Guidance for Industry

Manufacturing Equipment Addendum to the Guidance for Industry for Scale-up and Post-Approval Changes: Immediate-release Products (SUPAC-IR)

DRAFT GUIDANCE - NOT FOR IMPLEMENTATION

This guidance document is being distributed for comment purposes only.

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Comments and suggestions regarding this draft document should be submitted by April 3, 1997, to Ted Sherwood, Office of Generic Drugs, Center for Drug Evaluation and Research, HFD-600, 7500 Standish Place, Rockville, MD 20855. Comments and suggestions received after that date may not be acted upon by the Agency until the document is next revised or updated. For questions regarding this draft document, contact Ted Sherwood at 301-594-0340.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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GUIDANCE FOR INDUSTRY

MANUFACTURING EQUIPMENT ADDENDUM TO THE GUIDANCE FOR INDUSTRY FOR SCALE-UP AND POST-APPROVAL CHANGES: IMMEDIATE RELEASE PRODUCTS (SUPAC-IR) [1]

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to pharmaceutical manufacturers using the Center for Drug Evaluation and Research's *Guidance for Industry: Immediate Release Solid Oral Dosage Forms---Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995). This document was developed by the U.S. Food and Drug Administration (FDA) with the assistance of the International Society of Pharmaceutical Engineering (ISPE).

The document may be used in conjunction with the SUPAC-IR guidance document in determining what documentation should be submitted to FDA regarding equipment changes made in accordance with the recommendations in sections V and VI.A of the SUPAC-IR guidance document. The SUPAC-IR guidance document defines 1) levels of change; 2) recommended chemistry, manufacturing, and controls tests for each level of change; 3) in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change; and 4) documentation that should support the change for New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs).

This document is only an aid and, in some cases, specific equipment may not be listed. It does, however, include a representative list of equipment commonly used in the industry. The guidance does not address equipment that has been modified by a pharmaceutical manufacturer to fit its specific needs. If questions arise in using this guidance document please contact the appropriate reviewing office at CDER.

Although this guidance does not discuss validation, any changes should be validated in accordance with Current Good Manufacturing Practices (CGMPs) and the resulting data will be reviewed by field investigators during routine GMP inspections.

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[1]This guidance has been prepared under the auspices of the Chemistry, Manufacturing, and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration with the assistance of the International Society of Pharmaceutical Engineering (ISPE). Although this guidance does not create or confer any rights for or on any person and does not operate to bind the FDA or the industry, it does represent the Agency's current thinking on equipment changes under SUPAC-IR. An electronic version of this guidance is also available via Internet using the World Wide Web (WWW). To access the document on the WWW, connect to the CDER Home Page at http://www.fda.gov/cder and go to the “Regulatory Guidance” section.

The information is presented in broad categories of unit operation (blending and mixing, drying, particle size reduction/separation, granulation, unit dosage, coating and printing, soft gelatin capsule encapsulation). Definitions and classification are provided. For each operation, a table is presented that categorizes equipment by class (operating principle) and subclass (design characteristic). Examples are given within the sub-classes.

Equipment within the same class and sub-class would be considered to have the same design and operating principle under SUPAC-IR. Therefore, for example, a change from one type of diffusion mixer (e.g, V-blender from manufacturer A) to another diffusion mixer (e.g., V-blender from manufacturer B) generally would not represent a change in operating principle and would, therefore, be considered to be the same under SUPAC-IR.

A change from equipment in one class to equipment in a different class would usually be considered a change in design and operating principle. For example, a change from a V-blender to a ribbon blender demonstrates a change in the operating principle from diffusion blending to convection blending and would, therefore, be considered to be different under SUPAC-IR.

Applicants should carefully consider and evaluate on a case-by-case basis changes in equipment that are in the same class, but different sub-class. In many situations, this type of change in equipment would be considered similar. For example, within the Blending and Mixing section, under the Diffusion Mixers Class, a change from a V-blender (sub-class) to a Bin tumbler (sub-class) represents a change within a class and between sub-classes. Provided the manufacturing process with the new equipment is validated, this change would likely not need a pre-approval supplement. The applicant should have available at the time of the change the scientific data and rationale used to make this determination. This information is subject to FDA review at its discretion. It is up to the applicant to determine the filing requirement.

This guidance will be updated as needed to reflect the introduction and discontinuation of specific types of manufacturing equipment. Manufacturers of equipment are encouraged to help keep the document current by communicating changes to the Agency and by making suggestions regarding what equipment should be considered to be within the same class or subclass. The submitted information will be reviewed by FDA and incorporated in an updated guidance document as appropriate.

BLENDING AND MIXING

BLENDING AND MIXING

1.0 Definitions

1.1 Unit Operations

1.1.1 Diffusion Blending:

Blending occurs when particles are placed in random motion allowing them to re-orient with respect to each other when inter particular friction is reduced as the result of bed expansion to achieve uniformity. Tumble blending is another term often used to describe this type of blending.

1.1.2 Convection Mixing:

The reorientation of particles relative to one another as a result of mechanical movement to achieve uniformity. Paddle or plow mixing are terms often used to describe this type of mixing.

1.1.3 Pneumatic Mixing:

The reorientation of particles relative to one another in response to the expansion of a powder bed by a gas to achieve uniformity.

2.0 Equipment Classifications

2.1 Diffusion Blending

2.1.1 Operating Principle (Class):

Diffusion blending within a rotating container.

2.1.2 Design Characteristics (Sub-Class):

- Baffles
- Geometric shape
- Axis of rotation
- Discharge geometry

2.2 Convection Mixing

2.2.1 Operating Principle (Class):

Convection mixing affected by moving parts.

2.2.2 Design Characteristics (Sub-Class):

- Vessel geometry
- Impeller geometry
- Chopper geometry
- Chopper orientation
- Chopper and Impeller Seal Type
- Intensifier/Agitator Geometry
- Discharge Geometry
- Applied power constraints (horsepower, watts)

2.3 Pneumatic Mixing

The reorientation of particles relative to one another in response to the expansion of a powder bed by a gas to achieve uniformity.

2.3.1 Operating Principle (Class):

Mixing of powders affected by a flowing gas.

2.3.2 Design Characteristics (Sub-Class):

- Vessel geometry
- Air nozzle type
- Air nozzle configuration

Table 1 Unit Operation - Blending and Mixing

Class	Sub-Class	Examples
Diffusion Mixers (Tumble)	V-Blenders	Aaron Gemco Hosokawa Micron Jaygo Kemutec Lleal Lowe Patterson-Kelley Paul O. Abbe Pneuvac
	Double Cone	Aaron Gemco Jaygo Kemutec Lleal Lowe MO Industries Patterson-Kelley Paul O. Abbe Pneuvac Servo Lift
	Slant Cone	Gemco Lleal Patterson-Kelley
	Cube Blenders	Lightnin Servo-Lift Zanchetta (Romaco)
	Bin Tumblers	Cora International Creative Design & Machine Custom Metal Craft Gallay-Patriot Gemco Kemutec LB Bohle Matcon USA Paul O. Abbe Servo-Lift Tote Systems Zanchetta (Romaco)
	Horizontal/Vertical/Drum Blenders	Munson Mill Machinery
	Static Continuous	Ross
	Dynamic Continuous	Patterson-Kelley

Table 1 Unit Operation - Blending and Mixing (cont.)

Class	Sub-Class	Examples
Convection Mixers	Ribbon Blenders	Aaron Automatic Ind. Machines Azo-Ruberg Custom Metal Craft Jaygo Kemutec Lowe Paul O. Abbe Pneuvac Ross
	Orbiting Screw	Aaron Hosokawa Jaygo Littleford Ross Vrieco
	Planetary	Aaron Aeschbach AMF GEI Processing Hobart Jaygo Littleford Ross Vrieco
	Forberg	Dynamic Air Paul O. Abbe
	Horizontal Double Arm	Aaron Custom Metal Craft Dynamic Air Jaygo Kemutec Littleford Paul O. Abbe Ross
Convection Mixers	Horizontal High Intensity	Littleford
	Vertical High Intensity	APV Dierks & Shone Diosna Fielder PMA (GEA Niro) Key International LB Bohle Littleford Powrex Vector (GEI Processing) Zanchetta (Romaco)

Table 1 Unit Operation - Blending and Mixing (cont.)

Class	Sub-Class	Examples
Convection Mixers	Diffusion Mixers (Tumble) with Intensifier/Agitator	Gemco Patterson-Kelley Paul O. Abbe
Pneumatic	Pneumatic	Dynamic Air

DRYING

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DRYING

1.0 Definitions

1.1 Unit Operation - Drying:

Removal of a liquid from a solid by evaporation.

1.2 Dynamics of Solids Bed:

1.2.1 Static:

No relative motion among solid particles, dense bed, particles rest upon another.

1.2.2 Moving:

Solids motion achieved by either mechanical agitation or gravity force, slightly expanded bed, only enough to flow one particle over another.

1.2.3 Fluidized:

Expanded condition, particles supported by drag forces caused by gas phase. Solids and gas intermix and together behave like a boiling liquid.

1.2.4 Dilute:

Fully expanded, solids so widely separated that they exert essentially no influence on each other, density of the suspension is essentially that of the gas alone.

1.3 Method of Heat Transfer

1.3.1 Direct Convection

Heat transfer is accomplished by direct contact between the wet solids and hot gases. The vaporized liquid is carried away by the drying gases.

1.3.2 Indirect Conduction:

Heat transfer to the wet solid through a retaining wall. The vaporized liquid is removed independently from the heating medium.

1.3.3 Radiant:

Heat transfer accomplished with varying wavelengths of energy. Vaporized liquid is removed independently from the solids bed.

2.0 Equipment Classifications

2.1 Direct Heating, Static Solids Bed

2.1.1 Operating Principle (Class):

Direct convection heating with a static solids bed.

2.1.2 Design Characteristics (Sub-Class):

The method of loading the dryer.

2.2 Direct Heating, Moving Solids Bed

2.2.1 Operating Principle (Class):

Direct convection heating with moving solids bed.

2.2.2 Design Characteristics (Sub-Class):

The method of technology for moving the solids bed.

2.3 Direct Heating, Fluidized Solid Bed

2.3.1 Operating Principle (Class):

Direct convection heating with fluidized solids bed.

2.3.2 Design Characteristics (Sub-Class):

Not applicable

2.4 Direct Heating, Dilute Solid Bed

2.4.1 Operating Principle (Class):

Direct convection heating with dilute solids bed.

2.4.2 Design Characteristics (Sub-Class):

Fluid state of the feed solids (solution vs. slurry).

2.5 Indirect Conduction Heating, Moving Solid Bed

2.5.1 Operating Principle (Class):

Indirect conduction heating with moving solids bed.

2.5.2 Design Characteristics (Sub-Class):

The method or technology for moving solids bed.

2.6 Indirect Conduction Heating, Static Solid Beds

2.6.1 Operating Principle:

Indirect conduction heating with static solid bed.

2.6.2 Design Characteristics:

Not applicable.

2.7 Indirect Conduction Heating, Lyophilization

2.7.1 Operating Principle:

Lyophilization

2.7.2 Design Characteristics:

Not applicable.

2.8 Microwave Drying, Moving Solids Bed

2.8.1 Operating Principle (Class):

Generation, transmission and absorption of microwaves.

2.8.2 Design Characteristics:

Not applicable.

Note: If a single piece of equipment is capable of performing multiple discrete unit operations (mixing, granulating, drying) the unit was evaluated solely for its ability to dry. The drying equipment was sorted into similar classes of equipment based on the method of heat transfer and the dynamics of the solids bed.

Table 1 Unit Operation - Drying

Class	Sub-Class	Examples
Direct Heating, Static Solids Bed	Tray and Truck	Colton Despatch Gruenberg Oven Hot Pack Hull Proctor & Schwartz Trent
	Belt	Despatch Proctor & Schwartz
Direct Heating, Moving Solids Bed	Rotating Tray, Continuous	Krauss Maffi Wyssmont
	Horizontal Vibrating Conveyor	Carrier Witte
Direct Heating, Fluidized Solids Bed	Fluid Bed	Aeromatic (GEA Niro) APV Fitzpatrick Fluid Air Freund (Vector) Glatt Hutland (Thomas Engineering)
Direct Heating, Dilute Solids Bed	Spray	Aeromatic (GEA Niro) APV Glatt Vector
	Flash	Aeromatic (GEA Niro) APV Micron Powder Systems (Hosokawa)
Indirect Conduction, Moving Solids Bed	Paddle Dryers	Bepex (Hosokawa) Jaygo
	Rotary (Tumble)	Gemco Littleford Day Patterson-Kelley Paul O. Abbe
	Agitation	Bohle (Granumat) GEI Gral Krauss Maffei Nauta (Hosokawa)
Gas Stripping		Bohle (Vagas) Collette (Transflo) GEA Niro (Aerovac) Zanchetta (Romaco)

Table 1 Unit Operation - Drying (cont.)

Class	Sub-Class	Examples
Indirect Conductive Static Solid Bed		
Indirect Conductive Lyophilizers		Amsco Hull Stokes
Indirect Radiant, Microwave, Moving Solids Bed		Bohle (Vacumat) Collette (Vactron) GEA Niro (Fielder Spectrum®)

PARTICLE SIZE REDUCTION/SEPARATION

PARTICLE SIZE REDUCTION/SEPARATION

1.0 Definitions

1.1 Unit Operation - Particle Size Reduction/Separation

1.1.1 Particle Size Reduction:

The mechanical process of breaking particles or agglomerates into smaller pieces. The mechanical process used is generally referred to as "milling." Milling reduces particle size by one or a combination of the following mechanisms:

1. Impact - Particle size reduction by applying an instantaneous force perpendicular to the surface of the particle. The force can result from particle to particle or particle top mill surface collision.

2. Attrition - Particle size reduction by applying a force in a direction parallel to the surface of the particle.

3. Compression - Particle size reduction by applying a force slowly (as compared to Impact) to the surface of a particle in a direction toward the center of the particle.

4. Cutting - Particle size reduction by application of a shearing force to a material.

1.1.2 Separation:

Particle size classification according to particle size alone.

2.0 Equipment Classifications

2.1 Fluid Energy Mills

2.1.1 Operating Principle (Class):

High speed particle to particle impact or attrition.

2.1.2 Design Characteristics (Sub-Class):

1. No moving parts

2. Chamber
3. Nozzle
4. Classifier Design

2.2 Impact Mills

2.2.1 Operating Principle (Class):

Fracture of particles by mechanical impact or impact with other particles.

2.2.2 Design Characteristics (Sub-Class):

1. Feed Mechanism
2. Grinding Head
3. Chamber Grinding Liner
4. Classifier

2.3 Cutting Mills

2.3.1 Operating Principle (Class):

Particle size reduction by mechanical shearing.

2.3.2 Design Characteristics (Sub-Class):

1. Feed Mechanism
2. Rotating and Stationary Knives
3. Classifier

2.4 Compression Mills

2.4.1 Operating Principle (Class):

Particle size reduction by compression stress and shear between two surfaces.

2.4.2 Design Characteristics (Sub-Class):

1. Feed Mechanism
2. Two Surfaces

2.5 Screening Mills

2.5.1 Operating Principle (Class):

Particle size reduction by attrition through a screen.

2.5.2 Design Characteristics (Sub-Class):

1. Feed Mechanism
2. Screen and Impeller/Stator
3. Chamber

2.6 Tumbling Mills

2.6.1 Operating Principle (Class):

Particle size reduction by attrition from grinding media.

2.6.2 Design Characteristics (Sub-Class):

1. Shell Container
2. Grinding Media

2.7 Separators

2.7.1 Operating Principle (Class):

Classification of particles by size only.

2.7.2 Design Characteristics (Sub-Class):

1. Feed Mechanism
2. Mechanical Action
3. Screen Design

Table 1 Unit Operation - Particle Size Reduction

Class	Sub-Class	Examples
Fluid Energy Mills	Tangential Jet	Micro-Jet® (Fluid Energy Aljet) Micronizer (Sturtevant) Spiralplex AS® (Hosokawa)
	Loop/Oval®	Jet-O-Mizer® (Fluid Energy Aljet)
	Opposed Jet	Trost® (Garlock, Inc.)
	Opposed Jet with Dynamic Classifier	Alpine AFG (Hosokawa) Roto-Jet® (Fluid Energy Aljet)
	Fluidized Bed	
	Fixed Target	
	Moving Target	
Impact Mills	Hammer Air Swept	Alpine Circleplex ZPS (Hosokawa) Bepex Pulvocron® (Hosokawa) Mikro-ACM (Hosokawa) NSP Powderizer® (Sturtevant)
	Hammer Conventional	Fitz Mill® (Fitzpatrick) Fluid Air Mill (Fluid Air) Mikro-Pulverizer® (Hosokawa) Tornado® (Stokes-Merrill)
	Pin/Disc	Alpine UPZ (Hosokawa) Simpactor® (Sturtevant) Universal (Kemutec)
	Cage Mills	Cage Mill (Stedman)
Cutting Mills		Alpine Rotoplex® (Hosokawa) Comitrol® (Urschel)
Compression Mills		Crack-U-Lator® (MCA International)
Screening Mills	Rotating Impeller	Comil® (Quadro) Cone Mill (Kemutec)
	Rotating Screen	Quick Sieve® (Glatt)
	Oscillating	Oscillator (Frewitt) Oscillator (Jackson-Crockatt) Oscillator (Stokes-Merrill) Oscillator (Vector)
	Hammer Conventional	Fitz Mill® (Fitzpatrick) Fluid Air Mill (Fluid Air) Mikro-Pulverizer® (Hosokawa) Tornado® (Stokes-Merrill)

Table 1 Unit Operation - Particle Size Reduction (cont.)

Class	Sub-Class	Examples
Tumbler Mills	Ball	
	Rod	
	Vibratory	Vibro-Energy (Sweco)

Table 2 Unit Operation - Separation

Class	Sub-Class	Examples
Separators	Vibratory/Shaker	Rectangular (Ellipt Motion) - Sweco Rectangular (Round Motion) - Sweco Rotex® (Rotex, Inc.) Round Vibratory (Aligaier) Round Vibratory (Russell Finex) Round Vibratory (Sweco) Round Vibratory (VortiSiv) Vibratory Cascade (Mogensen)
	Centrifugal	Centri-Sifter® (Kason) Centrifugal Sifter® (Sweco) KEK Centrifugal Sifters (Kemutec)

GRANULATION

GRANULATION

1.0 Definitions

Granulation is defined as a process that will effect one or more of the following properties of powders:

- Enhance flow
- Increase compressibility
- Densification
- Alter physical appearance to spherical, uniform, or larger particles
- Enhance hydrophilic properties of particle surface

1.1 Dry Granulation

Densification of dry powders by direct physical compaction.

1.2 Wet High Shear Granulation

Densification and/or agglomeration of a powder by the incorporation of a granulation fluid onto the powder with high power per unit mass, through rotating high shear forces.

1.3 Wet Low Shear Granulation

Densification and/or agglomeration of a powder by the incorporation of a granulation fluid onto the powder with low power per unit mass, through rotating low shear forces.

1.4 Low Shear Tumble Granulation

Densification and/or agglomeration of a powder by the incorporation of a granulation fluid onto the powder with low power per unit mass, through rotation of container vessel and/or intensifier bar.

1.5 Extrusion Granulation

Plasticization of solids or wetted mass or solids and granulation fluid with linear shear through a sized orifice by means of a pressure gradient.

1.6 Roto Granulation

Densification, agglomeration, and or spheronization of a powder with the incorporation and subsequent drying of a granulation fluid while the powder is fluidized in a cylindrical pattern by a rotating disk with air flowing between the disk and vessel walls.

1.7 Fluid Bed Granulation

Densification and or agglomeration of a powder with little or no shear by direct atomization of a granulation fluid and impingement on solids while suspended by a controlled stream of gas with simultaneous drying.

1.8 Spray Dry Granulation

A pumpable granulating liquid containing solids (in solution or suspension) is atomized in a drying chamber and rapidly dried by a controlled stream of gas producing a dry powder.

2.0 Similar Equipment Classification and Sub-Classification

2.1 Dry Granulation

2.1.1 Slugging

Powders are compressed on a tablet press into tablets or slugs which are milled or screened to produce a densified dry granulation.

2.1.2 Roller Compaction

Powders are compacted between two rollers to produce a densified dry granulation. This material may or may not be milled or sieved.

2.2 Wet High Shear Granulation

2.2.1 Top or Bottom Driven

Granulation equipment where the primary source of high energy shear forces are imparted to the powders and granulation fluid through an impeller and chopper that are attached to either the top or bottom of the unit.

2.2.2 Side Driven

Granulation equipment where the primary source of high energy shear forces are imparted to the powders and granulation fluid through an impeller and chopper that are attached and driven from the side of the unit.

2.3 Wet Low Shear Granulation

2.3.1 Planetary

Granulation equipment where the primary source of low energy shear forces are imparted to the powders and granulation fluid through a rotating impeller.

2.3.2 Kneading

Granulation equipment where the primary source of low energy shear forces are imparted to the powders and granulation fluid through a reciprocal kneading action.

2.3.3 Screw

Granulation equipment where the primary source of low energy shear forces are imparted to the powders and granulation fluid through a convection screw action.

2.4 Low Shear Tumble Granulation

2.4.1 Slant Cone

A rotating twin shell blender with a dispersion bar for the addition of a granulation fluid to powders.

2.5 Extrusion Granulation

2.5.1 Radial or Basket

Granulation material is forced from a hollow cylinder by a screw or rotating arm mechanism through a sized screen located in a radial position on the outside of the cylinder.

2.5.2 Axial

Granulation material is forced from a hollow cylinder by a screw mechanism through a sized screen located in an axial or end plate position of the cylinder.

2.5.3 Ram

Granulation material in a hollow tube is forced by a plunger through a sized orifice or screen.

2.5.4 Roller

Roller, gear, or pelletizer granulators use gears or rollers to force the granulation material through a screen or other sizing apparatus.

2.6 Roto Granulation

2.6.1 Open

Roto granulation utilizing an open top architecture.

2.6.2 Closed

Roto granulation or roto fluid bed granulation utilizing a closed top architecture similar to a fluid bed granulator.

2.7 Fluid Bed Granulation

A granulation fluid is sprayed onto powders which are suspended, fluidized, mixed or dried in a controlled stream of gas. Mechanism for suspending, fluidizing, mixing and drying do not represent significant differences in principle of operation.

2.8 Spray Dry Granulation

A pumpable granulating liquid containing solids (in solution or suspension) is atomized in a drying chamber and rapidly dried by a controlled stream of gas producing a dry powder. Mechanism for atomization and drying do not represent significant differences in principle of operation.

Note: Specialty pieces of equipment or processes capable of granulating pharmaceutical products were discussed. If the equipment was highly specialized or insufficient information available, it was not included in this report. If a single piece of equipment was capable of performing multiple discrete processing steps (mixer, granulator, drier), the unit was evaluated solely for its ability to granulate. If multi-functional units were incapable of discrete steps (fluid bed granulator, drier), the unit was evaluated as an integrated unit.

Table 1 Unit Operation - Granulation

Class	Sub-Class	Examples
Dry Granulation	Slugging	*Various*
	Roller Compaction	Alexanderwerk Bepex Fitzpatrick Freund Vector
Wet High Shear Granulation	Top or Bottom Driven	Bohle Collette (GEI and Vector) Diosna Fielder (GEA Niro) Key Littleford Day Powrex Zanchetta (Romaco)
	Side Driven	Lodige
Wet Low Shear Granulation	Planetary	Aeschbach AMF Collette Hobart Ross
	Kneading	Day Sigma
	Screw	Nauta (Hosokawa)
Low Shear Tumbling Granulation	Slant Cone	Gemco Patterson-Kelley
Extrusion Granulation	Radial or Basket	Alexanderwerk LCI Nica System (GEA Niro) Ross Vector
	Axial	Bepex Gabler LCI
	Dome	LCI
	Roller	Alexanderwerk Bepex LCI

Table 1 Unit Operation - Granulation (cont.)

Class	Sub-Class	Examples
Roto Granulation	Open	Freund (Vector)
	Closed or Fluid Bed	Aeromatic (GEA Niro) Freund (Vector) Glatt LCI Vector
Fluid Bed Granulation		Aeromatic (GEA Niro) Fluid Air Freund (Vector) Glatt Vector
Spray Dry Granulation		Niro

UNIT DOSING

UNIT DOSING

1.0 Definitions

1.1 Unit Operation - Unit Dosage

1.1.1 Tablet Press:

Equipment by which compression force is applied across the powder blend to form a single unit dose.

1.1.2 Encapsulation:

Hard gelatin capsule filling machine that all have the following operating principles in common:

- Rectification (orientation of the hard gelatin capsules)
- Separation of capsule caps from bodies
- Dosing of fill material/formulation
- Rejoining of caps and bodies
- Ejection of filled capsules

1.1.3 Powder Filler:

Equipment by which a unit dosage of powder blend is dispensed into a container closure system.

2.0 Sub-Class Definitions

2.1 Sub-Class:

2.1.1 Tabletting

2.1.1.1 Gravity Feed:

Tablet press wherein powder flows into the die cavity without mechanical assistance.

2.1.1.2 Power Assisted Feed:

Table press wherein powder is mechanically moved into the die cavity by a series of paddles.

2.1.1.3 Centrifugal:

Tablet press wherein powder is forced into the die cavity by the rotational forces of the press.

2.1.1.4 Compression Coating

Specifically designed tablet press wherein both initial compression of a core tablet and secondary compression with a coating material take place on a single piece of equipment.

Rationale:

Tablet presses, as a class of equipment, utilize the same operating principle to compress powder blends into tablets. Different equipment vendors provide alternate means of delivering the powder blend to the die cavity as is represented by the different Sub-Classes.

2.1.2 Encapsulation:

2.1.2.1 Auger Fill:

Encapsulator wherein the powder/formulation is driven into the capsule bodies by means of a rotating auger.

2.1.2.2 Vacuum Fill:

Encapsulator wherein the powder/formulation is drawn by means of vacuum into cylinders containing porous pistons. The powder is scraped flush with the open end of the cylinders, and then ejected into the capsule bodies via pressurized air through the porous piston.

2.1.2.3 Vibratory Fill:

Encapsulator wherein a perforated plate is vibrated in the bed of the powder/ formulation. The vibratory action facilitates powder flow into the capsule bodies through holes in the plate.

2.1.2.4 Dosing-disk:

Encapsulator wherein soft powder plugs are formed from the powder/formulation when tamped into holes bored through a disk. The powder plugs are then pushed by pistons from the bored holes into the capsule bodies.

2.1.2.5 Dosator:

Encapsulator wherein cylindrical dosing tubes fitted with movable pistons are plunged into the powder/formulation bed to form soft powder plugs. The powder plugs are then pushed by the pistons from the dosators into the capsule bodies.

Rationale:

Encapsulators utilize the same operating principle of dispensing a powder slug into an empty capsule shell. Equipment vendors use different methods for forming the slug as is represented by the different Sub-Classes shown in the table.

2.1.3 Powder Fill:

2.1.3.1 ACCOFIL:

Powder is charged into a hopper and is pre-conditioned by mixing and/or agitator blade(s) to assist powder delivery and flow. The pre-determined amount of powder is drawn into the fill wheel ports with vacuum from the supply hopper. The powder is held by vacuum in the fill wheel ports until it is indexed into and dispensed into the container by use of compressed air.

2.1.3.2 Auger:

Powder is charged into a hopper and is pre-conditioned by mixing and/or agitator blade(s) to assist powder delivery and flow. An auger is utilized to deliver the powder from the hopper into the container using a pre-determined degree of revolution.

Rationale:

Powder fillers use different filling techniques for dispensing powder into a container. Both methods are proven to be capable of accurately and consistently dispensing a pre-determined amount of powder into the final container.

Table 1 Unit Dosing

Class	Sub-Class	Examples
Tablet Press	Gravity Feed	Manesty (Thomas Engineering) Stokes
	Force Feed	Courtoy (AC Compacting) Fette Hata (Elizabeth Carbide) Kikisui Kilian Manesty (Thomas Engineering)
	Centrifugal	Comprima (IMA)
	Compression Coating	Drycota Manesty (Thomas Engineering) Prescoter (Kilian)
Encapsulator	Piston	Macofar MG2 Romaco Zanasi (IMA)
	Tamp	H&K Bosch Index 1500
	Vacuum-Fill	Perry Accofil
	Vibratory	Osaka (Sharpley-Stokes)
	Auger-Fill	Capsugel Type B Elanco No. 8
Powder Filler	Accofill	Bosch Perry Zanasi (IMA)
	Augar	All-Fill Calumatic Cozzoli

COATING/PRINTING

COATING/PRINTING

1.0 Definitions

1.1 Unit Operation: Coating

Uniform deposition of a layer of material on or around a solid dosage form, or component there of, for the purpose of:

- Protecting the drug from its surrounding environment (air, moisture and light) with a view to improving stability.
- Masking of unpleasant tastes, odor or color of the drug.
- Protecting the drug from the gastric environment.
- Increasing the ease by which the product can be ingested by the patient.
- Imparting a characteristic appearance to the tablets which facilitates product identification and aides patient compliance.
- Providing physical protection for facilitating handling. This includes minimization of dust generation, in subsequent unit operations.
- Reducing the risk of interaction between incompatible components. This would be achieved by coating one or more of the offending ingredients.

The deposition of the coating material is typically accomplished through any one of four major techniques:

1. Sugar Coating
2. Film Coating
3. Microencapsulation
4. Compression Coating

1.1.1 Sugar Coating

The deposition of coating material onto the substrate from aqueous solution/suspension of coatings based predominately on sucrose as a raw material.

1.1.2 Film Coating

The deposition of polymeric film on to the solid dosage form.

1.2 Unit Operation: Printing

The marking of a capsule or tablet surface for the purpose of product identification. Printing may be accomplished by either the application of a contrasting colored polymer on to the surface of a capsule or tablet or by the use of laser etching.

The method of application, provided the ink formulation is not altered, is of no consequence to the physical-chemical properties of the product. Therefore, changes in this type of printing equipment are deemed not to be significant.

2.0 Equipment Classification

2.1 Conventional Coating System

A conventional coating pan system consists of a circular nonperforated drum, which may be mounted angularly on a stand. The drum rotates on its horizontal axis. Process air, if required, is directed into the drum and onto the material to be coated, and is exhausted by means of ducts located either at the front or rear of the drum. The coating material is applied to the moving substrate by one or more of the following methods:

1. Manual application
2. Spraying

2.2 Perforated Coating System

A perforated coating system consists of a horizontally rotating circular drum which passes process air through the product bed either through perforations integrated in the drum walls or through a perforated device immersed in the product bed. The coating material is applied to the moving (substrate) bed by spraying. The process air facilitates deposition of the coating on to the substrate, removal of dust during processing and accelerates the drying process.

The perforated coating system Sub-Class includes both batch and continuous coating processes. The traditional batch coating process reaches its end point when the required amount of solids has been applied.

The continuous coating process, relatively new to the pharmaceutical industry, involves metering the tablet feed into a long perforated cylinder and exiting the finished tablets at the other end. Control of the spray, air flow, heating, and pan speed variables is accomplished similarly to that of the batch coating process.

2.3 Fluidized Bed

Fluidized bed coaters achieve fluidization of the substrate by introducing a continuous stream of process gas into a chamber. The coating material is deposited onto the suspended substrate as it passes through the spray path. The process gas serves to maintain the substrate in motion, increases the area of contact between the drying medium and the product from the solvent (aqueous and non-aqueous) vehicle that must be removed, and facilitates removal of extraneous dust during processing.

2.4 Spraying Congealing/Drying

A process where by both a substrate and coating material are sprayed simultaneously into a chamber supplied with process gas to create a uniformly coated substrate and congeal/dry the mixture.

2.5 Compression Coating

Refer to the Unit Dosage section of this guide.

2.6 Electrostatic Coating

A strong electrostatic charge is applied to the surface of the substrate. The coating material containing oppositely charged ionic species is sprayed onto the substrate.

2.7 Dip Coating

Coating is applied to the substrate by dipping it into the coating material. Drying is accomplished using a conventional coating pan.

2.8 Vacuum Film Coating

This technique uses a jacketed pan equipped with a baffel system. Tablets are placed into the sealed pan, an inert gas (i.e. nitrogen) is used to displace the air and then a Vacuum is drawn. The coating material is applied via an airless hydraulic spray system.

References

1. Porter, S. “Remington’s Pharmaceutical Sciences”, ed. 18, 1990 p.p. 1666-1675

2. Seitz, J. et.al., "in Theory and Practice of Industrial Pharmacy", 3d ed., Edited by L. Lachman et.al. Lea & Febiger, Philadelphia, PA, 1986, p.p. 346-372

Table 1 Coating Equipment

Class	Sub-Class	Examples
Coating Pan	Conventional Coating System	Bruck Pellegrini Stokes-Merrill
	Perforated Coating System	Accela Cota (Thomas Engineering) Butterfly (Hutland) Continuous Accela Cota (Thomas Engineering) Continuous Coating System (CMS/Vector) Driacoater (Driam) Dumoulin (Raymond) Fast Coater (O'Hara) Hi-Coater (Vector) Pelligrini Pro-Coater or Glatt Coater (Glatt) Nicomac Strunck
Air Suspension Systems	Fluidized Bed	Aeromatic Precision Coater Multiprocessor (GEA Niro) Bohle Flo-Coater Freund (Vector) GPCG / Wurster (Glatt) Kugel Coater Hutland (Thomas Engineering) Nicomac Spir-A-Flow (Freund Industrial Co.)
	Spray Congealing/Dryer	Niro Spray Congealer/Dryer (GEA Niro)
Dip Coating		
Vacuum Film Coating		
Electrostatic Coating		

Table 2 Printing Equipment

Class	Sub-Class	Examples
Ink Based Printing	Off Set	Ackley Hartnett Markem Takeda
	Ink Jet	Image Linx
Laser Etching	Laser	

SOFT GELATIN CAPSULES

SOFT GELATIN CAPSULES

Introduction

A. This section of the guidance document deals with the manufacture of soft gelatin capsules. This dosage form is unique in the area of immediate release solid oral dosage forms since in many respects it borrows unit operation technology from various disciplines. This guide will permit evaluation of comparability of equipment for selected unit operations as they relate to soft gelatin capsule processing.

To further clarify the purpose of this guide the user must determine into which general category the soft gelatin processing train fits. These categories are discussed as:

1. Suspension/paste filled capsules

2. Solution/liquid filled capsules

3. Dry filled/powder filled capsules

B. The area of gelatin mass preparation is, for the purpose of this document, common to all three general categories of soft gelatin capsules. The idiosyncrasies of the gelatin mass behavior is driven by mass composition and these points are outside the purpose of this guide. To satisfy the needs of the user the gelatin process will be broken down into two general categories.

1. Hot melt process

2. Cold process

These will be further defined within this guide with their related unit operations.

C. The encapsulation process is generally accepted as being usage of a rotary die in conjunction with a positive displacement pump for liquids/solutions and suspensions/pastes or in the case of dry fill/powder fill a gravity or force fed dosing system (1,2). This is the present state of the art within this sector of the industry.

D. The subsequent washing and drying of soft gelatin dosage forms presents the most sensitive area of this process. It is the result of development and fabrication efforts which are unique to each manufacturer and machine type. Based on this nuance the equipment in this area will not be dealt with by this document.

1.0 Definitions

1.1 Unit Operation: Gelatin Mass Preparation (Hot Melt)

This is typically where all the solid and liquid components are weighed and subsequently mixed. The mixed material is then subjected to heat in the presence of vacuum in selected cases. The resulting liquid mass is held at elevated temperature until used in the encapsulation process.

- Mixing the combination of all components prior to the application of heat and vacuum if required. Mixing may involve high energy or low energy equipment.

- Melting is the application of heat to the gelatin mass to form a uniform liquid mass. The heat is applied using a jacketed kettle or reactor type vessel. The vessel is usually equipped with a vacuum source.

- Deaeration is the removal of entrapped air contained in the liquid gelatin mass prior to holding the material for further processing. This process may take place in the mixing/heating vessel by application of vacuum and/or off line via a separate step.

- Holding refers to the storage of the gelatin mass prior to use in the encapsulation process using a vessel which is supplied with a heating jacket.

1.2 Unit Operation: Gelatin Mass Preparation (Cold Process)

This is typically where all the solid and liquid components are weighed and subsequently mixed at ambient or lower temperatures in a jacketed vessel. The mixed material is then subjected to heat in the presence of vacuum in selected cases. The resulting liquid mass is held at elevated temperatures until used in the encapsulation process. (See Section 1.1 for additional definitions)

1.3 Unit Operation: Fill Mixing (Suspension/Paste Filled)

This process involves blending of the liquid base with the addition of the solids portion. Blending continues until all solids are wetted. Should a suspending agent be used, it is normally added first to the liquid base prior to solid additions.

- Mixing is the blending of the liquid base, suspending agents (if required) and the solid components. Mixing may involve high or low energy equipment.

- Deaggregation involves the passing of the mixed material through a suitable homogenizer/mill to remove lumps and provide a smooth, easily pumpable fill material. In general, this procedure has minimal effect on the particle size of the solid components. This procedure is looked upon as a processing aid for the vast majority of suspension/paste filled capsule products (3).

- Deaeration refers to the removal of entrapped air contained in the fill material prior to further processing. This process may take place in the mixing vessel by application of vacuum and/or off line via a separate step. The material is then stored in a holding vessel prior to encapsulation.

- Holding refers to maintaining the fill material in a jacketed vessel which may be equipped with a low speed sweep gate mixer. The jacket may be supplied with heat depending upon the product application.

1.4 Unit Operation: Fill Mixing (Solution/Liquid Filled)

This is the process wherein the liquid carrier and solids are blended to form a solution. The process may involve the application of heat using a jacketed vessel.

- Mixing the combination of all components with the application of heat if required. Mixing may involve high energy or low energy equipment.

- Dearation is the removal of entrapped air contained in the fill material prior to further processing. This process may take place in the mixing vessel by application of vacuum and/or off line in a separate step. The material is then stored in a holding vessel prior to encapsulation.

- Holding refers to maintaining the fill material in a jacketed vessel which may be equipped with a low speed sweep gate mixer. The jacket may be supplied with heat depending upon the product application.

1.5 Unit Operation: Fill Mixing (Dry Filled/Powder Filled)

Fill mixing categorizes the uniform combinations of dry inert materials as well as drug substance during capsule fill preparation. This fill material my take the form of immediate release powder, pellets/beads and or granulation.

Note: The basic operating principles used in this unit operation are defined elsewhere in this guide and are generally referred to as blending and mixing, drying, granulation and particle size reduction/separation.

1.6 Unit Operation: Encapsulation

Continuous casting of gelatin ribbons with liquid fill material being injected using a positive displacement pump or for dry material being gravity or force fed with capsule formation using a rotary die.

1.7 Unit Operation: Washing/Drying (see section D in the introduction)

Washing: Continuous removal of any lubricant material on the outside of the capsule. This lubricant material is present in order to prevent sticking of the gelatin ribbon to the rotary die during encapsulation. This lubricant application is a function of the encapsulation machine's design.

Drying: The removal of the washing solvent as well as the majority of water from the gelatin capsule shell which enhances the final size, shape and tensile strength of the final product. This process takes place in two stages: tumbling and tray. Conditioned air is continuously introduced during tumbling and subsequent tray drying.

1.8 Unit Operation: Inspection/Sorting

The process wherein undesirable capsules are removed this includes misshapen, leaking capsules as well as unfilled and agglomerates of capsules. Generally, this unit operation may take place at several points within the encapsulation process.

1.9 Unit Operation: Printing

The user of this guide is asked to refer to the Coating/Printing section wherein usage of various pieces of equipment are defined and categorized.

References

1. L. Lachman, H.A. Lieberman and J.L. Kanig (Eds.) "The Theory and Practice of Industrial Pharmacy", Chapter 3, J.P. Stanley, Lea & Febiger, Philadelphia, PA, 1971, p.359.

2. P. Tyle (Edition) "Specialized Drug Delivery Systems, Manufacturing and Production

Technology", Chapter 10, P.K. Wilkinson, F.S. Hom, Marcel Dekker, New York, NY, 1990, p. 409.

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Table 1 Unit Operation - Soft Gelatin Capsules
Gelating Mass Equipment (Hot Melt Process)

Class	Sub-Class	Examples
Mixing Vessel	Jacketed Vessel	Lee Industries Paul Mueller Co.
	Jacketed Reactor Systems with Vacuum/Mixing	
Melting Vessel	Jacketed Vessel	
	Jacketed Reactor Systems with Vacuum/Mixing	
Mixer	Low Energy Planetary	AMF Hobart Pony
	High Energy	Fielder PMA Melt Pelletizer (GEA Niro)
Deaeration	Vacuum Vessel/ Reactor System	Paul Mueller Co.
	Off Line/In Line Stand Alone System	Versator
Holding	Jacketed Vessel	Lee Industries
	Jacketed Vessel with Mixing System	Sweep Gate (Lee Industries)

Table 2 Unit Operation - Soft Gelating Capsules
Gelating Mass Equipment (Cold Process)

Class	Sub-Class	Examples
Mixing Vessel	Jacketed Vessel	Lee Industries Paul Mueller Co.
	Jacketed Reactor Systems with Vacuum/Mixing	
Melting Vessel	Jacketed Vessel	
	Jacketed Reactor systems with Vacuum/Mixing	
Mixer	Low Energy Planetary	AMF Hobart Pony
	High Energy	Fielder PMA Melt Pelletizer (GEA Niro)
Deaeration	Vacuum Vessel/ Reactor Systems	Paul Mueller Co.
	Off Line/In Line Stand Alone System	Versator
Holding	Jacketed Vessel	Lee Industries
	Jacketed Vessel with Mixing System	Sweep Gate (Lee Industries)

Table 3 Unit Operation - Soft Gelatin Capsules
Fill Mixing (Suspension/Paste Filled)

Class	Sub-Class	Examples
Mixer	Low Energy	Hobart Lightnin
	High Energy	Cowles
Mixing Vessel	Jacketed/Vacuum	Becomix Fryma Hicks Lee Industries Paul Mueller Co. Ross
	Conventional	Lee Industries
Deaggregation	Rotor Stator	Colloid Mill
	Roller	Stokes
	Cutting	Comitrol (Urschel)
	Stone Mill	Carborundum (Fryma)
	Paint Mill	
Deaeration	Vacuum Vessel	Fryma Paul Mueller Co.
	Off Line/In Line Stand Alone	Versator
Holding	Jacketed Vessel	Lee Industries
	Jacketed Vessel with Mixing System	Sweep Gate (Lee Industries)

Table 4 Unit Operation - Soft Gelatin Capsules Filling Mixing (Solution/Liquid Fill)

Class	Sub-Class	Examples
Mixer	Low Energy	Lightnin
	High Energy	Cowles
Mixing Vessel	Jacketed Vacuum	Becomix Fryma Hicks Lee Industries Paul Mueller Co. Ross
	Conventional	Lee Industries
Deaeration	Vacuum Vessel/ Reactor System	Fryma Paul Mueller Co.
	Off Line/In Line Stand Alone System	Versator
Holding	Jacketed Vessel	Lee Industries
	Jacketed Vessel with Mixing System	Sweep Gate (Lee Industries)

Table 5 Unit Operation - Soft Gelating Capsules Encapsulation

Class	Sub-Class	Examples
Rotary Die	Liquid Fill (Positive Displacement Pump)	
Rotary Die	Dry Fill (Gravity or Force Fed)	

Table 6 Unit Operation - Soft Gelatin Capsules
Inspection/Sorting

Class	Sub-Class	Examples
Belt	Visual Single Side Double Side	Lakso Merril
Vibratory	Visual Single Side Double Side	Stokes
	Size Exclusion	Stokes
Roller	Visual	Maschimpex
	Roller Grader Size Exclusion	Maschimpex
Rotary Table	Visual Single Side Double Side	Lakso Merril
Electro Mechanical	Weigh System Visual System	Mocon