Validation of Solid Dosage Forms

Dr. V K Deshmukh,
Principal
MES's College of Pharmacy, Sonai

INTRODUCTION

- The objective is to discuss aspects of **validation in terms of pharmaceutical unit operations**; that is, those individual technical operations that comprise the **various steps involved** in **product design** and **evaluation**.
- The focus of the discussion will be on **tablets & hard gelatin capsules.**

- All **pharmaceutical scientists**, whether in *development, quality assurance, production, or regulatory affairs,* are familiar with the axiom that **quality is not tested into a product but rather is built in.**
- **Four key elements** that form the basis of **a prospective process validation program.**
  - 1. Definition of the **desirable attributes** as well as those are not desired
  - 2. **Establishment of limitations or constraints** for these attributes
  - 3. **Determination of the controls or testing parameters** that will be measured or tested
  - 4. **Initiation of studies to establish control or boundary limits** for those key attributes that influence the product, process, quality, and performance

VALIDATION OF RAW MATERIALS

- **Active pharmaceutical ingredients** (APIs) and **excipients**
- Variation in raw materials is one of the major causes of product variation or **deviation from specification**.
- key **physical properties & Chemical characteristics**
- The **particle size, shape, and density of the drug can affect material flow and blend uniformity, hygroscopic nature**
- For example,
- A **water-insoluble drug** is usually milled or **micronized** in order to achieve rapid dissolution and in vitro availability
- **A greater volume of granulating agent** will be needed to wet-mass a powder bed comprising **finely divided particles**

- The **certification/validation of excipients** used in solid oral dosage forms is also extremely important. **Excipients can represent less than 1% -99%of a tablet formula** .
- Factors to be aware of are
- 1) ***The grade and source of the excipients,***
- ***2) Particle size and shape characteristics,***
- ***3) Lot-to-lot variability.***

The steps involved in the validation of a raw material or excipient

- 1. Each raw material should be validated by performing **checks on several batches (at least three)** from the primary supplier as well as the alternate supplier.
- Depending on the susceptibility of the **raw material to aging, physical, chemical, and/or microbiological stability** should be assessed.
- It may be appropriate to **manufacture several lots** of *final product* with raw material at the low and high ends of the specification limit
- The final step of raw material validation should involve **an on-site inspection of the supplier to review the vendor's manufacturing operations and control procedures**

- **III. ANALYTICAL METHODS VALIDATION**
- **IV. EQUIPMENT/FACILITY VALIDATION**
- **V. DEFINITION AND CONTROL OF PROCESS VARIABLES**
  - Process validation can be defined as **a means of challenging a process during development to determine which variables must be controlled to ensure the consistent production of a product or intermediate.**
  - It also provides the means for an **ongoing quality audit** of the process during the **marketing phase** of the product to ensure its **compliance with these specifications**.

Major steps in the development of a validation program are as follows:

- **Obtaining test data to determine the numerical range of each parameter**
  - e.g., assess the tablet hardness over a series of batches that achieves an acceptable friability, disintegration, and dissolution.
- **Establishing specification limits from the test data derived for a given parameter.**
  - Determine the extremes of acceptable hardness (high and low) that would provide 95% assurance that the friability, disintegration, and dissolution specifications would be met (upper and lower control/ release limits).

- **Determining how well the specification limit indicates that the process is under control.**
  - **Challenge the process by producing product at the extremes of the specification limit** to ensure all product specifications are met.
- **Certifying the equipment that is used in obtaining the data and controlling the process.**
  - Ensure that **equipment operating conditions** (e.g., rpm, temperature, power utilization) are within specification limits under variations of product load.

A. In-Process Tests

- 1. ***Moisture content of "dried granulation":*** *Loss on drying (LOD)* (usually less than 2% moisture).

- 2. ***Granulation particle size distribution****: An extremely important parameter* that can affect tablet compressibility, hardness, thickness, disintegration, dissolution, weight variation, and content uniformity.

- This parameter, which can be done by **sieve analysis**, should be monitored throughout the *tablet validation process.*

- 3. ***Blend uniformity***: *Samples of the blend are taken and analyzed to* ensure that the **drug is uniformly** dispersed throughout the tablet/capsule blend.

  - The proper blend time must be established so that the blend is not under- or over mixed.
  - The sampling technique is critical for this test to be valid.

- 4. ***Individual tablet/capsule weight***: *The weight of individual tablets or* capsules is determined throughout compression/encapsulation ***to ensure that the material is flowing properly and the equipment is working***.

- 5. ***Tablet hardness***: *Tablet hardness is determined periodically throughout* the batch to ensure that the tablets are *robust enough for coating, packing, and shipping and not too hard to affect dissolution*.
- 6. ***Tablet thickness***: *Tablet thickness is also determined periodically* throughout the batch and is **indirectly related to the hardness**. It is another indication of whether or not the *formulation has proper flow and compression properties*.
- 7. ***Disintegration:*** *Disintegration is determined during the manufacture* ***as a predictor of tablet performance*** (e.g., dissolution).

B. Finished Product Tests

- 1. ***Appearance:*** *The tablets should be examined for such problems as* tablet mottling, picking of the monogram, tablet filming, and capping of the tablets. If the tablets are colored, the color quality needs to be examined.

- 2. ***Assay:*** *This test will determine whether or not the product* ***contains*** **the labeled amount of drug**.

- 3. ***Content uniformity:*** *Samples are taken across the batch profile (****beginning,*** **middle, and end**) and analyzed to ensure that the dosage forms comply with compendial standards

- ***Tablet hardness:*** *A critical parameter for dosage form handling and* performance.

- 5. ***Tablet friability****: Friability is an important characteristic on the tablets'* ability to withstand chipping, cracking, or "dusting" **during the packaging operations and shipping.**

- 6. ***Dissolution:*** *Dissolution is important to ensure proper drug release* characteristics (in vitro availability) and batch-to-batch uniformity.

- Some other processing variables are:
- Mixing time and speed in blenders and granulators
- Solvent addition rates in granulators
- Time, temperature, and airflow conditions in dryers and coaters
- Screen size, feed rate, and milling speed in mills
- Machine speed and compression force in tablet presses
- Machine speed and fill volume in encapsulators

GUIDELINES FOR PROCESS VALIDATION OF SOLID DOSAGE FORMS –TABLETS (Figures)

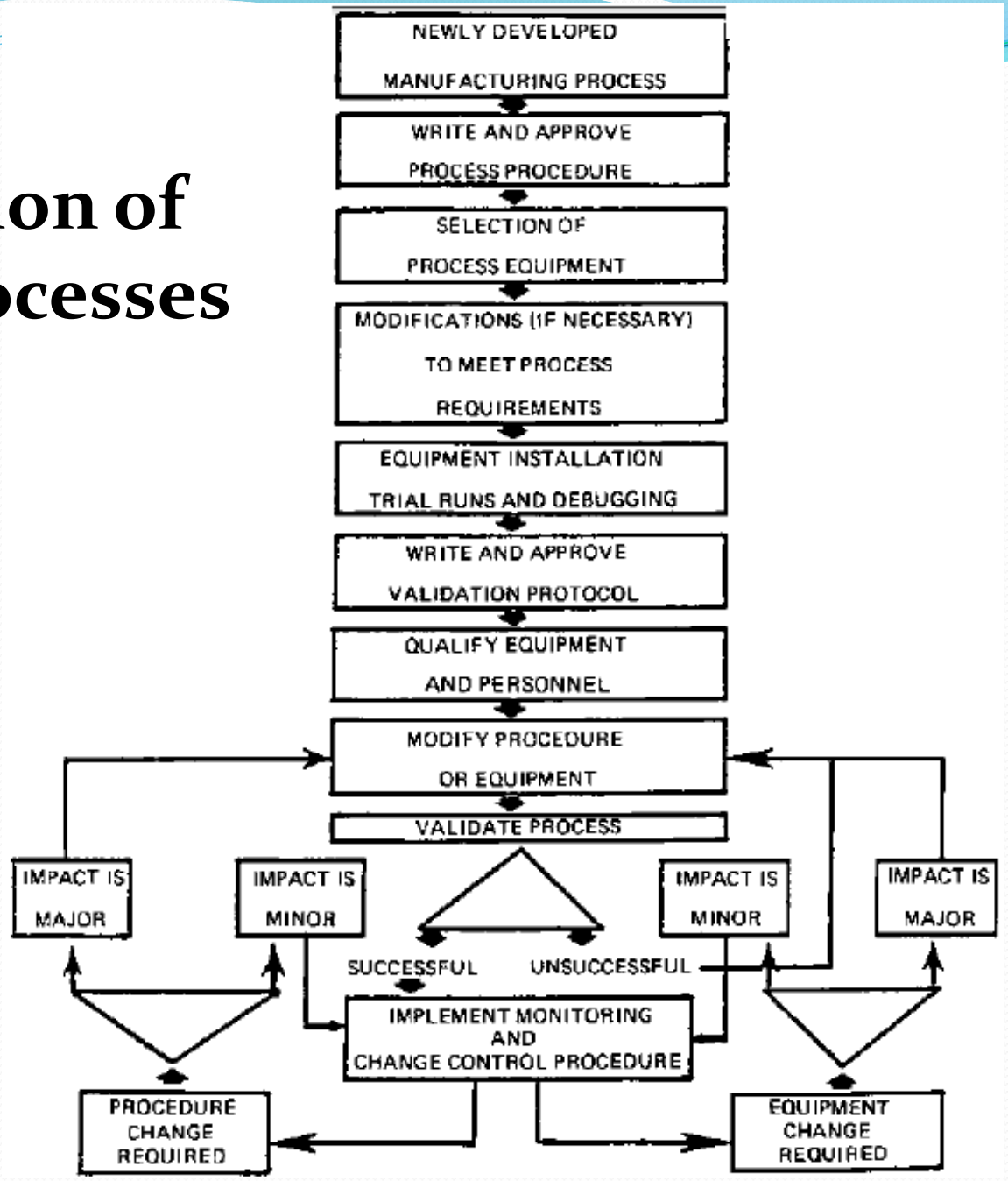
- **A. Tablet Composition** -***key physicochemical properties***
- ***Solubility of the drug substance throughout the physiological pH range****:*
  - Depending on the solubility of the drug, a surfactant may be needed to enhance dissolution.

- ***Particle size distribution and surface area:*** *The particle size distribution* of the drug may **determine what grade of an excipient** (e.g., microcrystalline cellulose) to use.

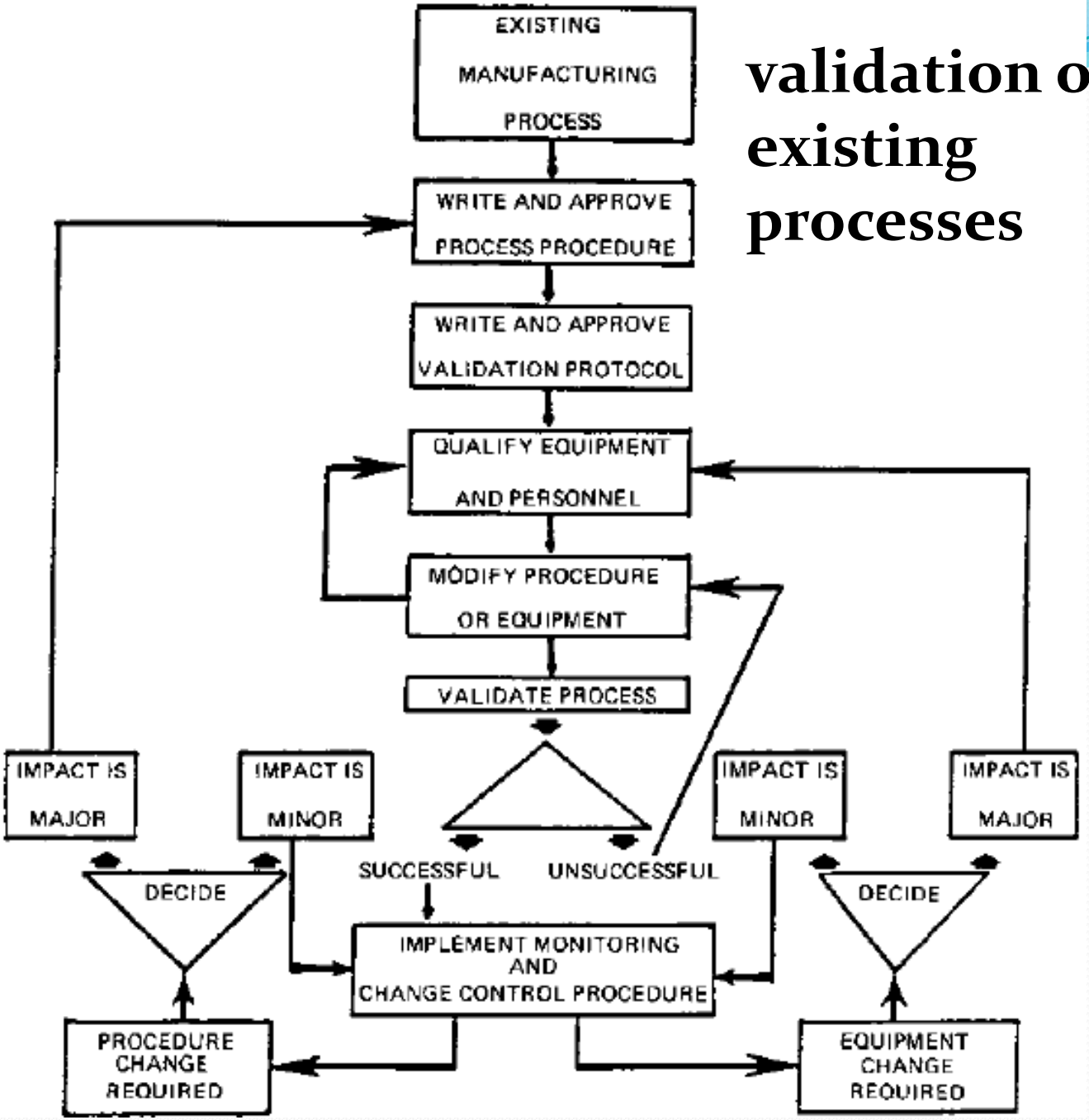
- ***Morphology****: If the drug is amorphous or has different polymorphs, certain* excipients may be used to prevent conversion of the drug to other physical forms.

- ***True and bulk density****: An excipient (e.g., diluent) that has a similar bulk* density as the drug may be selected to minimize segregation, especially **with a direct compression formulation**.

Validation of new processes



validation of existing processes



- ***Material flow and compressibility****: A free flowing, highly compressible material* such as microcrystalline cellulose may be used for **drugs with poor flow or compressibility properties.**

- ***Hygroscopicity:*** *Special environmental working conditions may be required* to ensure that moisture is not picked up during material storage or handling and during the manufacture of the tablet dosage form.

- ***Melting point:*** *If the drug has a* ***low melting point****, a direct compression* formulation may need to be developed instead of a wet granulation formulation to avoid drying the material and potentially melting or degrading the drug.

- **Provide the reason for the presence of each ingredient in the formula.**
- **Why was a particular ingredient used from an excipient class? Performance? Supply? Cost?**

- Indicate whether **a particular grade or manufacturer** is required for an ingredient and the reasons.

- Justify the **level or range of each ingredient**, especially the binder, disintegrant, and lubricant.

- Explain the required unit operations in relationship to the tablet formulation.
  - For example
  - Why was high shear wet granulation used instead of dry granulation?
  - Why is the tablet film coated?

B. Process Evaluation and Selection

- ***Determine the unit operations needed to manufacture the tablets***.

1. Mixing or Blending

- Direct compression formulation may involve one blending prior to compression.
- A wet granulation formulation may require twomixing/blending steps:
  - (1) **prior to granulating** to have a uniform drug/excipient mixture,
  - (2) **after milling** the dried granulation to add other excipients, such as the **lubricant.**
- The following **physical properties** of the drug and excipients are factors in creating **a uniform mix or blend**:
- Bulk density
- Particle shape
- Particle size distribution
- Surface area

- ***Mixing or blending technique***: ***Diffusion*** *(tumble)*, ***convection*** *(planetary* or high intensity), or **pneumatic** (fluid bed) techniques can be used to mix or blend materials.

- ***Mixing or blending speed***: *Determine the intensity* ***(low/high shear)*** *and/or* **speed** (rpm) of the mixing or blending. **Mixing the drug and excipient** will **require more intense mixing** than **adding the lubricant to the final blend.**
- *Mixing or blending time:*
- *Drug uniformity:*
- *Excipient uniformity- Lubricant & Color:*
- *Equipment capacity/load:* The **bulk density of materials** or granules will affect the capacity of the equipment.

2. Wet Granulation

- What type of wet granulation technique will be used?
- **low shear** (e.g.,Hobart), **high shear** (e.g., Diosna, GEI-Collette) or **fluid bed** (e.g., Glatt, Fluid Air)?
- ***Each technique will produce granules with different physical properties and will require monitoring of different processing parameters.***
- Wet granulation parameters to be considered during development and validation are:

- ***Binder addition**: Should the binder be added as a granulating solution or dry* like the other excipients? Adding the binder dry avoids the need to **determine the optimal binder concentration and** a **separate manufacture for the binder solution.**

- ***Binder concentration**: The optimal binder concentration will need to be* determined for the formulation.

- ***Amount of binder solution/granulating** solvent: How much binder or solvent* solution is required to granulate the material?

- ***Binder solution/granulating solvent addition rate**: Define the rate or rate* range at which the binder solution or granulating solvent can be added to the materials.

- ***Mixing time:** How long should the material be mixed to ensure proper* formation of granules? Should mixing stop after the addition of the binder or solvent solution or should additional mixing be required? Granulations that are not mixed long enough can form incomplete or weak granules.

- ***Mixing time***: *How long should the material be mixed to ensure proper* formation of granules? *Should mixing stop after the addition of the binder or solvent solution or should additional mixing be required?* Granulations that are not mixed long enough can form incomplete or weak granules

- ***Granulation end point***: *How is the granulation end point determined? Is* it determined or controlled by granulation end point equipment (e.g., **ammeter or wattmeter**)?
  - Is it controlled by specifying critical processing parameters? For example, a drug or excipient mixture may be granulated by adding a predetermined amount of water (granulating solution) at a certain rate. The granulation is completed after mixing for a set time after the water has been added.

Wet Milling

- Does the wet granulation need to be milled to break up the lumps and enhance
- drying of the granulation?
- **Factors to consider are**:

- 1. ***Equipment size and capacity****: The mill should be large enough to* delump the entire batch within a reasonable time period to minimize manufacturing time and prevent the **material from drying during this operation**.

- 2. ***Screen size****: The screen needs to be small enough to delump the material,*
- but not too small to **cause excessive heating of the mill**, resulting in drying of the granulation.

- 3. ***Mill speed****: The speed should be sufficient to efficiently delump the* material without straining the equipment.

- 4. ***Feed rate:*** *The feed rate of the wet granulation is interrelated to*
- screen size and mill size and speed.

4. Drying

- The type of drying technique (e.g., t**ray, fluid bed, microwave**)
- The type of technique may be dependent on such factors as drug or formulation properties and equipment availability. ***Changing dryer techniques could affect such tablet properties as hardness, disintegration, dissolution, and stability.***
- The optimal moisture content of the dried granulation needs to be determined.
  - High moisture content can result in (1) tablet picking or sticking to tablet punch surfaces and (2) poor chemical stability as a result of hydrolysis.
  - An over dried granulation could result in poor hardness and friability.
  - Moisture content analysis can he performed using the conventional loss-on-drying techniques or such state-of-the-art techniques as near infrared (NIR) spectroscopy.

- Parameters to consider during drying are:
  - *Inlet/outlet temperature:*
  - *Airflow: There should be sufficient airflow to ensure removal of moisture*
  - *Moisture uniformity: Heat distribution*
  - *Equipment capability/capacity: The load that can be efficiently dried*

5. Milling

- The milling operation will reduce the **particle size of the dried granulation**. The **resultant particle size distribution will affect such material properties as** flow, compressibility, disintegration, and dissolution. An optimal particle size/size distribution for the formulation will need to be determined.
- Factors to consider in milling are:
- ***Mill type****: What mill type (e.g., impact or screen) should be used? Each* has several variants, depending on the means to reduce the particles.

- ***Screen size****: The selected screen size will affect the particle size. A smaller* screen size will produce a smaller particle size and a greater number of fines.

- ***Mill speed****:* ***What is the optimal mill speed?*** *A higher mill speed will* result in a smaller particle size and possibly a wider particle size distribution. It can also generate more heat to the product, depending on the screen size and feed rate, which could affect the stability of the product.

- *Feed rate: The feed rate is dependent on the mill capacity, screen size,* and mill speed

6. Tablet Compression

- Compression is a **critical step in the production** of a tablet dosage form.
- The materials being compressed will need to **have adequate flow and compression properties.**
- The material should **readily flow from the hopper** onto the feed frame and into the dies.
- Inadequate flow can result in "**rat holing**" in the hopper and/ or **segregation of** the blend in the **hopper/feed frame.**
- This can cause tablet ***weight and content uniformity problems.***

- **Factors to consider during compression are as follows:**

- ***Tooling:*** *The* ***shape, size, and concavity of the tooling*** *should be examined* based on the formulation properties and commercial specifications.

- ***Compression speed****: The formulation should be compressed at a wide* range of compression speeds to determine the operating range of the compressor.

  - The adequacy of the **material's flow** into the dies will be determined by examining the tablet weights.
  - Is a **force feeder required** to ensure that sufficient material is fed into the dies?

- ***Compression/ejection force:*** *The compression profile for the tablet formulation* will need to be determined to establish the optimal compression force to obtain the **desired tablet hardness**.
  - The **particle size/size distribution** or level **of lubricant may need** to be adjusted in order to have a robust process on a **high-speed compressor**.

- The following in-process tests during the compression stage:
- Appearance
- Hardness
- Tablet weight
- Friability
- Disintegration
- Weight uniformity

Tablet Coating

- Tablets may be coated for various reasons.
  - Stability
  - Taste masking
  - Controlled release
  - Product identification
  - Aesthetics
  - Safety–material handling
- Tablet coating can occur by different techniques (e.g., sugar, film, or compression).
- Film coating has been the most common technique over recent years

- **Key areas to consider for tablet coating include the following:**

- ***Tablet properties***: *Tablet properties such as hardness, shape, and intagliation* (if required) are important to obtain a good film-coated tablet.

- The tablet needs to be hard enough to withstand the coating process. If **tablet attrition occurs**, the tablets will have a **rough surface appearance.**

- For tablet shape, a round tablet will be easier to coat **than** tablets will multiple sides or edges because of the uniformity of the surface.

- For **intagliated tablets**, the intagliation **style and depth** should be developed to **prevent fill-in or chipping** of the intagliation.

- ***Equipment type*:** *The type of coater will need to be selected.*
  - *Conventional* or **perforated pan** and fluid bed coaters are potential options.

- ***Coater load**: What is the acceptable tablet load range of the equipment?*
  - Having **too large a pan load could cause attrition** of the tablets because of the overall tablet weight in the coater.
  - In the case of a fluid bed coater, there may **not be sufficient airflow** to fluidize the tablets.

- ***Pan speed**: What is the optimal pan speed?*
  - *This will be **interrelated** to* other coating parameters, such as **inlet temperature, spray rate, and flow rate**.

- ***Spray guns**: The **number and types of guns** should be determined in **order** to efficiently coat the tablets.*

  - The spray nozzles **should be sized properly** to ensure **even distribution** over the tablet bed and to **prevent blockage** of the nozzles.

  - The **location and angle** of the spray gun(s) should be positioned to get **adequate coverage.**

  - Having the guns positioned **too close** together can lead to a portion of the tablets to **be over wet**.

- ***Application/spray rate**: The optimal application/spray rate should be determined.*

  - **Spraying too fast** will cause the tablets to become **overwet**, resulting in **clumping** of tablets and **possible dissolution** of the tablet surface.

  - **Spraying too slowly** will cause the coating materials to **dry prior to adhesion to the tablets**. This will result in a **rough tablet surface** and **poor coating efficiency**.

- ***Tablet flow**: The flow or movement of the tablets in the coater should be* examined to ensure proper flow.
  - There should be sufficient tablet bed movement to ensure even distribution of the coating solution onto the tablets.
  - The addition of baffles may be required to provide adequate movement of tablets for tablet coating.
- ***Inlet/outlet temperature and airflow**: These parameters are interrelated and* should be set to ensure that the atomized coating solution ***reaches the tablet surface and then is quickly dried.***

- ***Coating solution:*** *The* ***concentration and viscosity*** *of the coating solution* will need to be determined.

  - The solution will need to be **sufficiently diluted** in order to spray the material on the tablets.

  - The concentration of the coating solution will also determine the **amount and volume of solution** to be applied to the tablets.

  - The stability of the **coating solution** should be investigated to establish its **shelf life**.

- ***Coating weight:***
  - *A minimum and maximum coating weight should be established* for the tablet. Sufficient coating material should be applied to
- The tablets to provide a uniform appearance; however, it should not be great enough to cause fill-in of the intagliation.

- ***Residual solvent level:*** *If solvents are used for tablet coating, the residual* solvent level will need to be determined.

- **Appearance testing** of the tablets is critical during the coating operation.
- Items to look for include :
  - ***Cracking or peeling of the coating***
  - ***Intagliation fill-in***
  - ***Surface roughness***
  - ***Color uniformity***
- Coating efficiency should be determined for the coating operation.
- The ***efficiency will determine the amount of coating solution overage that may be required.***

Equipment Evaluation

- To manufacture tablet dosage forms would be selected based on factors such as:
  - formulation,
  - safety requirements,
  - handling/production efficiencies,
  - commercial demands.
- *In reality, the equipment used is usually what is already available at the development facility or production plant.*
- In either case,
  - The equipment should be **qualified** before being used.
  - **Cleaning procedures** should also be available
  - The equipment design, **operating principles, and capacity** should be investigated

items should be considered when evaluating equipment

1. **Mixer/granulator**

- What is the **method** of mixing (e.g., planetary, plow, chopper, pneumatic)?
- Is the equipment capable of providing low and/or high shear to the material?
- Can the mixing be varied (e.g., changing the rpm of the impeller)?
- Does the mixer/granulator have a monitoring system (e.g., end point detection) or can it accommodate one?
- What is the working load range and capacity of the equipment?
- How is material charged and discharged from the unit? Is it manual, semiautomated, or automated?
- Are there options to introduce the granulating fluid (e.g., dump,
- meter, or spray)?

2. Blender

- What type (i.e., geometric shape) is the blender? Is it a *V blender, double cone, cube, or bin?*
- What is the positioning of the axis rotation (e.g., horizontal, slant)?
- What is the working load range and capacity of the equipment?
- What features does the equipment have for ease of handling powders, automated charging, and discharging (e.g., Vac-U-Max, Gemco valves)?
- Can samples be easily taken from the unit? Can samples be taken
- from more than one location?
- Are there dead spots (inefficient mixing areas) on the unit? Can the equipment be easily cleaned?
- Can the equipment **heat the powder blend** if needed? What is the heating source?

3. Dryer

- What is the operating principle of the dryer ?
  - **direct heating fluid bed,**
  - **indirect conduction—tray,**
  - **indirect radiant—microwave**

- Will the wet material be static ?
  - e.g., tray or fluid

- What is the working load range and capacity of the equipment?

- What is the **heating range and airflow capabilities** of the equipment?

- What is the heat distribution of the unit? Are there any hot and/ or cold spots?
- Can the unit pull a vacuum? What is the vacuum range of the unit?
- Can the equipment handle **different types of filter bags**? For example, can a filter bag be dedicated to a particular product?
- Does the equipment have a filter bag shaking mechanism to prevent material from adhering to the bags?
- Does the shaking mechanism have options (e.g., intermittent, continuous)?

4. Mills

- What is the mill type (e.g., impact or screen)?
- What is the configuration of the impact mill (e.g., hammer or pin/disc) or screen mill (e.g., rotating impeller or screen, oscillating bar)?
- What type or size hammers or pin/disc can be used on the unit?
- Can the impeller (e.g., hammers) be positioned in different ways?
- What size screens or plates can be used on the unit?
- Is the speed on the impeller/screen variable? What is the rpm range?
- What is the throughput range of the unit?
- What type of feed system is required? What feed rate can the unit handle?
- Can the unit wet- and/or dry-mill materials?
- Does the unit generate a significant amount of heat, possibly affecting the product?
- Is the unit portable?

5. Tablet compressor

- How many compression stations does the compressor have?
- What is the operating range (rpm) of the unit?
- What is the output range of the compressor ?
- Will the unit meet the demands (sales forecast) for the product?
- What kind of powder feeding capabilities does the equipment have (e.g., gravity, power-assisted, or centrifugal)?
- Can this capability be altered or controlled (e.g., open feed frame, forced below feeder)?

- What is the compression force range of the quipment?
  - Some products, especially **large tablets or slugs**, require a significant **compression force** (greater than 5 to 25 kN).

- Is the equipment capable of monitoring compression and ejection force?

- Does the unit have precompression capabilities?

- How long can the equipment **operate without routine maintenance?**

- How long is the turnaround time for complete cleaning? One shift? Two shifts? This downtime can be significant and may affect the need for a multishift tableting operation or numerous tablet machines.

- Does the equipment possess automated weight control capability
- (e.g., Thomas's Sentinel device)?

- Does the equipment require specialized tooling, or can the equipment use tooling from other equipment (e.g., **length of punch shafts, diameter of dies)?**

- Can the equipment perform a **specialized function** in addition to
- basic tablet compression (e.g., **multilayer tablet compression, compression coating)?**

- Is the unit capable of being contained to **protect the operator and environment?**

6. Tablet Coater

- What is the **coater type** (e.g., pan or fluid bed)?
- Is the pan perforated?
- Can the coater accommodate different size pans?
- What is the working capacity range of the coater (i.e., pan load)?
- Does the pan coater have a "variable drive" capability? This maybe needed to achieve proper tablet mixing in the pan so that the coating solution is applied uniformly to the tablets

- Can the angle of the pan's pitch be varied?
- What kind of air input (volume and temperature) and vacuum drag-off is required for optimal operation of the coater?
  - What type of spray system can be used with the equipment?
- What is the shape of the coating pan (e.g., oval, mushroom, round)?
  - The shape characteristic will affect the degree of agitation and the direction of tablet flow in the pan.
  - The spray nozzle configuration will have to be designed to ensure adequate spray coverage over the tablet bed.

- Is it possible to utilize the equipment for sugar coating as well as film coating?
  - Certainly, if this were possible, capital **expenditures would be reduced.**
- Is it possible to modify the pan with the **installation of baffles?**
  - Baffles may be needed to ensure good tablet movement in the pan.
- Can various solvents (ethanol) be used in the equipment?
- Does the equipment require a specialized room condition (e.g.,being explosion-proof)?

HARD GELATIN CAPSULES

- Many of properties and processes for hard gelatin capsules are the same as with tablet dosage forms
- **A. Capsule Composition**
- ***Solubility of the drug substance throughout the physiological pH range***:
- ***Particle size distribution and surface area:***
- ***Morphology***:
- ***True and bulk density***
- ***Material flow and compressibility***
- ***Hygroscopicity:***
- ***Melting point:***

1. Capsule Shell

- Provide the reason for the presence of each ingredient in the capsule formula.
- Justify the level and grade of each ingredient.
- Explain the selection of the capsule size and shape.
- Discuss the need for capsule identification (e.g., color or imprinting).

2. Capsule Shell Contents

- Establish the compatibility of the capsule shell and the capsule contents.

- Determine the hygroscopic nature of the capsule formulation. For example,
  - A hygroscopic formulation (active ingredient and/or excipients) can pull water from the capsule shell, which could affect the
  - Active ingredient- stability issues such as degradation and morphology changes
  - Formulation -hardening on the materials, resulting in a decreased dissolution rate
  - Capsule shell—more brittle

B. Process Evaluation and Selection

- The process to manufacture the contents of a hard gelatin capsule is the same as a tablet.

- It may required only a blending step, such as a direct compression tablet, or several unit operations, such as a wet granulation tablet (e.g., mixing, wet milling, drying, dry milling, and blending).

- In either case, the materials are then encapsulated in a capsule shell.

C. Encapsulation

- Encapsulation is a critical step in the production of capsules, similar to the compression step for tablet dosage forms.

- The materials to be encapsulated will need to have good flow properties and a consistent density.

- The materials may also need to be compressible in order to be dosed into the capsules; however, they should also be easily disaggregated so not to adversely affect the dissolution of the drug.

Factors to consider during encapsulation are:

- ***Encapsulation type:*** *The type of encapsulation technique (e.g., auger, vacuum,*dosator) required for the formulation needs to be determined and justified. Examples are
  - Auger: Capsugel Type B or Elanco No. 8
  - Vacuum: Perry
  - Vibratory: Osaka
  - Dosing disk: H&K
  - Dosator: MG2 or Zanasi

- *Encapsulation speed: The formulation should be encapsulated at a wide* range of speeds to determine the operating range of the encapsulator .

- By examining the capsule weights, the adequacy of the material's flow will be determined.

- The following in-process tests should be examined during the encapsulation step:
  - Appearance
  - Capsule weight
  - Disintegration
  - Weight uniformity

D. Equipment Evaluation

- Encapsulator
  - What is the encapsulation mechanism (e.g., auger, dosing disk, dosator)?
  - How many encapsulation stations does the encapsulator have?
  - What is the operating range of the unit?
  - What is the output range of the encapsulator (i.e., capsules per min)?
  - Will the unit meet the demands (sales forecast) for the product?

- What kind of powder feeding capabilities does the equipment have
- (e.g., gravity- or power-assisted)? Can this capability be altered or controlled?
- How long can the equipment operate without routine maintenance?
- How long is the turnaround time for complete cleaning? This downtime can be significant and may affect the need for a multishift operationor additional machines
- Does the equipment possess automated weight control capability?
- Can the equipment perform a specialized function in addition to basic encapsulation (e.g., tablet in capsules with excipient backfill)?
- Is the unit capable of being contained to protect the operator and environment?