forms
Tablets

- **Product quality** depends on the *cohesive forces* acting on the powder under compression.
- These cohesive forces are influenced by the *selection of additives* in the dosage formulation.
- One method of evaluating tablet manufacture considers the effect of applied pressure on porosity of the compressed powder.
- Data may be plotted as the *negative natural logarithm of porosity against applied pressure* in the form of a **Heckel plot**.

Heckel Plot

$$\ln \frac{1}{1-D} = PK + A$$

D = relative density of compacts (ratio of density to compact true density of powder).
P = applied pressure.
K = slope of Heckel plot; K = $1/P_y$
(P_y is the mean yield pressure).
A = densification at low pressure (constant).



Solid Dosage Forms
Tablets

- The tooling of a tablet press varies according to the tablet design.
- Consideration must be given to the distribution of forces across the faces of the tablet punches as they are brought together to compress the tablet in the die.
- As more unusually shaped tablets are produced and more elaborate embossing tools are required, the forces are not distributed evenly across the punches, and care must be taken if they are to have a reasonable, useful life span.

Solid Dosage Forms
Tablets

- Tablets have been prepared with different characteristics and for different purposes.
- The most common tablets are **uncoated**, **coated**, **chewable**, or **effervescent**.
- Some specialized dosage forms have been developed for *sublingual* and *buccal* delivery.
- Examples of uncoated conventional tablet include generic aspirin and Valium.
  - These tablets are designed for *rapid dissolution*.

Solid Dosage Forms
Tablets

- A typical **uncoated conventional tablet** might have the following composition:

Purpose	Examples
Drug	Generic aspirin, Valium
Filler	Lactose, sucrose, phosphates
Binder	Starch, polyvinylpyrrolidone, cellulosics
Glidant	Talc, silicon dioxide
Lubricant	Magnesium stearate
Disintegrant	Starch, sodium starch glycolate
Colorant	Various

Solid Dosage Forms
Tablets

- Tablets may be **coated** for a variety of reasons:
  - better appearance
  - taste masking
  - ease of swallowing
  - protection from light
  - protection from gastrointestinal irritation
  - facilitating tablet printing
  - control release

Solid Dosage Forms
Tablets

- The formulation of a coated tablet is similar to that of an uncoated tablet.
- Usually, it is coated from a solution of polymer, for example, methylcellulose, enteric polymer.
- Bayer aspirin or erythromycin products are examples of **coated tablets**.

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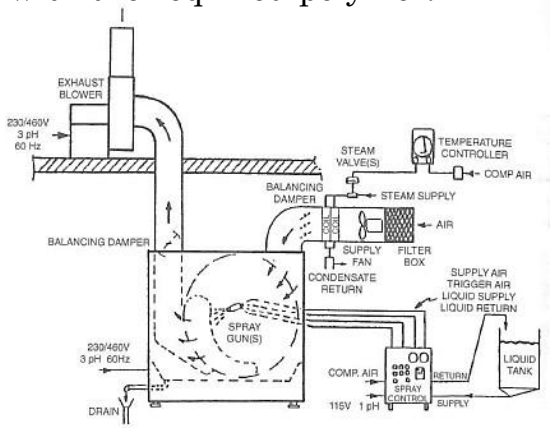
Solid Dosage Forms
Tablets

- **Coating** is achieved by placing a batch of tablets in a coating pan and spraying or coating from solution with the required polymer.
- **Accela-Cota** is one of the more common coating systems.



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Solid Dosage Forms
Tablets

- **Chewable tablets** are usually flavored and contain additives that contribute to a smooth texture, including glycerin and sugars such as mannitol and sorbitol.
  - An example is *Tylenol* chewable tablets.

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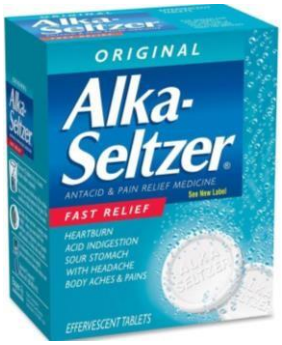
Solid Dosage Forms
Tablets

- **Effervescent tablets** are formulated so that an acid-base reaction occurs when they are combined with water. This is achieved by using weak acids (e.g., citric, malic, tartaric, or fumeric acids) or bases (e.g., sodium or potassium carbonates) in the product.
  - The best known of these products is *Alka-Seltzer*.



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Solid Dosage Forms
Tablets

- **Sublingual tablets** are designed to disintegrate and dissolve instantly.
- Hence, they must have structural integrity sufficient for storage, transport, and administration but capable of dissolution on the oral mucosa under the tongue.
- Nitroglycerin tablets designed for treating angina are prepared in a compositionally simple formulation of lactose massed with 60% ethanol.
- This route of administration is intended to avoid first-pass liver metabolism.

Solid Dosage Forms
Tablets

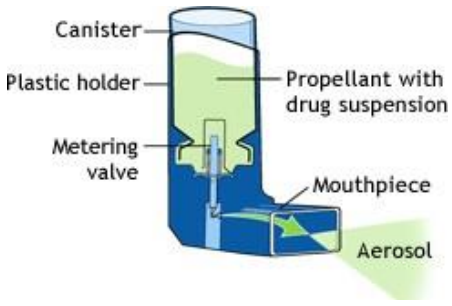
- Testosterone tablets have been prepared for **buccal** delivery by slow dissolution.
- The tablet does not contain a disintegrant and is intended to have an extended residence time in the buccal cavity at the rear of the mouth.
- Since release is not immediate, drug dosage may be significantly reduced by this route.

Solid Dosage Forms
Inhalation Products

- Solid particles are employed in two types of inhalation product:
  - the pressurized metered-dose inhaler (pMDI) and
  - the dry powder inhaler (DPI).
- In both cases, the method of choice for manufacturing particles in an appropriate size range to deposit in the lungs (<5 μm) is *attrition milling* by air jet mill.

Solid Dosage Forms
Inhalation Products

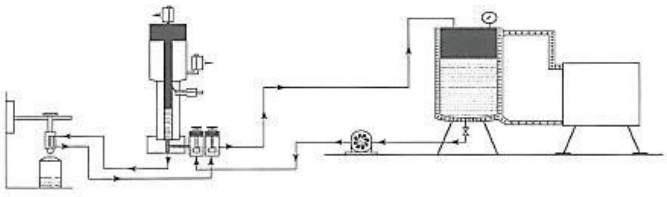
- The **pMDI** product is prepared as a nonaqueous suspension in which surfactant is used to disperse the drug particles in high-vapor pressure propellants.



Solid Dosage Forms

Inhalation Products - pMDI

- Once the particles are prepared, the product formulation depends only on the **particle dispersion in suspension**, their **ease of redispersion**, and their **physical stability upon aerosolization**.



Metered-dose inhaler filling line

Solid Dosage Forms

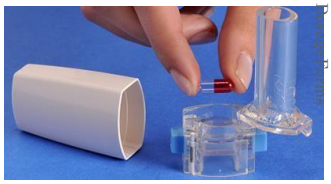
Inhalation Products

- **DPI** formulations usually involve a combination of the micronized drug with a carrier, notably lactose.
- The carrier particles are usually larger than the drug particles and outside the range required for lung deposition (>30μm).
- The purpose of these large particles is to help disperse the respirable drug particles carrying them into the inspiratory airflow where they are stripped from the surface as a function of the large shear forces.

Solid Dosage Forms

Inhalation Products - DPI

- These formulations are prepared in **capsules**, **blisters**, or **reservoir** devices.
- The filling technology has been developed to accurately meter small doses into the unit-dose packaging.



Solid Dosage Forms

Inhalation Products

- Other methods of particle preparation have been evaluated, including *spray drying* and *supercritical fluid* manufacture.
- The capacity to manufacture particles with known and optimized **particle size**, **shape**, and **surface characteristics** is intriguing
- It seems likely that these methods will become more significant in the future and may even surpass micronization for aerosol delivery of drugs.