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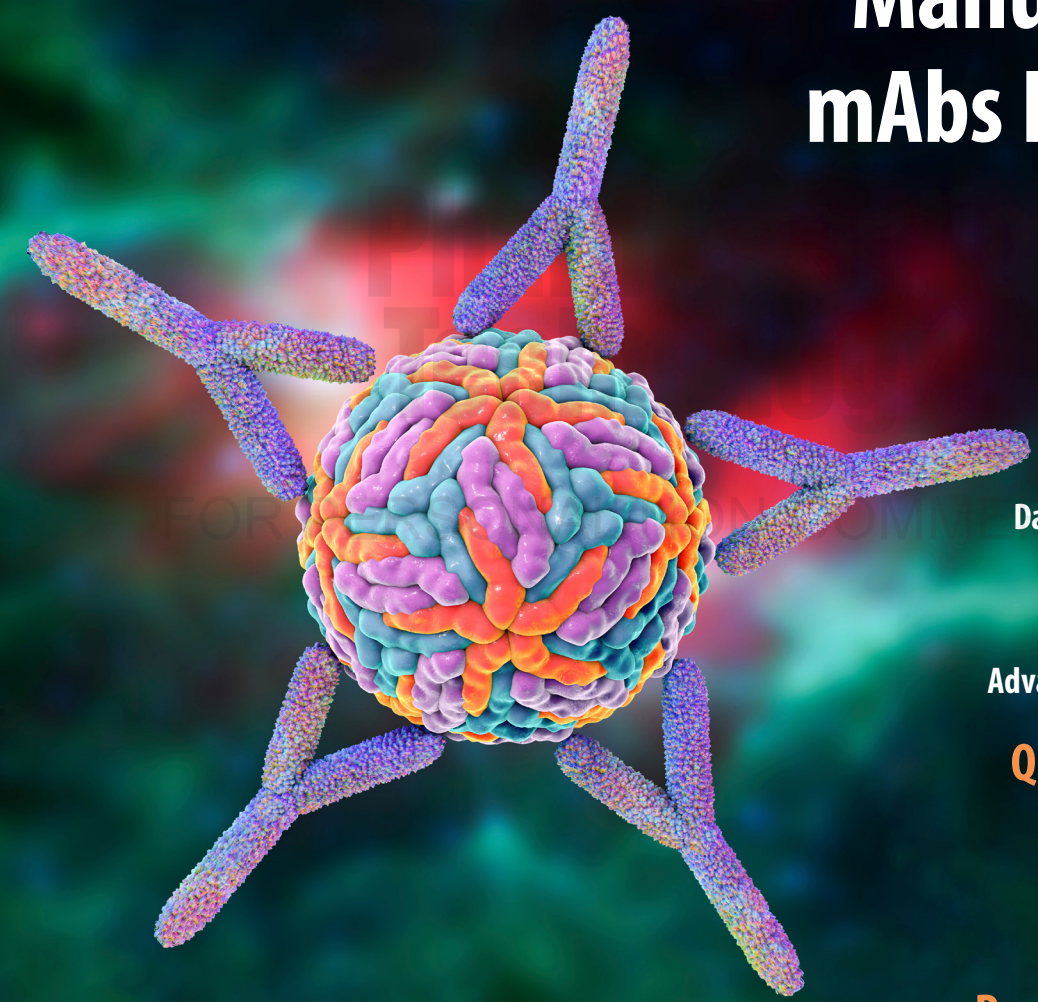

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Topical Formulations in Pharma–Balancing Form and Function

Suzanne Shelley

Ongoing advances in technology and modeling techniques are helping to align all the objectives of both drug manufacturers and patients.

Where applicable, therapy options that are available in a topical format are often preferable for patients, compared to alternatives that may involve injection or oral dosing (especially as oral alternatives often involve higher doses, because the drug must first be metabolized by the liver). This preference is an attributable factor to the growth in the topical pharmaceuticals market, which is projected to reach US$150 billion by 2028, expanding at a compounded annual growth rate of 6.4% between 2021 and 2028, according to market research (1).

When it comes to manufacturing successful topical formulations, a lot of pressure rests on the shoulders of the drug developer and its contract manufacturing partners. Fundamentally, two things are required for developing any successful topical drug—establishing the optimal formulation and then developing a robust and reliable manufacturing, monitoring, and quality control process.

Semi-solid topical therapies (e.g., creams, ointments, lotions, hydrogels, and foams) must deliver the required clinical attributes while providing the desired mix of physical properties that will make the product appealing to the patient. Otherwise, product uptake will be hindered. For instance, patients managing acne may reject creams or lotions that feel greasy or clog the pores, while those being treated for eczema are more likely to abandon a medication that irritates the skin. Other patients may avoid their disease-specific creams, lotions, or gels—whether they are prescribed or over-the-counter (OTC) products—because they feel sticky, have an unpleasant odor, or stain their clothing. When patients reject specific topical therapies, it creates both clinical and commercial implications—undermining adherence to therapy (and hence, reducing desired clinical outcomes) and undercutting revenue and market share for brand teams.

"Human skin is a complex organ, and each of the distinct layers (epidermis, dermis, and hypodermis) differ in functionality, so formulating the right dosage form that can produce the required therapeutic effect can be challenging," notes Chetan Chure, senior manager, Formulation Development at CPL, a contract development and manufacturing organization (CDMO) based in Mississauga, Ontario. Once the optimal blend of excipients and APIs has been identified, all steps in the manufacturing process—from mixing of ingredients to blending in APIs and excipients to homogenization/emulsion to heating, cooling, and filling packaging and more—and related monitoring systems must be designed and operated.

Managing manufacturing challenges

"The number of excipients required by a topical formulation can be significantly higher compared to a solid oral dose or injectable, thereby compounding the opportunities to create potential incompatibilities between excipients, API, packaging, and the manufacturing process," says Lynn Allen, vice president of Business Development for MedPharm, a CDMO. "Changing anything from the grade of excipient to a process parameter during manufacturing can significantly impact the stability and performance of the product." Once the target formulation has been identified, a reproducible and replicable manufacturing process must be established to ensure that the desired API payload will be delivered with every dose.

Today, a broad range of excipients are available to help manufacturers achieve desired therapeutic outcomes and improve the quality and shelf life of the product, noted Daryl Bassett, product owner, Bora Pharmaceutical CDMO, in a published article (2). These excipients include:

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- Polymers to control viscosity; these may be fermented (such as Xanthan gum) or synthetic (such as hydroxypropyl methylcellulose or hydroxypropyl cellulose).
- Surface active agents, to help solubilize APIs in the formulation.
- Preservatives to extend shelf life and control microbiological activity.
- Penetration enhancers to promote absorption.

Competing kettle designs create varying heat-distribution profiles.

"If an excipient requires more steps to process (adding to timelines) or requires extra inputs of solvents, energy, or control (thereby adding to cost and complexity), those aspects must be factored in accordingly," Bassett said (2). The addition of different excipients often requires manufacturing tradeoffs related to stirring rates, process temperatures, or the need for solvents or surface-active agents to enhance dissolution in the product. "To overcome these challenges, a disciplined analytical approach is required to obtain the economies of scale and quality control needed to keep product prices competitive and affordable," he added (2).

"Improper design, lack of knowledge, and inadequate observation of the process can lead to critical failures," notes Chure. "Each step of the process is directly linked to the important physical and chemical quality parameters of the drug product, impacting appearance, pH, viscosity, specific gravity, rheology, drug content, preservative level, and degradation." Taking the time to develop a complete understanding of the CMA for each of the ingredients in a given topical product will help to inform equipment selection—which is particularly important during scaleup efforts.

For example, competing kettle designs (such as cylindrical, conical, and hemispherical options, and jacketed versus non-jacketed designs) create varying heat-distribution profiles, which then impact other key process parameters and the quality of the final product. Similarly, Chure notes that the type of heat source available for heating the kettle should also be critically evaluated, because slow versus fast heating can have a dramatic impact on the quality of the final drug product. Factors such as whether ingredients are added from the top or bottom of the kettle, whether manual transfer or vacuum transfer is used, and how fast the various phases are added can impact the formation of the product's appearance, microstructure, rheology, viscosity, bulk homogeneity, specific gravity, and mixing efficiency, therefore careful evaluation is imperative to choose the correct process design, he adds.

"Taking the time to methodically work through all aspects of process development and scale-up can ultimately speed up the time to commercialization. This includes using a design of experiment (DoE) methodology to understand the impact of time, temperature, mixing speeds, homogenization, hold times, and more," says Allen. "Stakeholders should also study all off-specification results. Problems not addressed and resolved early on are much more costly to rectify during the full-scale manufacturing stage."

Ultimately, the final manufacturing process design should be established by using a quality-by-design (QbD) approach whereby the DoE is conducted to establish the ranges of the process parameters, notes Chure, who adds: "Establishing critical ranges for key processing parameters—including temperature of the phases, mixing speed and time, homogenization speed and time, cooling rate, recirculation cycles, and batch turnovers—will ensure the product meets the final product quality requirements."

During validation efforts, routine in-process sampling should also be performed to identify and correct any issues related to equipment operation. "Similarly, bulk uniformity samples that are collected in a statistically sound way can help to both verify uniformity and homogeneity and inform continuous-improvement efforts," notes Chure.

Selecting the most appropriate packaging option for today's topical formulation route brings its own challenges.

"Unfortunately, we often find that drug developers have not performed initial pre-formulation, formulation-development, and process-development steps to gain a fundamental understanding of the drug and identify the optimal formulation as it passes through the initial phases of product development," notes Allen. "Such early risk-mitigation work is critical to support troubleshooting efforts if or when an issue arises unexpectedly—for example, if the manufacturing process results in out-of-specification product or a change in performance."

Meanwhile, in recent years, manufacturers of topical pharma products have been impacted by the same persistent supply chain challenges that have been shaping the landscape across many industry sectors. "We've seen supply interruptions related to APIs, excipients, and packaging supplies, with availability issues arising from pandemic staffing shortages to pinch points in upstream suppliers and transportation issues," says Allen. "As a result, it's more important than ever for CDMOs to establish strong, collaborative relationships with all of their suppliers, and to establish transparent lines of communication and improved supply stability protocols to help navigate these very unpredictable times," she adds.

Scaleup invites its own issues

The ability to translate successes developed at process-development scale to full-scale operation, and to move to new equipment trains from different vendor during scaleup is another challenge today's CDMOs must manage. "It's important to take the time to fully understand how the DoE process translates to new vessel sizes and mixing parameters," says Allen. "Stakeholders should work closely with their equipment vendors, as they can facilitate the translation of critical process parameters from one type of vessel to another."

"Online monitoring of globule size and particle size has allowed for deeper understanding of the impact of changes in process parameters to product quality and thereby allow for process designs that are more robust and repeatable," adds Chure. Investment in ongoing upgrades is increasingly important as more drug manufacturers incorporate innovations—such as microspheres, nanospheres, nano-emulsions, emulgels, and other specialized transdermal delivery systems such as liposomes and ethosomes—into their topical formulations.

Packaging and shelf-life considerations

Selecting the most appropriate packaging option for today's topical formulation route brings its own challenges. The goal is to balance the need for proper dose dispensing or metering while safeguarding the product against degradation from exposure to light or oxygen.

Meanwhile, packaging decisions must also balance other considerations, such as ensuring a patient-friendly ergonomic design, the need for child-proof and/or senior-friendly designs and enable reliable dosing. "Such specialized systems, while useful, can be challenging to integrate into standard packaging lines and require experienced engineers to develop processes and retrofitted filling systems to execute successful scale up. [Therefore,] that must be taken into consideration as early as possible in the planning process," notes Allen.

As drug manufacturers work to ensure that topical pharma products retain their quality and performance over their intended shelf life, many are increasingly using *in vitro* release testing (IVRT). This quality test can be described as a topical dissolution assay where the release rate of the API is compared to a reference product, says Allen. She notes that MedPharm is also developing a number of models and systems to evaluate both marketed and topical products under development.

Recent investment and expansions

Thanks to strong growth in the development of, and demand for, topical formulations in pharma, many CDMOs are in expansion mode. Several recently announced investments or expansions include:

- MedPharm opened a new location in Raleigh-Durham, NC, to expand its capabilities in topical and transdermal delivery. The new facility will double the company's existing footprint and will support process development and clinical and small-scale commercial manufacturing for semi-solid and liquid pharmaceutical products (3).
- In January 2022, Cambrex celebrated its 40th anniversary by announcing $100 million of investments to expand capacity and modernize its global manufacturingcapabilities (4). In March 2022, the company announced that it was significantly expanding its biopharmaceutical testing services business, adding 11 additional current good manufacturing practice (CGMP) laboratories at its Durham, NC, facility and broadening its service offering for large molecule and viral/cell-based therapeutics (5).
- In January 2022, Recro Pharma (which changed its name to Societal CDMO in March 2022) was awarded a multi-year, $1.5-million contract from the US government. The company will formulate, manufacture, and supply a topical dermal drug containing a prespecified API, as well as a matching placebo, for a planned clinical study for the prevention of recurring basal cell carcinoma (6).
- Over the past four years, CPL has invested in new manufacturing and packaging equipment and built out new quality control lab space and equipment to support GMP product testing.

Conclusion

The development and production of consistent, reliable topical formulations presents a number of challenges. The pressure is on to ensure that products can perform as expected and have qualities that are acceptable to patients. By working closely with equipment vendors and CDMO partners to assess the impact on product components on process parameters and final product quality as early in the process, drug developers can shorten the timeline between development and commercialization, minimize wasted expenditures associated with off-spec products, troubleshooting and timeline delays, and improve the odds of commercial success.

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