An Integrative Approach to Product Development — Topical Skin Preparation Formulation

Xiang Chen, Jin Wang, and Zhenrong Guo Email: paul.vanstralen@medicilon.com

Abstract

Skin topical medicine is a kind of preparation that can act as local or systemic treatment. The semi-solid topical preparation, which is a type of common preparation for skin medicine, is multiphase, thermodynamically unstable, and complex in composition. It is classified as a complex preparation and has applications in the field of innovative drugs, improved new drugs and generic drugs[1-3]. Medicilon offers a professional formulation technology platform, keeping up with the pace of innovation in drug research and development, and meeting the diverse requirements of our clients. Medicilon supported a number of innovative drugs to complete the R&D and receive approval for clinical use.

Background

The skin is the first line of physical defense in the human body. It is the largest organ of the human body and participates in various physiological functions. It consists of three easily distinguishable layers: the stratum corneum, the living epidermis and the dermis. Skin diseases are complex and diverse, causing various degrees of disease, and can put significant burden on patients through their entire life[1-3].

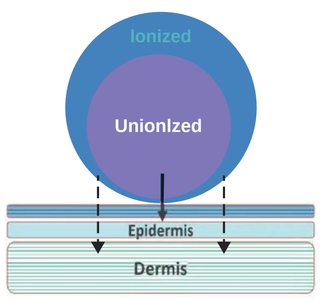
Topical Skin Preparations		
◆ Gel	◆ Ointment ・ Solution type ointment ・ Suspended ointment	◆ Cream ・ Oil-in-water cream ・ Water-in-oil cream

R&D Platform for Topical Skin Preparations

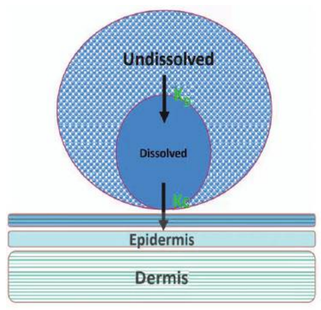
Medicilon's R&D Platform for Topical Skin Preparations can undertake the development of ointment, cream, gel and other semi-solid preparations. Medicilon has completed the R&D and filing of several topical preparation research projects for pharmaceutical companies and scientific research units.

Quality Study of Topical Preparations

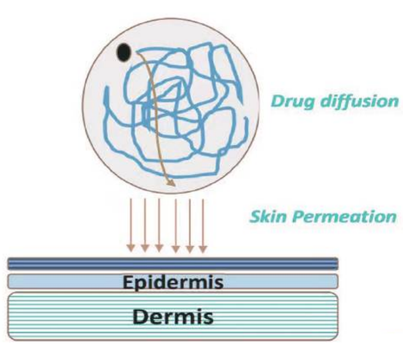
- ◆ Formulation pH
- ◆ Water Activity
- ◆ Ratio of Undissolved Drug/Dissolved Drug
- ◆ Rheological Properties
  - ・ Characterization of Shear Stress and Shear Rate
  - ・ Yield Stress Value
  - ・ Linear Viscoelastic Response
  - ・ Viscosity Curve
  - ・ Linear Viscoelastic Range
- ◆ *In Vitro* Release Test/*In Vitro* Permeation Test (IVRT/IVPT)
- ◆ Particle Size and Droplet Size Distribution Measurement
- ◆ Establishment of Microbiological Inspection Methods
  - ・ Establishment of Test Method for Burkholderia cepacia
- ◆ Establishment of Antibacterial Efficacy Method



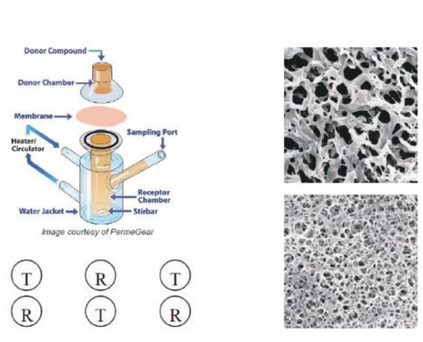
Schematic Diagram of Rheological Research in Semi-Solid Formulations



Schematic Diagram of Drug Absorption in Topical Formulations



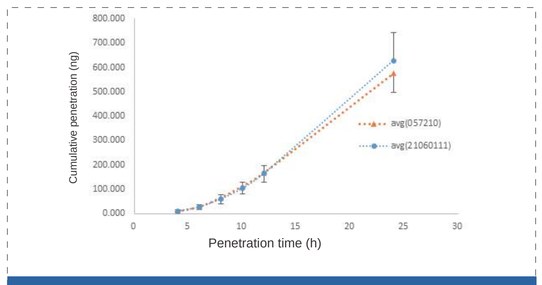
Schematic Diagram of Rheological Research in Semi-Solid Formulations



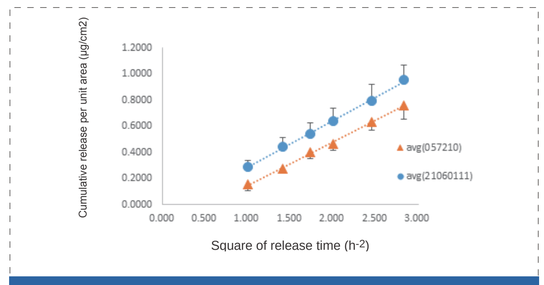
In vitro release and in vitro penetration tests - IVRT, IVPT

Case Study 1 – Ointment

Rx	◆ The excipient type and quantity (Q1 and Q2) of the generic drug is equivalent to the reference listed drug (RLD). ◆ Effects of excipient's quantity on permeation of skin were studied. ◆ Primary objective was to analyze excipient parameters such as viscosity, degree of polymerization, molecular distribution, etc, . ◆ Method was modified to prevent batch variation, nonuniformity and rheological properties change in the final product.
Process	◆ Preprocessing of raw materials, alternative method of addition, melting point, shear velocity, preparation temperature and time.



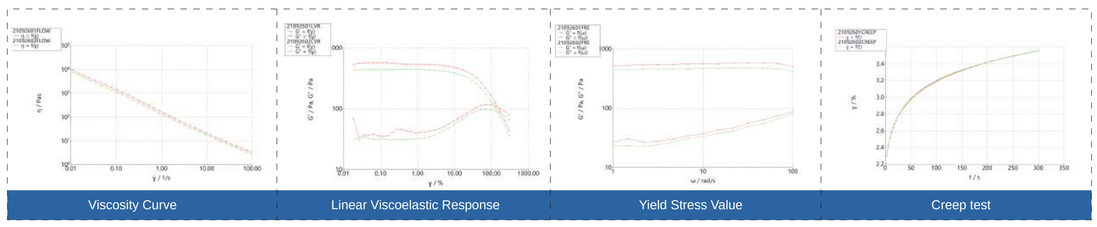
057210 Reference batches & 21060111 Medicilon batches
In vitro transdermal cumulative release (n=6)



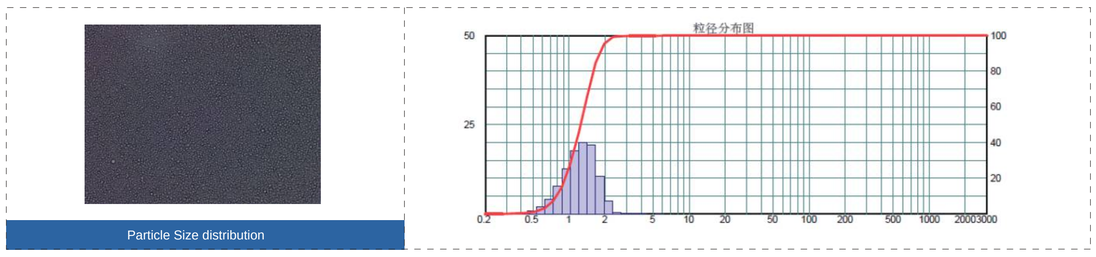
057210 Reference batch & 21060111 Medicilon batch
In vitro cumulative release profile

Case Study 2 – Compound tincture

Rx Background	◆ An improved new drug, category 2.3. ◆ A compound tincture with low API proportion and complex excipients . ◆ Antibacterial efficacy studies was conducted to select the proper bacteriostatic agents and quantity.
Process	◆ Method of addition of raw materials, the order of adding excipients, time and temperature for emulsification, shear velocity and time.
Packaging	◆ Comparison and selection of alternative packaging materials from validated vendors.
Analysis	◆ Sample preprocessing. ◆ Impurity profiling.
Technical Challenges and Resolution	◆ Medicilon CMC team modified the addition method and determined adding API after cooling as a solution can solve the lows stability issue. ◆ Conducted extensive literature and market research on individual formulations on behalf of the client. ◆ Focused on tincture rheology and provided formulation development of the current Rx. ◆ Improve and ensure the feasibility of the process for scale-up, from 2kg→5kg→20kg→50kg→200kg. ◆ Complete curve of shear stress and shear velocity, yield stress and creep test and viscoelasticity. ◆ Study the relationship between emulsion size and stability, and control the appropriate particle size of the sample.



Viscosity Curve | Linear Viscoelastic Response | Yield Stress Value | Creep test



Particle Size distribution

Summary

Medicilon can support your development process of various topical skin preparations, including ointments, creams, gels and other semi-solid preparations, as well as lotions, liniments and other solutions.Medicilon fully complies with all relevant global laws and regulations, and has many years of development and research experience. Medicilon has completed the development and application of a number of external preparation research projects for pharmaceutical companies and scientific research institutes.

References

[1] Hyunjae Lee, et al. Device-assisted transdermal drug delivery. Adv DrugDeliv Rev. 2018 Mar 1;127:35-45.

[2] Mark R Prausnitz, et al. Transdermal drug delivery. Nat Biotechnol.2008 Nov;26(11):1261-8.

[3] Muhammad Yasir Siddique, et al. Microemulsified Gel Formulations for Topical Delivery of Clotrimazole: Structural and In Vitro Evaluation. Langmuir. 2021 Nov 23;37(46):13767-13777.