Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion

This document provides an explanation of the semi-solid Drug Product dosage form and recommendations for analysis of the manufacturing process critical process parameters.

Semi-solids come in a variety of dosage forms, yet significant steps and equipment used for the manufacturing processes share commonality. The critical process parameters will often be the same from process to process.

Semi-Solid Dosage and Process Parameters
The most common presentations of semi-solid dosage formulations are therapeutic creams, ointments, gels, lotions, emulsions, salves, pastes and other forms of similar viscous consistency. Topical and ophthalmic are the primary routes of administration for semisolids. Semisolid drug products, depending on their use, can be sterile or nonsterile. Requirements of process validation that are specific to semisolid drug products are stated in another document.

Creams/ointments typically contain one or more drug substances dissolved or dispersed in aqueous, oil or a suitable base. Creams posses a fluid consistency and have traditionally been called oil-in-water or water-in-oil emulsions. They also could be dispersions of long-chain fatty acids or alcohols that are water washable or miscible.

Some common manufacturing processes are mixing, heating/cooling, dispersion /homogenization, deaeration, transfer and other techniques for these viscous substances.

Filling and packaging is typically into single-or multiple-unit containers such as rigid bottles or jars, collapsible tubes or flexible pouches.

The critical process parameters and attributes that need to be monitored during process validation for bulk semi-solid dosage formulations depend on dosage presentation and the drug or formulation characteristics. The following table of process parameters and attributes can be used as a starting point for the selection of CPPs for process validation.

Each application should be evaluated on a case-by-case basis to determine which parameters are critical. Also, depending on the specific dosage form and route of administration, some of the attributes listed below may not be applicable or additional attributes could be warranted. For example, the attributes for ophthalmic ointments should include a test for metal particles (e.g., USP <751>). Another example would be if preservatives or antioxidants are used in the product, tests for their content should be included and acceptance would be based upon the level that will maintain product quality throughout shelf life.

Process Step	Equipment Type (Examples)	Potential Critical Process Parameters[a]	Potential Critical Attributes
Transfer/Holding	Low Shear (gravity, peristaltic, screw, diaphragm) High Shear (centrifugal, piston, rotating gear)	• Flow rate • Agitation speeds • Type and size of tube or pipe • Temperatures • Protection from environment (e.g. cover, plastic)	• Viscosity • Density or specific gravity • Phase stability • Pourability • Resuspendability • Uniformity • Drug release/dissolution (if applicable)

Filling	Auger, Gear, Peristaltic, Piston (e.g.cream filling)	• Filling equipment parameters
		  • Speed
		  • Volume or weight
		  • Nozzle size
		• Hopper (stirring speed, heat, evaporation)
		• Filtration type/parameters
		• Inert gas (before/after)
		• Tube loading (manual vs. automatic)
		• Tube cleaning (compressed air, vacuum)
		• Embossing (tube)
		• Temperatures
			• Fill weight variation
			• Content uniformity
			• Assay/Degradation
			• Visual inspection
			• Viscosity
			• Density/Specific gravity
			• Fill accuracy (% from target) and fill precision (%RSD, CP, CPK)
			• Minimum fill
			• Drug release (in vitro) /dissolution (if applicable)
			• Other (e.g. metal particles for ophthalmics, gel strength)
			• Microbial (if applicable)

Sealers (capping, cutting)	Romaco (Unipac), M& O Perry, Kaps-All, Auto-Mate Tech.	• Speed • Temperature (heat seal) • Head or Seal pressure , (crimp/torquing) • Electromagnetic (induction) • Applied force (capping torque)	• Removal torque • Leakage/integrity • Eveness (of cut)

[a] Parameter of holding time (in-process material) is common to all unit process steps.

