

# Pilot plant scale up for Hard Gelatin Capsules

- Overly lubricated capsule granules-delay-disintegration and dissolution-reduced bioavailability
- Prolonged trials-multiple batches-routine production
- Size and type of equipment-finished product
- Type of encapsulating equipment chosen-dictate properties required of a powder blend
- Optimum process conditions-need for controlled environmental conditions must be considered
- Humidity-significant effect on moisture content of granulation and on empty gelatin capsules

# Pilot plant scale up for Hard Gelatin Capsules


- Granulation moisture content-chemical or physical stability of finished product
- Uncontrolled moisture-machine problems-flow and sticking-material transfer and filling
- Empty gelatin capsules:  
Recommended storage conditions- 15 to 25 degree celsius and RH between 35 and 65%
- These conditions-minimize moisture absorption or loss and the resultant changes in physical dimensions during the encapsulation operation
- Room humidity during encapsualtion: 45 to 55%

# Pilot plant scale up for Hard Gelatin Capsules

- Higher humidities-capsules swell-may make separation of capsule parts difficult-interfere with transport of capsule-encapsulation
- Low humidity-capsules become brittle-increase static charge-interfere-encapsulation



# Pilot Plant Scale-up for Liquid Dosage Forms

- Nonsterile Solutions
  - Nonsterile Suspensions
  - Nonsterile Emulsions
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# Pilot Plant Scale-up for Nonsterile Solutions

- **SIMPLE SOLUTIONS:**
- Tanks of adequate size and suitable mixing capability
- Heating and cooling capabilities-rapid dissolution
- Transfer systems and filtration equipment-clarify product-no removal of active or adjuvants
- Equipment – non-reactive, sanitary materials-design-facilitate easy cleaning
- Material of fabrication-Stainless steel-type 316-less reactive

# Pilot Plant Scale-up for Nonsterile Solutions

- Stainless steel does react with some acidic pharmaceutical liquids-problem can be minimized by prereacting the stainless steel with an acetic acid or nitric acid solution to remove its surface alkalinity
- This procedure-*Passivation*-repeated at periodic intervals-eg. alkaline cleaning agent being used between batches
- Interaction with metallic surfaces-minimized by use of glass or polytetrafluoroethylene (Teflon) liners
- Disadvantage-cracking, breaking, flaking and peeling-product contamination

# Pilot Plant Scale-up for Nonsterile Suspensions

- **NONSTERILE SUSPENSIONS:**
- Require more attention-additional processing needs
- Lab-scale –addition and dispersion of suspending agents-sprinkling material into the liquid vortex
- Pilot scale-vibrating feed system
- Powder eductor-addition of material that tends to clump-difficult to disperse
- In some cases-slurry of suspending agents with a portion of the vehicle-easier to wet-more completely dispersed using high-shear mixer in a smaller volume of the vehicle-rapid and complete hydration when added to larger portion of vehicle

# Pilot Plant Scale-up for Nonsterile Suspensions

- Time and temperature required to hydrate suspending agents-critical for quality of suspension
- **Active ingredients:**  
Must be uniformly distributed-best dispersion procedure depends on its *physical characteristics*
- If diffusible-simple addition at a convenient stage
- If indiffusible-prepare slurry with wetting agent and with the aid of high-shear mixing equipment



## Pilot Plant Scale-up for Nonsterile Suspensions

- Another method-pretreat hard-to-wet material by blending it in a high-shear powder blender with one or some of the liquid ingredients-possibly with a surfactant included-converts bulky material to dense readily wettable powder-easier to handle
- Such approaches minimize formation of dry agglomerates in finished product-otherwise air entrapped in this dry material-cause the product to 'cream'- cause physical instability or poor content uniformity

# Pilot Plant Scale-up for Nonsterile Suspensions

- Preparation of suspensions-mixer,pumps,and mills,and horsepower of motors –carefully selected based on scale-up performance
- Equipment selection-size of batch and the maximum viscosity of the product during manufacturing process
- If mixer undersized-inadequate distribution-excessive production time
- Mixing at too high speed-incorporation of excessive amount of air into the product
- Air entrapped-small bubbles –difficult– time-consuming to remove-if not removed-affect physical and chemical stability-filling operation
- If air entrapment-problem-cannot be rectified with process or equipment modifications-use vacuum unit such as Versator

# Pilot Plant Scale-up for Nonsterile Suspensions

- **VERSATOR:**

Product-drawn-vacuum chamber-inlet line-spread onto centre of a high –speed rotating disc-centrifugal force-thin film on disc surface-film thins-moves towards outer edge of the vacuum chamber-entrapped air drawn off-deaerated product-outer edge of the vacuum chamber

- Unwanted and discolored particulate material-raw material or bags,cases,and drums in which raw materials supplied
- Also unwanted material-during manufacturing-filtration of final suspension through appropriate size screen
- Mesh size chosen-must remove unwanted foreign particulates-not any of the active ingredients
- Select sieve based on production batch size trials

# Pilot Plant Scale-up for Nonsterile Suspensions

- Most active ingredients-particle sizes less than 10 microns-none over 25 microns
- Hence for particulates-screens of 150 mesh having openings of around 100 microns-remove unwanted suspended materials that are below easily visible range without retaining API(s)
- Transfer and filling of finished suspension-should be carefully monitored
- If suspensions not constantly mixed or recirculated during transfer processes-may 'settle out'-adversely affect the uniform distribution of API