GENERIC SEMI-SOLIDS – AN OVERVIEW OF CURRENT REGULATORY REQUIREMENT

Drug delivery via the skin is a growing area of interest among scientists due to its many benefits. The skin provides an ideal site for the delivery of drug substances for both local and systemic effects. However, it can also act as a barrier preventing the penetration of many drug substances.

Scientists have been trying to understand skin structure so it can be manipulated to allow effective drug delivery. Through selecting compatible excipients, the residence time can be optimised and the drug can be effectively transported through the skin layers.

Formulation challenges

The most common dosage forms used for topical treatment are ointments, gels and creams. Incorporating the active pharmaceutical ingredient (API) into these formulations presents formulation scientists with many challenges. These include dose, solubility, particle size, polymorphism, compatibility with excipients and formulation factors like selecting the right excipients for a safe and stable formulation. The concentration of excipients to facilitate the permeation of drug through skin layers is an important factor. Patient usability also needs to be considered. A primary challenge also lies in the scaling up from development scale to commercial scale whilst maintaining the Critical Quality Attributes (CQAs) obtained during the development phase.

Regulatory hurdles

As well as the above formulation challenges, the advancement of regulatory requirements places further demands on these dosage forms. A new drug product must be evaluated in clinical trials against the placebo, a compactor product.

Generic semi-solid formulations were conventionally evaluated using performance tests to prove bioequivalence by clinical end point studies. Other methods of analysing bioequivalence are pharmacokinetic studies, pharmacodynamic end points and dermatophamacokinetic studies. These studies are very costly and time-consuming in many cases. Requirements for such methods to demonstrate bioequivalence leads to either a delayed and high-cost product in the market or no competition to the existing brands.

In order to promote the development of generic formulations and to provide affordable medications to patients, the regulatory authorities have devised different methods to expedite the development process and reduce the time required to prove the equivalence with a Reference Listed Drug (RLD). These studies involve the evaluation of generic and RLD formulations in-vitro based on qualitative sameness (Q1), quantitative sameness (Q2) and microstructural sameness with the RLD (Q3). There are a few other tools like IVRT (synthetic membrane) and IVPT (human cadaver skin) which also help to prove the sameness of release to that of RLD.

Regulatory guidelines

The regulatory agencies in both the US & EU publish the Product Specific Guidance on how to prove the bioequivalence. There are many examples now where the bioequivalence can be proven by in-vitro options and the clinical end point studies can be waived. Where bioequivalence is required; uniformity across Q1, Q2 & Q3 is not mandatory from a regulatory point of view but it increases the chance of a successful bioequivalence study.

A draft guideline on quality and equivalence of topical products, published in October 2018 by EMA, has defined the European regulatory requirements on equivalence testing of topical products in lieu of therapeutic equivalence clinical trials . The guideline uses the term "Extended Pharmaceutical Equivalence", which covers establishing comparative data with the comparator medicinal product comprising pharmaceutical form; qualitative and quantitative composition; microstructure/physical properties; product performance and administration. The guideline also outlines how to perform pharmaceutical equivalence in terms of qualitative and quantitative composition, microstructure/physical properties including an emphasis on rheology and product performance. If a generic product is pharmaceutically equivalent with the comparator product, then clinical end point studies can be waived or replaced either by pharmacokinetic studies like IVPT, tape stripping or PK endpoint or pharmacodynamic studies.

Like the biopharmaceutics classification system (BCS) based biowaiver for solids, a similar approach is suggested for topical formulations called Topical Classification System (TCS). As per this system, there are four classes of topical formulations.

TCS Class I: Q1, Q2, Q3 Same → Biowaiver

TCS Class II: Q1, Q2 same; Q3 different → BE study

TCS Class III: Q1, Q2 different; Q3 same → Biowaiver based on IVRT

TCS Class IV: Q1, Q2, Q3 different → BE study

Recipharm solution

At Recipharm, we have the expertise to develop stable and scalable topical formulations. We use the Quality by Design (QbD) concept and perform all the required Q1, Q2 and Q3 sameness testing, including:

- Microscopical observations of RLD
- API particle size and polymorphism in RLD
- Globule size determination in case of emulsions
- Reverse engineering of RLD for grade & quantity of excipients
- Viscosity and rheology profiling of RLD
- IVRT & IVPT testing

1.EMA Draft Guideline Draft guideline on quality and equivalence of topical products
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-equivalence-topical-products_en.pdf