

Formulation development of topical semisolids

The formulation development process characterizes the physiochemical characteristics which are unique to each molecule, such as solubility, stability and permeability. As for any drug that is nominated from discovery for further development, formulation development is a function of the physiochemical characteristics of the molecule of interest, as well as mode of administration, market demands, manufacturing process and product costs.



There are additional factors to consider for a topical formulation which add to the challenge of this task. The drug must penetrate the formidable barrier of the stratum corneum (and be delivered through this approximately pH 5 barrier) to either the epidermis or dermis. Additionally, the final product must be close to the skin pH of 5 to eliminate chances of irritation. The goal of formulation development is to achieve successful delivery of the drug in a product that is pleasant to use by the consumer. A product that is unpleasant to use may risk lowering patient compliance. This often, but not necessarily, drives a complex combination of excipients, each of which will be carefully and rationally selected based on expected improvements in the drug penetration or other performance criteria. Unless otherwise demanded by the formulation research and development, SPF will employ excipients that are generally regarded as safe (GRAS) and already reported for use in topical formulations in the FDA Inactive Ingredient Guide. Furthermore, all ingredients used meet the specification as reported in either USP and/or EP. Based upon years of experience in the topical development field, SPF has devised and tested a library of semi-solid formulation prototypes that is often employed in the development process.

The inclusion of possibly many excipients will place greater demands on the analytical methods, ensuring the appropriate analysis of API concentration and purity. An extraction method will be required for sample preparation and analysis. Following the development of suitable analytical methodology, formulation research and development can be executed and includes the following tasks:

- Excipient selection and screening via compatibility studies
- Compound stabilization
- Screening of various dosage form prototypes from the SPF library
- Short-term accelerated stability studies on prototypes
- Freeze-thaw and hot-cold cycle exposures
- Troubleshooting as needed: API degradation, phase separation, container-closure, etc.
- Optimization studies to justify formulation composition and process
- Real-time and accelerated stability studies of drug product and placebo
- Established specificity for assay of the drug in its formulation
- Stability-indicating analytical method that also analyzes degradants
- Characterization of degradants and degradation mechanism; may feed back into formulation development
- Validatable methods for late-stage clinical programs

Research on the target product profile will provide guidelines for the final product. Formulation development will provide data on which product strength, dosage form, physical properties, cosmetic properties, and shelf life will be based. SPF can also coordinate testing to evaluate release profile and penetration properties of prototype or final formulations. SPF can develop gels, creams, lotions, or ointments, and design experiments to achieve the target product strength and properties. Excipients will be selected based on experience obtained from the development of other topical formulations and generally include solvents and co-solvents (both hydrophilic and hydrophobic), buffers (if drug has ionizable group), surfactants, emulsifiers, antioxidants or preservatives.

The target product profile may change as data on solubility, stability and other parameters are collected. SPF will collaborate closely with the client to ensure that a successful target product profile remains within reach. The goals of the development program will include a formulation that:

- Achieves desired product strength and penetration
- Offers adequate shelf life
- Offers pleasant consumer experience
- Excipients are GRAS and convincing rationale for inclusion of each
- Robust formulation that can sustain minor changes in processing
- Scalable formulation amenable to packaging and production needs
- Will achieve regulatory compliance

Following development of the topical formulation, the SPF project manager (PM) will be very familiar with nuances of the drug product. The PM is then available to work with alliance and other development partners, to manage technology transfer processes for manufacturing, assist with scale-up troubleshooting, and management of clinical supply manufacturing. The continuity of personnel will save both time and money. Further, SPF can leverage its global presence to identify manufacturing capabilities world-wide that can offer a competitive combination of production cost savings without compromising regulatory requirements.

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