Understanding Oral Solid Dose Form (OSD) Manufacturing

The Process/Equipment and Technology

Presented by:
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Tuesday March 18, 2014 – 10am
AGENDA

- Session Stage Setting
- OSD Processing Goals
- Main Types of OSD Processes
- The OSD Primary Unit Operations Matrix – our road map
- Primary Unit Operations
  - The process; technology/equipment; process/facility considerations
- The Owner/Engineer/Vendor Considerations
- Wrap Up
SESSION STAGE SETTING

- Who is Dave DiProspero?

- Who are you?

  - Industry: Pharma Co’s, Equip Vendors, Service Providers, Other
  - Industry Experience: >15 yrs, 5-15yrs, <5yrs
  - Role/Function: Engineering, Manufacturing, Management, Sales, Other
  - OSD Experience: lots, some, none
STAGE SETTING (cont’d)

- Typical Drug Delivery Systems and Drug Forms
  - Liquids: Suspensions, Solutions, Syrups
  - Creams/Ointments
  - Sprays/Inhalers
  - Transdermal Patches
  - Injectibles
  - Non conventional: Suppositories and other

THE PREFERRED DOSAGE FORM, by far:
SOLID DOSE: Tablets/Capsules

Primary reasons for preference are:
- Easy to administer
- Easy to identify
- Relatively acceptable taste
Primary Manufacturing Goal:

To create a formulation that has a highly repeatable distribution of ingredients that are:

- Compressible (in a tablet form) or Coatible (in a capsule form)
- Readily/Easily ingestible (via oral means)
- Bioavailable according to indication requirements
  - IR/SR/CR
    (immediate, sustained, controlled, extended release)

- in sustained release there is release of drug at predetermined rate by maintaining a constant drug level for specific period whereas in
- controlled release delivery of drug is at desired rate for a desired length of time
a.) High Shear Granulation Process (involves liquids/solids)

b.) Wet Spray Granulation Process (involves liquids/solids)

c.) Direct Compression Process (involves solids only)

d.) Particle Coating Process (involves liquids/solid—usually capsules)
High Shear Granulation

- **Goal** is to create a rather “dense” granule made up of active drug and excipient.
- **Involves** the addition of liquids onto the dry powders to act as a conduit for densification.
- **Main pieces of equipment** are:
  1. High Shear Granulator (create the motion/energy to integrate solids/liquids efficiently and under control)
  2. Solution Delivery System (for processing/pumping liquids)
  3. Dryer (evaporate the liquids added and appropriately change the characteristics of the particles)
HSG – Graphically

Dust free
Good flowability
Easy to dose/handle
Good dispersion
Compact structure
Low hygroscopic
**Good solubility**
High bulk density
Wet Spray Granulation

- Goal is to create a rather “loose” granule made up of active drug and excipient.
- Involves the addition of liquids onto the dry powders to act as a conduit for densification.
- Main pieces of equipment are:
  1. Low Shear Granulator/Fluid Bed (create the motion/energy to integrate solids/liquids efficiently and under control)
  2. Solution Delivery System (for processing/pumping liquids)
  3. Dryer (evaporate the liquids added and appropriately change the characteristics of the particles).  *Usually same machine as #1.*
WSG – Graphically

Dust free
Good flowability
Easy to dose/handle
Good dispersion
**Excellent solubility**
Low bulk density
Direct Compression

- Goal is to create a “homogeneous distribution” of active drug and excipient.
- Entirely a dry process.
- Main pieces of equipment are:
  1. Tumble Blender
  2. Loading/Unloading Equipment
Good flowability
Easy to dose/handle
**Good solubility**
Easy Process
No physical changes
Goal is to create a “coating” of active drug and/or sealer onto a seed material.

Involves the application of a liquid/solid suspension to the face of the seed material.

Main pieces of equipment are:

1. Fluid Bed Coater (create the motion/energy to integrate solids/liquids efficiently and under control)
2. Solution Delivery System (for processing/pumping liquids)
3. Dryer (evaporate the liquids added and appropriately change the characteristics of the particles). *Usually same machine as #1.*
Coating – Graphically

- Low abrasion, smooth surface
- Good flowability
- Masking of taste and smell
- Good protection against light, air and moisture
- Impervious separating layers in the case of multi-layer composition
- Systematic release of active ingredients
- Retardation, delayed dissolving
- Visual attractiveness (pharmaceutical drug safety)
## PROCESSING UNIT OPS

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* Optional Unit Operations
The OSD MATRIX

ORAL SOLID DOSAGE (OSD) PRIMARY UNIT OPERATIONS MATRIX
(The typical operations in an OSD Manufacturing Process)

INGREDIENT DISPENSING & FORMULATION
  ACTIVE DRUG (API)
  EXCIPIENT MATERIAL
  CONTAINED PROCESS
  OPEN PROCESS
  CONTAINMENT BOOTH and/or ISOLATION
  LOCAL EXHAUST VENTILATION
  BAG/DRUM SUPER SAC HANDLER
  WEIGHT BATCH RECORD

BLENDING
  BIN BLENDING
  TWIN/VEE SHELL

GRANULATION
  WET GRANULATION
  DRY GRANULATION
  HIGH SHEAR TOP or BOTTOM DRIVE
  ROLLER COMPACTION
  FLUID BED (top spray)
  CONTINUOUS GRANULATION And DRYING
  SINGLE-POT MULTI PROCESSOR

DRYING
  FLUID BED
  VACUUM TUMBLE
  TRAY OVEN

COMPRESSION ENCAPSULATION
  TABLET PRESS ENCAPSULATOR POWDER FILLER
  METALCHECK DEDUSTER POLISHER
  WEIGHT HARDNESS THICKNESS CHECKER
  MICRO Waves SINGLE-POT PROCESSOR

TABLET COATING
  PERFORATED PAN (sugar/film/ or functional)
  CONTINUOUS TABLET COATER
  SOLUTION PREPARATION
  WURSTER COLUMN FLUID BED

OTHER OSD PROCESSES
  INGREDIENT and RAW MATERIAL SAMPLING
  EXTRUSION and SPHERONIZATION
  BEAD COATING (wurster)
  SIFT SCREEN MILL MICRO NIZE
  DRILL/PRINT SORT/BAND SEAL
  PACKAGE SERIALIZE

Primary Processing Methods for OSD Tablet/Capsule Manufacture
1.) Wet Granulation
2.) Dry Granulation
3.) Direct Compression

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MATRIX IS FOR GENERAL REFERENCE ONLY
Does not account for all possible OSD Unit Operations and/or Processes

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One of the key challenges in dispensing is dealing with the wide range of containers and packaging types that the ingredients and materials come in.

“Introducing the Formulation Ingredients (actives, excipients, and misc material) Into the Process”

Primary Equipment to Configure:

- Containment Devices (LEV, Downflow Booth, Isolator)
- Container Handling (bags, drums, supersacks, other)
  (ergonomic lifts, inverters, manipulators)
- Sifters/Mills (Bench, vibratory, etc)
- Scales/Controllers (Bench, Floor, Printers)
- Possibly IBC’s
Typical Equipment
Dispensing Configuration

NOTES:
1. Dispensing, milling, and blending operations take place within contained dispensing suite.
2. Dispensing isolator provided with integral drum tipper.
3. Split butterfly valves used for transfer connections between isolator system and IBCs as well as IBC and conical sieve mill.
4. Bin Blender / Lift used for inverting IBCs, raising IBCs above conical sieve mill, and blending.
5. Main dispensing chamber of isolator and conical sieve mill designed configured for inert processing. IBCs to be inverted prior to processing.
Process/Facility Considerations

Consider use of Containment Slides in a Downflow Booth as an alternative to an Isolator

Consider separation of API Dispense and Excipient Dispense
“Combining of Actives and Excipients and/or Lubricants for Homogeneity”

Primary Equipment to Configure:

- Blender (Vee, Cone, Ribbon, IBC)
- Charging Devices (inverters, lifts, vacuum, etc)
- Handling Equipment (lifts, bins, drums, etc)
- Dust Collection (Hoods, Horseshoes, etc)
- Controls, Batch Record Printers
- Safety Enclosures, Barriers and Alarms

One of the key challenges in blending is dealing with the loading and Unloading of the blender and understanding segregation issues.
Typical Equipment
Consider use of IBC In-Bin Blending as an alternative to fixed.

Consider a Through-the-Wall configuration.
One of the key challenges in granulation and drying is to provide and configure the space required to accommodate the process.

"Creating a Workable Formulation"

Primary Equipment to Configure:

- Charging Devices (inverters, lifts, vacuum, etc)
- Granulator (Gral, Vertical, PK)
- Solution Prep System
- Mills (Wet/Dry)
- Dryer (Fluid Bed, PK)
- Handling Equipment (lifts, bins, drums, etc)
Typical Equipment
Granulation Configurations

Integrated Process Train

Bowl In Bowl Out

Hybrid
One of the key challenges in compression/capsule fill is the type of charge
Mechanism and/or strategy used to feed the material to the machine.

“Creating the Final Dose Form”

Primary Equipment To Configure:

- Charging Devices (inverters, lifts, vacuum, funnels)
- Feed Control and Down Chutes
- Tablet Press or Encapsulator
- Metal Detector, De-Duster, Tester, etc
- Collection Containers (Pail, Drum, Poly IBC?)
- Controls, Batch Record Printers
Typical Equipment

CDM Charging Examples
Compression Configuration
Process/Facility Considerations

Consider a Room High Hat around Press as opposed to a single tall room

Consider On-Line fully integrated Tablet Testing
One of the key challenges in tablet coating is the safety and ergonomic issues associated with the loading and unloading of the coater.

“Applying a Film or Functional Coat”

Primary Equipment to Configure:

- Charging Devices (inverters, lifts, vacuum, scoop)
- Coater w/Guns
- Solution Prep System
- Unloading Devices
- Collection Containers (Pail, Drum, Poly IBC?)
- Controls, Batch Record Printers
- Testing Equipment
Typical Equipment
Coating Configuration
Process/Facility Considerations

Consider use of Tablet Containers over Pails

Consider separation of Spray Solution Operation
"As appropriate for the needs of the processing of the product"

Hot Melt Extrusion for Low Solubility API’s (polymer/api blend)
OWNER/ENGINEER/VENDOR CONSIDERATIONS

- OSD Facility upgrade and build projects benefit from close communication and tight collaboration among owner/engineer/vendor parties.

- Once A&E is selected, owner and engineer should pre-plan and strategize on the various technology/vendors options.

- Involve the operators. They know better than the engineers.

- Consider a focused pre-qual strategy
  - Vendor profile/Budget Bid/Presentations/Short Listing

- Address the Integration aspects early and impacts of vendor to vendor

- Be Careful on URS’s…

- More bidders are not always better…
  - More Bids = More time = More $

- Consider sole source in ideal cases

- Check references and make visits
A special thanks and acknowledgement to several vendors who’s equipment photos and graphics were included in this presentation. Please stop by their booths to say hello....
WRAP UP/THANK YOU

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