Topical products

Aim for quality, simplicity, and cost-efficiency in the development, scale-up, and manufacturing of semi-solid dosage forms

Michael Legendre
Solids Manufacturing Operator

Topical products, whether prescription dermatological drugs or over-the-counter lotions, creams, or gels, present unique challenges in terms of development and manufacturing. The inherent complexity of semi-solid dosage forms derives from their composition – a mixture of an oil and a water phase in varying ratios, plus an active pharmaceutical ingredient (API) and a host of other ingredients that may include thickening/gelling agents, emulsifiers, preservatives, antioxidants, and solvents. Additional properties of topical products also make them especially challenging to formulate and manufacture consistently. These include their mechanism of action and sensory characteristics. Mechanism of action refers to whether they are intended to act at the skin surface or to penetrate the skin layers and to what extent. The ease of application, texture, and sensory properties of topical products – how they feel, look, and smell, at first use and over time – are difficult to replicate from batch to batch. When faced with the many challenges of producing a safe, cost-effective, high-quality topical product, many companies will seek the expertise and experience of a CDMO partner.

Introduction

Formulation and manufacturing of prescription dermatological and OTC topical products is a highly specialized area. Formulating products that have the proper composition, viscosity, texture, and stability, and can also be shown to be safe and effective, is both a science and an art. It requires having access to proper techniques and skill sets, state-of-the-art equipment, process scientists and engineers who have a deep understanding of Quality by Design (QbD) principles, and methods for product and process characterization. Expertise in analytical testing, validation, and quality control are also essential. The preparation of a semi-solid dosage form – from formulation and development, to scale-up, commercial manufacturing, and packaging – should ideally take place under one roof in a contiguous, end-to-end workflow to avoid unnecessary equipment and process changes. Without proper precautions, knowledge gaps can occur and important details may be overlooked when a product is transferred from one site to another.

Our drug product manufacturing and packaging capabilities cover a range of specialist dosage forms.

About Cambrex

Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance, drug product, and analytical services across the entire drug lifecycle.

With over 40 years of experience and a growing team of over 2,200 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and finished dosage form development and manufacturing.

Simplicity matters

Cambrex is an experienced provider of development and manufacturing services for producing a range of semi-solid dosage forms, including creams, ointments, lotions, and gels. Experience matters when you are choosing a CDMO partner. Cambrex offers the full range of capabilities and services needed to create a topical formulation and produce it at large scale for the global market, as proven by our commercial successes.

It is important for a CDMO to understand the market it serves and, in the dermatologic arena, that means the demand for topical agents across a broad array of indications, including dermatitis, eczema, pain relief, psoriasis, antimicrobial/anti-infective, diabetic ulcers, and acne. Staying up-to-date on the latest science and emerging technology is also essential. Knowledge matters, and Cambrex knows how to develop high-quality, high-performance semi-solid dosage forms ranging in cGMP batch sizes from 10kg to 900kg, and how to package the bulk formula into tubes or jars of various sizes.

Above all else, when it comes to developing and delivering a safe and effective product cost efficiently and on time, simplicity matters. At Cambrex, quality comes first, and the same expectations for quality apply equally to prescription and OTC topical products. Cambrex's one-stop-shop approach ensures that all aspects of product formulation, analysis, and manufacturing can be performed on-site, by our trained scientists and engineers, using the same advanced equipment and validated methods. This applies to new products and tech transfers, thereby avoiding the problems that can arise when existing methods and processes are transferred to a new site. Cambrex provides end-to-end formulation and manufacturing at our Mirabel facility (Québec, Canada) with production of sterile ointments carried out at our Whippany site (NJ, US).

> Cambrex brings experience, knowledge, and simplicity to the complex task of developing and manufacturing semi-solid dosage forms at commercial scale.

Optimizing development and scale-up

When initiating the development of a prescription dermatological product, topping the to-do list is selection of the formulation. Topical formulations can be categorized according to their skin feel and viscosity. Ointments and lotions have a richer feel than do lighter creams and gels, whereas ointments and creams have a higher viscosity than lotions. Choosing between an ointment, gel, or cream will depend on multiple factors, including the following: the indication, the area to be treated, how the drug will be applied, physicochemical properties of the API, whether the API acts on the skin surface or must be absorbed into the skin, potential incompatibility issues between ingredients, and stability factors.

Physicochemical properties

The texture and quality of any topical formulation is critical. The main targeted attributes are a non-gritty texture, smooth to the touch, pleasant smelling, non-irritating, and easy to apply. To achieve these properties, development work should focus on optimizing five key physical characteristics of the product formulation:

- Homogeneity
- Particle distribution
- Grittiness
- Spreadability (ease of application vs. tendency to drip)
- Need for surfactants

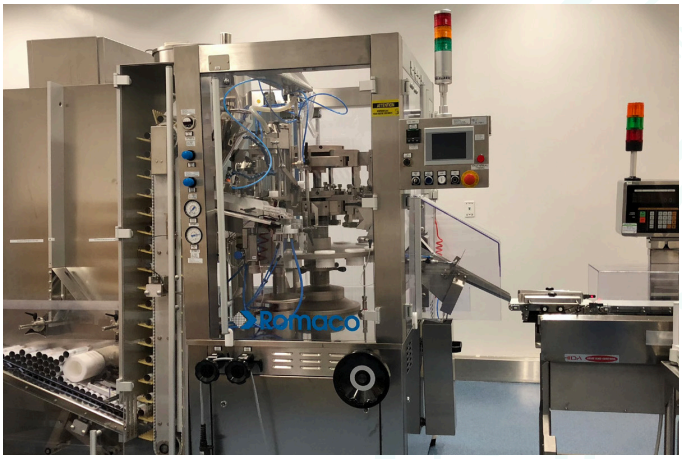
Proper equipment is essential. This includes mixers, emulsifiers, mills, and agitators. Temperature control, and specifically the cooling rate during mixing of the oil and water phases, is crucial. Process design studies will identify the ideal temperature ranges for each process step, and precise monitoring will ensure that temperatures remain in the sweet spot needed for adequate mixing at each time point. Heated and cooled jacketed mixing tanks are required to provide precision temperature control. Appropriate mixing and temperature-control technology is also important during the addition of gelling agents and APIs to ensure proper particle distribution and to maintain the stability and uniformity of the formulation. The extensive range of mixing equipment, temperature-controlled tanks, and filtration vessels available in Cambrex's development and manufacturing suites allows for experimentation and optimization of process design and scale-up through to cGMP commercial production.

Rigorous process design and analytical testing are needed to optimize and maintain product characteristics and process parameters.

To ensure that semi-solid dosage forms remain stable and maintain the desired physicochemical characteristics over time, testing must be performed to assess for separation of the oil and water phases, color or pH changes, crystallization, changes in particle distribution, and product degradation. Cambrex offers a full range of chemical testing needed to characterize and monitor the properties of products in development. These include the tests listed in Table 1.

Table 1. Chemical and biological testing of semi-solid dosage forms

Description/purpose	Strategy
Color	Visual inspection
Crystal growth	
Phase separation	
API	Measure concentration and homogeneity of API in the product
Bioassays	Determine concentration or potency of an API, usually of a biologically active substance (e.g., an antibiotic) in a cream or ointment
Alcohol	Measure concentration of alcohol in a lotion
Degradation products	Measure stability of the formula
pH	Measure stability of the formula
Preservative	Measure concentration of preservative in the product
Microbial limits	Measure presence of total aerobic microbes, yeasts, and molds
Antimicrobial Effectiveness Testing (AET)	Measure the activity of the preservative system



In vitro release testing to demonstrate bioequivalence

The Scale-Up and Post Approval Change Semi-Solids (SUPAC-SS) Working Group of the US Food and Drug Administration has issued recommendations related to changes in components and composition and in vitro release testing (IVRT) for bioequivalence to support any modifications in formulation, manufacturing (processes and equipment), scale-up/scale-down of production, and/or the site of manufacture of a nonsterile prescription semi-solid topical preparation (www.fda.gov/cder/guidance.htm).

Cambrex can support Q1-3 testing as follows:

- **Q1** = products have the same components
- **Q2** = products have the same components in the same concentrations
- **Q3** = products have the same components in the same concentrations with the same arrangement of matter (microstructure) and the same permeability rate

IVRT is intended to mimic what would happen when a topical formulation is applied to human skin, as a means of assessing skin penetration. "Important changes in the characteristics of a drug product formula or the thermodynamic properties of the drug(s) it contains should show up as a difference in drug release," according to the SUPAC-SS guidance. "In vitro release method for topical dosage forms is based on an open chamber diffusion cell system such as a Franz cell system, fitted usually with a synthetic membrane. The test product is placed on the upper side of the membrane in the open donor chamber of the diffusion cell and a sampling fluid is placed on the other side of the membrane in a receptor cell. Diffusion of drug from the topical product to and across the membrane is monitored by assay of sequentially collected samples of the receptor fluid."

Cambrex performs validated IVRT on product development batches. We also offer a range of bioassays to demonstrate product potency when applicable.

Bioburden and microbial testing

Products must also be tested for bioburden to demonstrate that they do not harbor microbial contaminants. Cambrex's microbiology laboratory has the capability to perform all necessary microbial testing. Depending on the product, the range of tests may include the following:

- **Microbial limits testing** – to determine whether a product complies with compendial specifications; targets specific objectionable organisms and assesses their presence or absence in a product
- **Microbial enumeration** – quantifies the total number of aerobic organisms and determines a total combined yeast and mold count

- **Microbial bioassay** – measures the potency of a biological active substance (e.g., an antibiotic)
- **Bioburden testing** – measures the population of viable microorganisms in a product
- **Preservative efficacy testing/Antimicrobial Effectiveness Test (AET)** – assesses the effectiveness of the antimicrobial preservatives added to the formula

Simplifying technology and site transfer

Tech transfer presents particular challenges when it comes to producing semi-solid dosage forms because of the difficulty in achieving the exact same texture, viscosity, and homogeneity of a product when changing even a single method or piece of equipment in the production process. Site transfer requires a company to go back to the very early stages of product formulation and development, including sourcing and analysis of raw materials, characterization of critical product attributes, and defining the process design space. Even the smallest details can have a big impact on the end result, especially when it comes to the sensory characteristics and the bioequivalence of a topical product. Table 2 presents several of the technical challenges related to the site transfer of a sterile topical jelly for production at Cambrex and the creative solutions introduced at our Whippany facility.

Table 2. Technical challenges in site transfer of a topical jelly

Technical challenge	Innovative solution
Optimal concentration of gelling agent	Conducted multiple experiments to identify concentration of gelling agent needed to match the viscosity of the RLD
Solubility of gelling agent	Experimented with different temperatures for the addition of gelling agent. Decided to add at higher temperature (80-90°C)
Solubility of preservative in API	Evaluated effects of different temperatures on preservative solubility. Higher temperature (80-90°C) shown to be optimal
Degradation of API at higher temperature	Temperature of solution lowered to 65°C before addition of API
Temperature during sterile filtration (to prevent absorption of preservative onto filter at lower temperatures)	Used jacketed filtration unit at 65°C
Final mixing of gelling solution and API/preservative solution	Conducted several experiments to determine best mixing speed and time to achieve a uniform semi-solid formulation

Conclusions

The complexities and risks associated with the development and manufacturing of semi-solid dosage forms, whether prescription dermatological drugs or OTC topical products, can be managed with the knowledge, experience, and support of a full-service CDMO partner. Cambrex has proven expertise in manufacturing a broad range of formulation types at scales ranging from 10kg to 900kg. With commercial semi-solid products on the market, Cambrex offers its customers the technical capabilities, expert people, and advanced technology needed for the seamless transition of a topical product from development to clinical material to large-scale commercial supply. Simplicity matters when it comes to early-stage product formulation; high-quality, consistent, and cost-efficient scale-up, manufacturing, and packaging, and comprehensive analytical testing and quality control. Cambrex's one-stop-shop makes it possible to develop and manufacture prescription and OTC products, whether sterile or non-sterile, in one location in a streamlined, cost-efficient workflow. This increases confidence, reduces the risk of uncertain outcomes that can result from changing equipment and processes, and may even accelerate the path to regulatory approval.