

FORMULATION DEVELOPMENT OF MODERN DERMATOLOGICALS

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INTRODUCTION

Historically, topical pharmaceuticals were developed by incorporating new drug compounds into off-the-shelf vehicles such as Eucerin[®] or Hydrophilic Petrolatum, USP.

In the last two decades, progress in pharmaceutical technology, dermatopharmacology and dermatotoxicology has radically changed the manner in which dermatologicals are formulated, developed and tested. Industry invests heavily in discovery programs to identify and isolate potential new topical drug therapies. As a consequence, dermatologicals must be formulated to optimize drug release and delivery to ensure a valid proof-of-principle clinical evaluation.

A new drug product must be shown to be both safe and effective. Input from research, development, clinical, marketing and regulatory affairs perspectives is

coalesced into specific performance criteria. This requires the multidisciplinary team to synthesize the stringent safety and efficacy requirements of FDA and the clinical needs and expectations of the clinician and the patient into a well-defined product profile.

Formulation and pre-clinical development of new dermatologicals consists of several distinct steps, all of which generate requisite data for the IND application.

APPROACH TO FORMULATION

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PREFORMULATION

First, the literature is reviewed for pertinent information regarding specific aspects of the project, e.g., drug substance, disease state, excipients, etc. Physicochemical characteristics of the drug substance such as pKa, solubility parameter, partition coefficient, mechanism of degradation and stability characteristics are reviewed. Preformulation studies include solubility determination in appropriate excipients. Preferably all the excipients should be listed in the USP or NF, or have a history of use on the skin. Compatibility studies are performed to assess drug substance stability in the presence of

potential excipients. The preformulation results provide an important database for rational formula design.

FORMULATION DEVELOPMENT

Formulation development is intertwined with concurrent evaluations. The modern formulator uses a multifactorial approach to formula design to create high-performance, “designer” vehicles.

Typical product performance objectives:

- Drug delivery to target skin layer is optimized
- Topical dosage form is compatible with the target disease
- Excipients are not sensitizers and have low irritation potential
- Formulation is cosmetically elegant and user-friendly
- Formulation is physically stable
- Active ingredients is chemically stable in the vehicle
- Formulation can be scaled-up and produced commercially

Prototype formulae are designed theoretically to meet objectives, and then they are evaluated and reformulated as required. As data are generated during the evaluations, promising formulae are improved and retested. Formulations and

improved formulations are evaluated in this development loop until a specific formula is selected.

EVALUATION

Evaluation of the prototype formulae is multifactorial. The evaluation matrix is determined by the specific product performance criteria. Testing generally includes:

- Vehicle release
- *In vitro* skin penetration
- Efficacy in animal models
- Vehicle irritation screening in humans
- Cosmetic acceptability
- Physical and chemical stability

DRUG DELIVERY

Drug release from vehicles is assessed using Franz cells with synthetic membranes and conventional analytical techniques such as HPLC.

In vitro skin permeation studies are essential to evaluate characteristics of drug penetration into and through the skin. Human cadaver skin, pig skin or rodent

skin is used in a Franz diffusion cell apparatus, typically using radiolabeled drug substance. These studies are used to compare the relative drug delivery efficiencies of prototype formulae. Formulations that provide superior drug delivery to the target skin layers are progressively improved by formula refinement.

SAFETY AND EFFICACY MODELS

Safety screening and efficacy studies in animal models can provide further insight in predicting comparative human safety and efficacy.

Although not available for disease states, animal pharmacology models can be a useful screening tool for comparing efficacy performance of various candidate formulae.

ACCEPTABILITY

Acceptability evaluation is an eclectic collection of pharmaceutical and cosmetic parameters. Pharmaceutical attributes may include:

- pH
- Appearance
- Container compatibility

- Viscosity

Cosmetic characteristics are very important in dermatologicals. The following area carefully rated:

- Odor
- Spreadability
- Skin feel
- Lubrication

STABILITY

Dermatologicals must be both physically and chemically stable. Physical stability is assessed by monitoring the product for such changes as color, odor, viscosity and consistency. Chemical stability is evaluated by a stability-indicating analytical method developed specifically for the drug substance in the formulation. Accelerated stability testing is used to predict long-term room temperature shelf life of the product by assaying samples stored at elevated temperature, e.g., 40°C and 30°C. Stability assessments begin when a formula is first made and continue until the formula is discarded. The stability testing becomes progressively more extensive as a formulation progresses to clinical trials and ultimately NDA submission. Stability data is used to establish expiration dating.

FORMULA SELECTION

The culmination of the multiple evaluations of various prototype and improved formulations is selection of an optimized vehicle for the particular new chemical entity. Typically a back-up formula is selected for insurance. The selection process involves a multidisciplinary project team.

MICROBIOLOGY

Once a formula is determined, it is necessary to select an antimicrobial preservative system to protect the product from microbial contamination during clinical use and commercial distribution. Dermatologicals challenge the formulator to select an effective preservative system while avoiding sensitizers, keeping preservative levels below the irritation threshold, preventing inactivation by excipients, and maintaining a stable formulation. The Antimicrobial Preservatives Effectiveness Test is used to demonstrate the ability of the preservative system in the formulation to reduce viable counts of added bacteria, yeasts and molds. *Candida albicans*, *Aspergillus niger*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* are the organisms tested according to the USP methods.

TOXICOLOGY

Safety evaluation of the product in animals must be completed before the IND can be submitted and the proof-of-principle clinical study can be initiated. The most common dermal toxicology tests include:

- Contact irritation
- Contact Allergy
- Phototoxicity
- Photoallergy

SUMMARY

The formulation and pre-clinical activities in the development of new dermatologic agents can take 6 to 18 months to complete. Timing varies with the complexities and complications of the project, e.g., solving a difficult stability problem. Good planning and scheduling of the various activities in a complementary sequence help minimize the time required. This involves an understanding of the multidisciplinary development process and use of project management techniques. Careful execution of all the steps in a specific and purposefully prepared development plan assure that a potential new dermatologic product has the greatest chance for success in clinical trials.

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