Excipients in cutaneous medicinal products: permeation enhancers and more

Tommaso Eliseo

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3. Strategic advisory role for a company	☐	☐	☐	☐ optional
4. Financial interests	☐	☐	☐	☐ optional
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6. Principal investigator	☐	☐	☐	☐ optional
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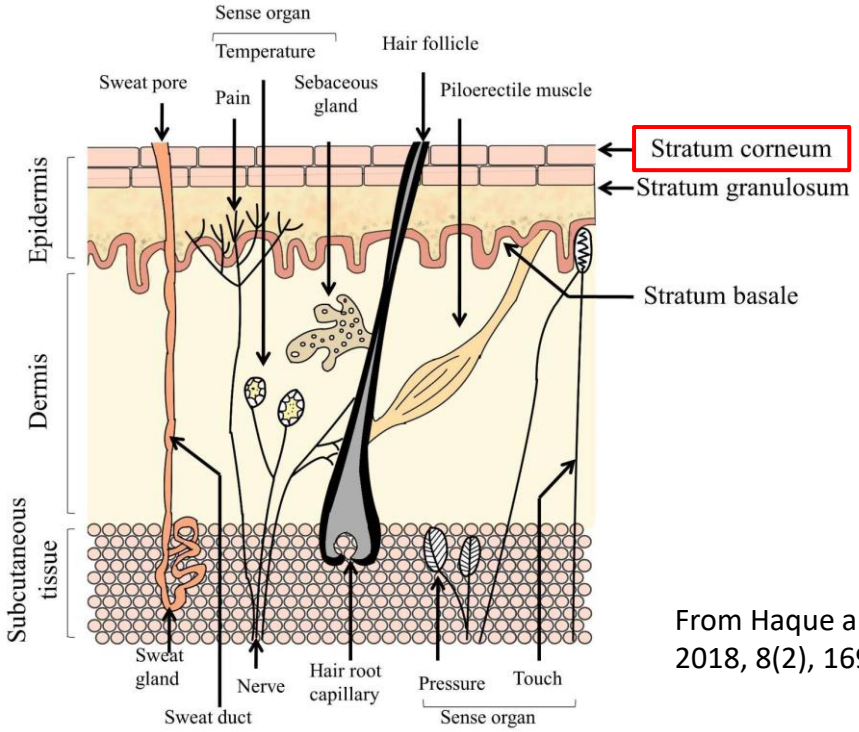
Undercover



Most effective body barrier

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Impact of formulation

Factors affecting extent of DS activity in cutaneous products

- Concentration
- **Pharmaceutical formulation**
- Site of application
- Skin condition
- Conditions of application

- Even more complex and unpredictable. See Law *et al.,* Am J Clin Dermatol 21 (2020): *Twenty Clinically Pertinent Factors/Observations for Percutaneous Absorption in Humans*.

Impact of formulation

NfG on clinical requirements for LALA (CPMP/EWP/239/95 final)

- change in formulation or in dosage form may influence the efficacy and/or safety
- change in physicochemical properties
- **change of non-active ingredients**
- **change of extent of penetration of the active substance**
- **dermatological products: vehicle may influence disorder (*and not only*)**

Impact of formulation

GL on quality and equivalence of LALA cutaneous products
(EMA/CHMP/QWP/708282/2018)

Changes significantly influencing efficacy and/or safety

- **formulation**
- dosage form
- method of administration
- manufacturing process (sequence of addition, structure-forming steps, equipment design, processing parameters)

Impact of formulation

Effect of formulation/excipients on absorption/permeation

- thermodynamic activity (solubility, crystallisation, supersatusaturation)
- diffusivity in skin (e.g., lipid fluidification, pore formation)
- altering skin barrier properties (e.g., perturbing lipid packing, denaturing proteins)
- altering skin hydration (moisturisers, hygroscopic compounds, occlusive effect)
- perturbation of physiological processes (e.g., skin pH, skin microflora, desquamation, immune response, cell differentiation)

Dossier sections

P.1 Description and Composition of the Drug Product

- pharmacopoeial nomenclature (where available), chemical name
- state grade where relevant
- state brand only if required for manufacturability and product quality
- identify and state function(s)

Dossier sections

3.2.P.2.1 Components of the Drug Product

- justify selection of the given excipient and its concentration (P.2.3)
- inert ingredient (non-pharmacologically active)
- safety (non-toxic, non-irritant, non-sensitizing, flammability)
- compatibility and stability (binary or more complex combinations, development data, stability studies: maintaining performance through formulation, processing and storage

Dossier sections

P.2.1 Components of the Drug Product

- identify and describe function, impact on product quality and manufacturability
- identify and justify grade (potential source and batch variation)
- identify and justify FRCs
- composition for mixtures and/or specific attributes (rheology, molecular weight, substitution grade, etc.)

Dossier sections

P.2.3 Formulation development

- laboratory trials and scale-up, stability batches
- pivotal batches (non-clinical studies, clinical trials, equivalence testing)
- validation batches (same formulation/process/packaging as pivotal batches)
- development vs final formulation: thorough characterisation of impact of changes on QTTP and CQAs through informative testing (e.g., **viscosity/rheology**, **IVDR**, IVPT if necessary, QbD)

Dossier sections

P.4 Control of Excipients

- Ph. Eur. or national EU quality whenever present
- monograph mandatory tests (+ microbial quality/sterility + FRCs)
- description and validation of non-compendial tests
- CoAs are wellcome
- for novel excipients full details on quality and safety in dossier

Equivalence testing

Conditions and criteria for equivalence testing (waiving)

- same active substance, strength, solution state (in the same phase)
- same salt form and polymorphic form (othewise justify by step-wise approach)
- same pharmaceutical form
- same administration mode
- similarity assessment by **Q1**, **Q2** and Q3

Equivalence testing

Q1: same qualitative composition

- ALL excipients that influence:
  - active substance solubility and/or thermodynamic activity
  - bioavailability (local and/or systemic)
  - product performance (e.g., *in vitro* release, residence time, occlusivity)
- including excipient grade

Equivalence testing

Q1 permitted exceptions

- excipient function not related to product performance or administration, i.e. antioxidants, antimicrobial preservatives, colorants, fragrances

  AND

  no other functions or effect that influences the active substance solubility, thermodynamic activity or bioavailability, product performance, local tolerance and/or safety

- excipient paraffin homologues if function relates to the vehicle or emolliency and no influence on active substance solubility, thermodynamic activity or bioavailability, product performance (moisturing effect remains the same)

Equivalence testing

Q2: similar quantitative composition

- ALL excipients that influence:
  - active substance solubility and/or thermodynamic activity
  - bioavailability (local and/or systemic)
  - product performance (e.g., *in vitro* release, residence time, occlusivity)

Equivalence testing

Q2 permitted difference

- in general, not greater than ±5% w.r.t. RefMP quantity
- specifically , not greater than ±10% w.r.t. RefMP quantity if:

  - function relates to the vehicle properties or emolliency

  AND

  - no function or effect that influences the active substance solubility, thermodynamic activity or bioavailability and product performance (e.g. moisturising or occlusive effect) demonstrated by appropriate data.

Equivalence testing

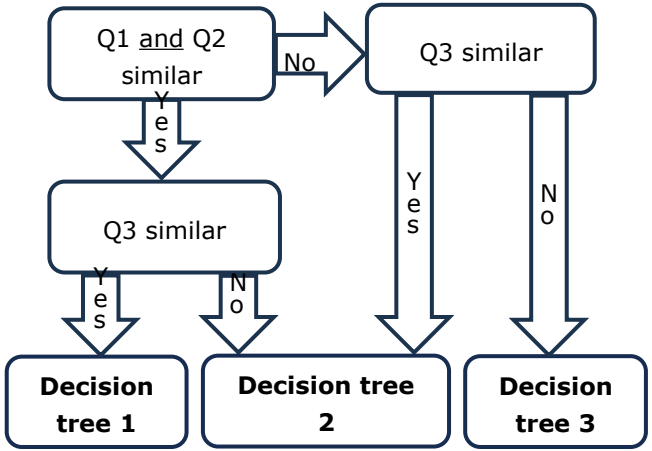
Identify Q1 and Q2 of RefMP

- RefMP Product Information
- produced by same manufacturer (declaration)
- patents, bibliographic data
- reverse engineering
- confirmatory analytical testing (at least for critical excipients)
- development data to establish impact of excipient concentration to match RefMP Q3

Equivalence testing

What if Q1/Q2 different?

STEPWISE APPROACH: just follow the GL Scheme 1 and the related Decison Trees (1, 2 or 3):



Scheme 1

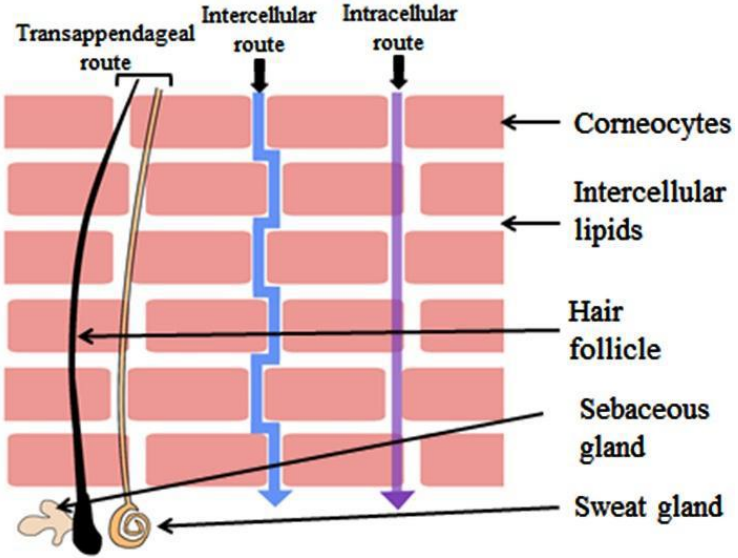
Permeation ennhancers

Permeation enhancers

- permeation enhancers (EMA GLs) or penetration enhancers or absorption promoters
- (chemical) components of the formulation
- promote and accelerate penetration and permeation (and/or accumulation/depot): enhance or modify *in vivo* flux
- permeant themselves and interact with skin (*stratum corneum*) constituents
- unidirectional and possibly reversible effect

Permeation ennhancers

Stratum corneum



- bricks and mortar model
- corneocytes, lipid lamellae, corneodesmosomes and extracellular matrix, water and natural moisturising factor
- highly heterogeneous
- thickness dependent on body site and subject condition

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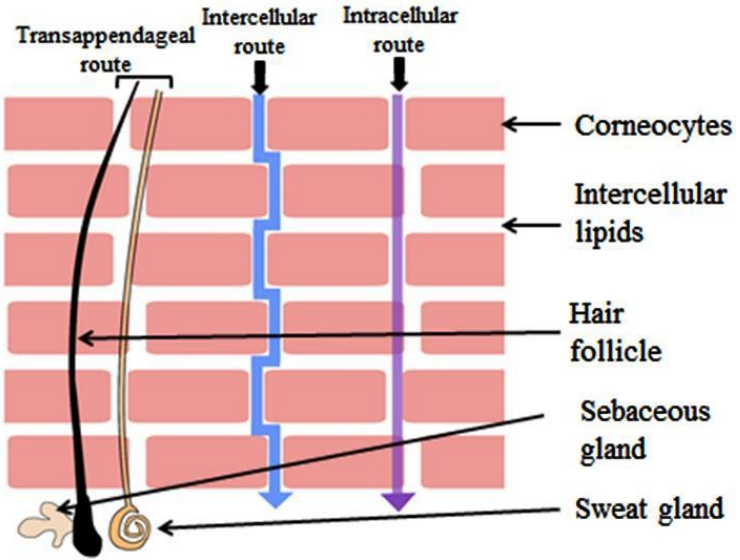
Permeation ennhancers

Permeation process



Permeation:

- sequential steps of **partition** and **diffusion** down a concentration gradient throughout lipophilic and hydrophilic domains.
- Clearance relevant at specific sites

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Permeation ennhancers

Enhancing permeation: the basic model

From rearranged, simplified Flick's First and Second Law:

$$J_{SS} = \frac{DK_{pc}c_0}{h}$$

J_{SS} = Flux (transfer of permeant masS per unit area per unit time) at steady state
D = Diffusion coefficient of permeant in the skin
K_{pc} = Partition coefficient (skin/product)
C_0 = Concentration of permeant in the product at T_0
H = Skin thickness
P = Permeability coefficient

Permeation ennhancers

How to enhance permeation: **push or pull**

- increase C_0 (increase solubility in formulation, saturation, supersaturation)
- increase D (*stratum corneum* structure/order perturbation/disruption, loosening lipid packing, lipid fluidification, lipid domain/phase separation, lipd extraction)
- increase K_{pc} (partion into lipid bilayers, increase solubility in skin, drag effect, decrease solubility in product)
- decrease h (shorter permeation pathway, *stratum corneum* structure perturbation/ perturbation/disruption)

Permeation enhancers act on some or all the above elements

Permeation ennhancers

Commonly used permeation enhancers

- **ethanol** (solvent, volatile), **isopropanol** (solvent, volatile), other fatty alcohols
- **propylene glycol** (solvent, volatile)
- **oleic acid** and other long chain fatty acids
- fatty acid esters (e.g., **isopropyl myristate**, propylene glycol monocaprylate, propylen glycol monolaurate)
- **diethylenglycol monoethyl ether** (Transcutol®)
- pyrrolidones (e.g., 2-pyrrolidone, NMP)
- terpens and terpenoids (e.g., menthol, 1,8-cineole, D-limolene), essential oils
- surfactants (non-ionic as ionic are typically irritant), some peptides
- **water!**

Permeation ennhancers

Permeation enhancers: what is common?

- high diversity of structural classes, MW, lipophilicy (logP), ion/H bonding capacity
- many (not all) have a polar head and a hydrophobic chain (short/medium/long)
- Quantitative Structure Permeability Relationships (QSPR) specific to each chemical class
- high diversity in mechanisms of action (typically multiple modes)
- enhancement depends on skin membrane and experimental setting

- **some clearly identified as PEs in MA applications and some NOT** (Annex 3 of EMEA/CHMP/QWP/396951/2006)
- in case of doubt, search in literature, MA registries, assessment reports, request (documented) justification

Permeation ennhancers

Non-chemical permeation enhancers

- efforts in research for alternative ways to enhance permeation
- formulation-related or nano-carrier based: microemulsions and nanoemulsions, liposomes and liposome-like carriers, nanoparticles, etc.
- physical methods: iontophoresis, sonophoresis, electroporation, microneedles, etc.
- more relevant for Transdermal Delivery enhancement

Moisturisers

Impact of hydration on permeation and skin integrity

- the stratum corneum contains up to 15-20% of water (deeper epidermis and dermis even more)
- hydration and occlusion enhance permeation
- EMA/CHMP/QWP/708282/2018: choice of excipient and its quantity critical for hydration capacity and potential occlusive effect of the formulation
- if Q1/Q2 non similar but Q3 similar or Q1/Q2 similar but Q3 non similar: products should produce a **similar occlusion, hydration of the skin, transepidermal water loss**

Moisturisers

Types of moisturisers

- **humectants**: bind and retain water molecules within the *stratum corneum* with long-lasting effect (e.g., glycerol, sorbitol, propylene glycol, panthenol, urea, pyrrolidone carboxilic acid, lactate)

- **occlusive agents**: fill the gaps between skin cells and produce a hydrophobic barrier on the skin preventing water loss (e.g., liquid and white soft paraffin, silicone oils, lanolin, fatty alcohols/esters/ethers, vegetable oils or purified mono- di- triglycerides).

- some humectants and occlusive agents have **emollient properties** contributing also to softening and smoothing the skin, enhanced flexibility, lubricating, spreading, adhesivity, skin feel and perception, patient acceptability and therapy adherence (strong placebo effect).

Moisturisers

How to measure hydration and emolliency

- no guidance in the GL (TEWL only mentioned in Annex III as supporting and check test for tape stripping; TEWL commonly used as skin integrity test in IVPT protocols)
- Is *in vitro* testing (e.g., appearance, water activity, viscosity/rheology, spreadability, adhesivity) sufficient and predictive?
- *In vivo* measurements for clinical development typially on healthy skin subjects (e.g., corneometry/electrical/optical methods for skin hydration, transepidermal water loss, skin elasticity, erithema index, skin topography/imaging, sensory assessment, user perception/satisfaction)

- **Abridged applications: better matching Q1 and Q2 of the RefMP or SA request**

Volatile excipients

Transformation (metamorphosis) of product upon administration

- critical aspect especially for volatile solvents (e.g., ethanol, isopropanol, propellants) and certain dosage forms (e.g., foams, film-forming preparations)
- evaporation impacts thermodynamic activity, rheology, physico-chemical characteristics and permeation rate
- risk of crystallisation in product and in skin
- risk of flammability
- attention to packaging and stability data (solvent loss, low humidity conditions)

Volatile excipients

Quality attributes of product upon administration

- characterisation of residue (e.g., time to drying/evaporation, appearance, residue weight/thickness, polymorphic state, viscosity/elasticity, adhesivity/stickiness, TEWL, IVDR/IVPT, ease of removal)
- **test and reference medicinal product residues should be equivalent with respect to quality** (pharmaceutical equivalence): identify and compare critical QAs of the residue
- set few, appropriate (*in vitro* surrogate) parameters in specification for product following transformation based on characterisation and development data)

References

Guidelines

- Quality and equivalence of locally applied, locally acting cutaneous products (EMA/CHMP/QWP/708282/2018)
- Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95 final)
- Clinical investigation of corticosteroids intended for use of the skin (3CC26A)

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Thank you all!

Tommaso Eliseo
t.eliseo@aifa.gov.it