

Quality Factors Influencing Semi-Solid Manufacturing

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QUALITY FACTORS INFLUENCING SEMI-SOLID MANUFACTURING

Kalpen Patel, Research and Development Manager, WDPPrx

Angela Holley, Business Development Director, WDPPrx

Although the name suggests otherwise, manufacturing semi-solid pharmaceutical drug products cannot be done ‘half-way.’ The making of semi-solid dosage forms, including pastes, ointments, gels and creams, requires specialized production techniques to assure high-quality results.

TRAITS OF QUALITY SEMI-SOLIDS

Several characteristics define the quality of semi-solid pharmaceuticals. Under cGMP compliant manufacturing and production conditions, semi-solid pharmaceutical drug products are generally smooth to the touch. They minimize dehydration, grittiness, and are cosmetically elegant. Their application does not irritate the skin and offers a pleasant scent. They also apply easily to the affected area with the appropriate use of plastic or aluminum tubes and other unique delivery mechanisms.

Poorly manufactured semi-solids may produce undesirable results that affect patient outcomes.

Several domestic and international standards have been adopted to create efficiencies in the manufacturing process including QbD (Quality by Design), DoE (statistical Design of Experiments) and FMEA (Failure Mode and Effects Analysis) to mitigate risk.

Producing quality semi-solids literally boils down to five key physical characteristics: homogeneity, particle distribution, spreadability, grittiness and use of surfactants. If one element fails, then the entire process breaks down. Each element must be closely monitored from beginning to end and after sale to assure patients receive the correct medication in the specified concentration throughout the life of the product.

PHYSICAL PROPERTIES AFFECTING QUALITY

HOMOGENEITY – Homogeneity is the state of being all of one kind.

The manufacturing process for creams involves two separate phases: an oil phase and a water phase. The degree to which these two phases are properly treated is the key element of quality semi-solid manufacturing.

For manufacturing semi-solids, homogeneity refers to the proportionate distribution of ingredients. Unlike liquid medications, proper homogeneity must exist within the large vessels used in the manufacturing

process as well as within each individual tube and jar of product marked for commercial sale. The distribution of API and other ingredients must be uniform in all container closure systems. For example, the same proportional distribution of medication must exist in a 2,000 gallon tank and also within a 1.75 ounce tube.

A faulty homogenization process may result in significant deficiencies in semi-solid quality. Poor homogenization may create lumpiness or globules due to insufficient or incomplete mixing of oil and water phases. This reduces the patient experience with the product and can create significant challenges during product application. Finally, irregular amounts of the API will be distributed on affected areas producing less than optimal effectiveness.

Another significant problem area that occurs in the manufacturing process is flow restriction where material gathers together in a vessel and resists homogenization. This can be eliminated with proper equipment when correctly used.

Proper homogeneity produces even distribution of medication in ointments, gels and creams.

PARTICLE DISTRIBUTION – Proper distribution of molecules affects formulations in which material is not soluble including ointments and pastes.

Particle size, distribution and shape are important properties of the finished product and can significantly affect stability, appearance, usability and performance.

The need to consistently recreate uniform particle sizing techniques is growing to meet demand for newly developed active pharmaceutical ingredients with poor aqueous solubility well-suited for semi-solid dosage forms.

SPREADABILITY – The degree of spreadability is an important factor in determining therapeutic value of a semi-solid drug product. Spreadability for semi-solid dosage forms describes the action of a product as it is applied to the skin or other surfaces.

Product spreadability determines the proper distribution of the drug on the target area, plays a role in creating a positive patient experience with the product and affects how the product is removed from the primary package.

Factors known to determine desirable spreadability are temperature, particle distribution and rate of flow from the primary package.

When felt in hand, a quality spreadable product should have sufficient viscosity while enabling optimal spreadability. For example, a semi-solid product with the consistency of honey has viscosity however spreads too rapidly, producing undesirable dripping upon application. Similarly, wax when heated or cooled shows poor viscosity and produces optimal spreadability only under specific conditions.

A product with poor spreadability fails to provide proper distribution of active pharmaceutical ingredients and produces a negative patient reaction and has a high degree of application difficulty.

GRITTIENESS – Grittiness is defined as having the characteristics of sand and is generally avoided in quality semi-solid manufacturing.

The potential for irritation of the affected area increases with particle size. As grittiness is directly related to particle size and shape, semi-solid products manufactured with high quality standards show little to no gritty appearance or texture.

SURFACTANTS – Integral to the formulation of quality semi-solid pharmaceutical drug products are inactive ingredients called surfactants that facilitate the combination of aqueous and oil phases during the manufacturing process for creams or wetting of particles in gels or ointments.

During manufacturing, procedures are followed to avoid bleeding, separation and other phase changes that negatively affect the finished product.

Surfactants are an important factor for the production of stable semi solid dosage forms.

The amount of surfactant in every formulation affects many key quality factors including surface tension, the ability of water to penetrate the oil barrier, removal of contaminants (detergency) and conductivity.

When surfactants are not properly and carefully utilized, the entire manufacturing process is compromised. When the two miscible oil and water phases are improperly treated, visible characteristics of the product suffer, the breakdown of separate ingredients takes place and effectiveness and performance suffer.

MANUFACTURING PROCESSES AFFECTING QUALITY



Proper temperature monitoring at every stage helps assure quality semi-solid product results. Photo credit: WDPPrx

In real estate the key is location, location, location. In quality manufacturing of semi-solid products, the key is temperature, temperature, temperature.

The essence of quality semi-solid manufacturing is the proper treatment of oil and water phases to optimize effectiveness and produce desired physical qualities of homogeneity, particle distribution and spreadability.

Proper temperature monitoring helps assure successful results for production of creams, ointments and gels. Grittiness and poor spreadability are two symptoms of poor temperature regulation in low quality products.

Creams – During the manufacturing process for most creams, for example, all oil phases and water phases are weighed before surfactants are added to the water phase. Temperature is generally raised to 70 degrees Celsius separately for each phase. When the correct temperature is reached, the phases are mixed together and the process of harmonization begins.

Ingredients are broken down during homogenization. In water-in-oil formulations, water is broken down and oil is broken down in oil-in-water formulations until an emulsion is formed.

Gels – Temperature is equally important for proper manufacture of gels. Hand soaps and other cold method gel formulations involve cooling water to a range of four degrees to ten degrees Celsius before adding to the mixing container. Gelling agent is added at the aqueous phase to increase viscosity and improve stability before medication is introduced. If the gelling agent mixes improperly with the dispersing medium, clumping

may occur. During the 24-48 hour swelling period, the liquid permeates the gel and volume increases. Then, entrapped air is removed as needed by mixing and other techniques before the product is cooled.

Ointments – Ointments are translucent, viscous preparations formulated for topical or transdermal application. Common formulations involve bases of petrolatum and mineral oil. Ointments perform specialized functions because they act as the carrier of the medication and also control the rate of absorption upon application.

Temperature again figures prominently in the manufacture of quality ointments. Constant monitoring is required to regulate temperature of each ingredient. An ointment formulation with an oleaginous base containing four ingredients, for example, involves first heating to the highest melting point of all ingredients and then cooling as other elements are added to the mixture.

A process including four ingredients with melting points of 70 degrees Celsius, 40 degrees Celsius, 30 degrees Celsius and 80 degrees Celsius would begin by setting the highest melting point temperature. When added, the mixture is cooled to 70 degrees Celsius, when the ingredient with the next highest melting point temperature is introduced. The cooling process continues with additional stages added at 40 degrees and 30 degrees Celsius. Subsequent ingredients are then added and the product is cooled to room temperature.

Failure to adhere to quality manufacturing procedures for ointments will result in decomposition of raw materials and adverse patient experience.

EQUIPMENT



Bulk homogeneity for semi-solid ingredients is achieved with correct and appropriate

use of tanks, agitators, scraper blades and other manufacturing equipment. Photo credit: WDPrx

Proper equipment is equally important as correct formulation in the manufacture of quality semi-solid pharmaceutical drug products.

Mixers, emulsifiers, jackets, tanks, agitators, mills and other equipment are integral to the manufacturing process and must function at high efficiency for desired results.

Tanks are the standard receptacles for storing and processing semi-solids. They must meet or exceed certification requirements of ASME and USDA. They may have pitched, dish or cone bottoms and come in a variety of capacities from 25 gallons to 2,000 gallons and greater.

Heating and cooling jackets are designed to provide temperature regulation with extreme responsiveness and exacting precision. When performing effectively, open, dimple and coil style jackets reduce batch processing time, increase production capacity and eliminate temperature variances.

Agitators, mixers, dispersers, mills and emulsifiers mix, blend, dissolve, disperse and emulsify ingredients across a range of viscosities. High quality equipment is made with heavy-duty gearboxes for durability and may also have variable-speed capabilities. Agitators may be fitted with bars and scrapers that work to increase product uniformity. For example, scraper blades contact the walls of the tank for enhanced mixing, especially useful for higher viscosities up to and beyond 2,000,000 cps found in certain cream formulations.

Sigma blade mixers or shearers create minimum dead space during mixing and are particularly suited for

wet granulation processes. Homogenizers force mixes through small ports at high pressure, reducing particle sizes to meet product specifications.

When these sophisticated machines complete their work, the mixture should achieve 'bulk homogeneity,' with uniform distribution of ingredients throughout the tank.

TESTING



Microbiological testing performed with physical and chemical tests prevent unfavorable results during the manufacturing process. Photo credit: WDPPrx

Monitoring the quality of drug products requires physical, microbiological and chemical testing throughout development and manufacturing.

Specific testing of semi-solid formulations maintains quality control and prevents unfavorable results.

Physical tests determine visual and chemical separation, color change, pH, crystallization and any degradation of appearance, viscosity or spreadability.

One of the key chemical tests determining high quality semi-solid products measures the degree that ingredients are uniformly distributed in the product. Assays for potency are conducted during bulk manufacture within mixing tanks and also throughout the packaging run within tubes and jars. Additional analytical tests are conducted during the manufacturing process to monitor for product degradation and any impurities.

Microbiological stability is assured by testing for microbial limits and preservative effectiveness.

PACKAGING AND STORAGE



Store products in a controlled area that avoids variances in temperature, humidity and light. Photo credit: WDPPrx

The complexities involved in producing quality semi-solid pharmaceutical products require that attention be paid to packaging and storage procedures to maintain effectiveness.

It is normal practice to store the product until all quality control tests are completed before packaging. Storage location should avoid variations in light and temperature that may negatively affect product integrity.

The storage container must be checked for any indication of peeling and leakage, penetration, adherence and deformation.

Active ingredients may react with improper packaging. Vigilance is required to monitor migration and color change of ingredients as these are indications of product instability.

QUALITY PEOPLE MAKE QUALITY PRODUCTS



Highly trained scientists, technicians, project managers and other administrators focus on quality in processes and procedures that save time and avoid additional cost. Photo credit: WDPrx

The quality manufacturing of semi-solid dosage forms relies on a continuum of factors occurring consecutively, continuously and simultaneously to produce successful results.

The variety of dosage forms including ointments, gels, creams and pastes employ different production techniques but all rely on the correct functioning of human and machine elements from formulation, manufacturing and production to testing, storage, packaging and fulfillment.

With production lines becoming increasingly automated, the need is more acute than ever before for experienced technicians to guide semi-solid products along the path from development to commercial sale.

FUTURE OF SEMI-SOLID DOSAGE FORM

Personalized medicine is spurring interest in patient-centric treatment modalities. Oral solid dosage manufacturing is being transformed by 3-D printing technology that enables customized dosing. Similarly, semi-solids provide an ideal delivery method for customized doses of medications created on a patient-by-patient basis.

Different quantities of active ingredients incorporated into semi-solid dosage forms can be precisely delivered to specific patients for maximum effectiveness.

Growing interest in semi-solid products is based partly on the convergence of personalized medicine and specialty pharma distribution that are poised to become an ever-larger percentage of total volume of medications available on the market.

Another factor heightening interest in semi-solid dosage forms is the quantity of new active pharmaceutical ingredients (API) lacking aqueous solubility. Developments in various dispersion techniques are producing positive results that in certain cases may be incorporated into semi-solid products.

As their popularity grows, manufacturers of quality semi-solid medications must continue to maintain patient trust to assure their continued adoption in the market for the benefit of patients.

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About WDPrx – Woodfield Pharmaceutical, LLC

WDPrx – Woodfield Pharmaceutical, LLC is a proven and reliable CMO partner specializing in oral solutions, liquid solutions, suspensions and semi-solids. Our established record of commercialization success spans more than 30 years in continual operation built upon a strong foundation of financial strength and stability.

Our experienced team provides end-to-end pharmaceutical outsourcing services from Research and Development, Commercial Manufacturing, Regulatory Support, Primary and Secondary Packaging and Labeling.

The modern facility in Houston, TX is DSCSA compliant and Serialization-ready. WDPrx is cGMP compliant and utilizes advanced technology to support full Technology Transfer and System Integration for minimal production down-time. "Crafting Contract Manufacturing Solutions" is the WDPrx mission. We value our reputation earned over time as creative problem-solving specialists with flexible capabilities committed to

client communication and success.

WDPx extends client capabilities, efficiency and reach from development through production with the highest levels of quality pharmaceutical manufacturing.