Effect of Formulation Differences on Critical Quality Attributes and Performance of the Complex Topical Products

FDA-CRCG Workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Topical Product Development

SESSION 1: Understanding the Influence of Formulation Differences on Product Performance

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Outline

- Concepts of Q1/Q2/Q3
- Arrangement of matter (Q3 attributes) and its Importance
- Product complexity/non Q1/Q2 formulations
- Product development approaches
- Studies to demonstrate BE

Complex Topical Products
Q1/Q2/Q3 Concepts

- Q1: Components – Qualitative composition
  - ❖ Chemistry and grade of each inactive ingredient
- Q2: Concentration – Quantitative composition
  - ❖ For Sameness- difference should not exceed 5%.
- Q3: Physicochemical and Structural attributes
  - ❖ Arrangement of matter
  - ❖ pH, globule size, particle size distribution, rheological behavior, drug polymorphic form etc.

Raney S. When do formulation differences in topical dosage forms impact their function: Emerging insights and implications for bioequivalence approaches. SBIA September 2020

Complex Topical Products

Q3- Arrangement of matter

- Q3 Sameness
  - ❖ Q1-same components and Q2 – same composition (±5%) as RLD and Q3 – same physical and structural properties
- Q3 Similarity
  - ❖ Q1/Q2-Difference in components and composition and similar Q3 properties
- Q3 Difference
  - ❖ Q1/Q2-same/difference in components and composition but different Q3 properties

Q3 Attributes

- Appearance and texture
- Phase states
- Organization of matter
- Drug polymorphic form
- Rheological behavior
- Water activity/drying rate
- pH
- Oleaginous components
- Specific gravity
- Metamorphosis changes

Importance of Q3 Characterization

- Matching Q3 attributes to that of RLD demonstrates pharmaceutical and bioequivalence and mitigates the risk of potential failure modes related to differences/changes in-
  - ❖ Q1/Q2 sameness tolerance
  - ❖ pH that may irritate skin
  - ❖ Polymorphic form of the drug
  - ❖ Rheological behavior
  - ❖ Diffusion/partitioning of the drug
  - ❖ Drying rate and metamorphosis etc.

Raney. S. Use of Q3 characterization test for Topical semisolid drug products. SBIA. September 2021

Product Complexity

- Due to product complexity, formulations having the same quantitative and qualitative composition (Q1/Q2) may result in different appearing, functioning products.
- A Q1/Q2 formulation can have different Q3 attributes and affect product performance.
- A test product with same Q3 attributes as a reference product, could prevent the risk of known failure modes.

Non Q1/Q2 Formulations

- Generic topical products may not be Q1/Q2
- Clinical data demonstrates that several topical products are bioequivalent even if they are not Q1,Q2 or Q3 same as RLD
- Situations which may lead to non Q1/Q2-
  - ❖ Difficult to reverse engineer
  - ❖ Intellectual property issues
  - ❖ RLD discontinued etc.

Product Development Approach

Non Q1/Q2

- When a product does not prequalify for characterization-based approaches, it is very important to understand the reference product in respect of-
  - ❖ Composition of inactive ingredients and how it impacts CQA's
  - ❖ Grade of each inactive ingredient and how it impacts CQA's
  - ❖ The phase states and arrangement of matter and how it impacts CQA's
  - ❖ Drug diffusion within the dosage form and how it impacts CQA's

- Importance of Process Understanding
  - ❖ Sequence of mixing
  - ❖ Mixing speed and durations
  - ❖ Temperatures and other process as these can result in different Q3 attributes

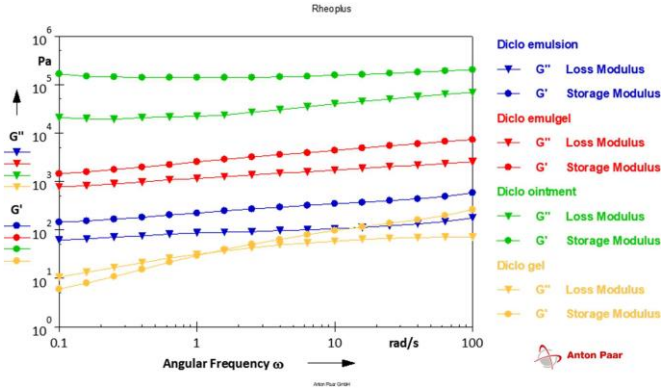
- Can you still achieve Q3 similarity as the reference product?

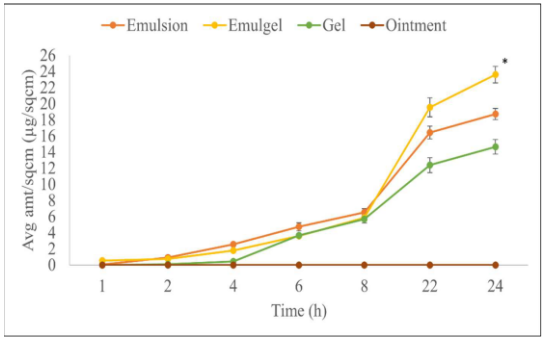
Product Development Approach

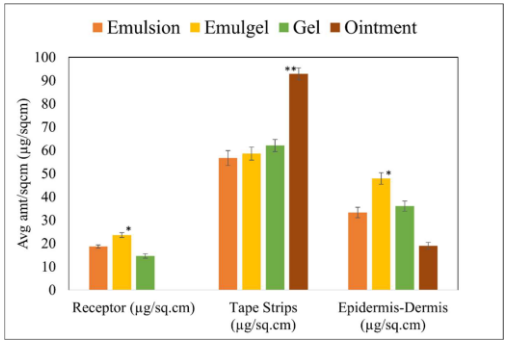
- Goal should be to achieve Q3 similarity when there is no Q1/Q2 sameness
- Match Q3 attributes and CQA's as close to the RLD
- Characterize extensively change in the formulation and impacted failure modes.
- Purposely changing the % of the ingredients and test the failure mode
  - ❖ Does the difference/change in polymer/ surfactant changes the CQA's?
  - ❖ Is change in CQA alters the product performance?

Formulation Differences and Product Performance

Components	Emulsion (% w/w)	Emulgel (% w/w)	Gel (% w/w)	Ointment (% w/w)
Diclofenac sodium	1.00	1.00	1.00	1.00
Propylene glycol	5.00	5.00	5.00	-
Transcutol®	10.00	10.00	10.00	-
Ceto Stearyl Alcohol 50	2.00	2.00	-	-
Liquid Paraffin	7.50	7.50	-	-
Span™60	4.50	4.50	-	-
Tween™ 60	0.50	0.50	-	-
Klucel®	-	1.00	2.00	-
PEG 400	-	-	-	59.00
PEG 3350	-	-	-	40.00
Benzoic acid	0.25	0.25	0.25	-
Water	Q.s. to 100%	Q.s. to 100%	Q.s. to 100%	-
TOTAL	100%			







Manian, M. et al. Formulation and Evaluation of the In Vitro Performance of Topical Dermatological Products Containing Diclofenac Sodium. Pharmaceutics **2022**, 14, 1892.

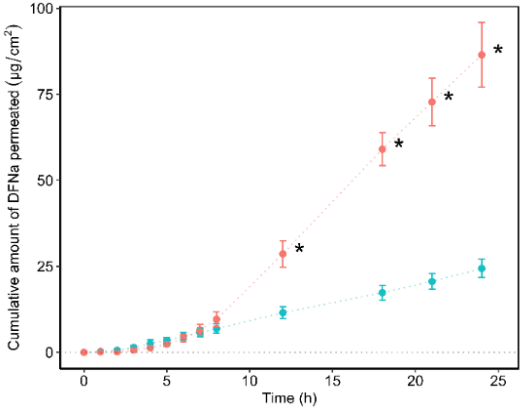
BE Approaches

- Characterization Based
  - ❖ Q1/Q2 sameness
  - ❖ Q3 sameness
  - ❖ IVRT
  - ❖ IVPT
- Alternative approaches for BE
  - ❖ Clinical end point study
  - ❖ Pharmacokinetic study (If applicable)
  - ❖ In vivo cutaneous PK
    - ❖ Confocal Raman /Simulated Raman Spectroscopy (Epidermal)
    - ❖ Dermal Microdialysis
    - ❖ Dermal Open Flow Microperfusion

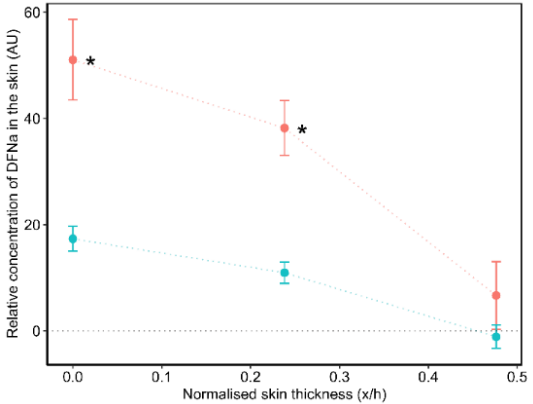
Confocal Raman Spectroscopy (CRS) to Determine Drug Permeation

Table 1. Ingredients of the topical formulations, Diclac® and Primofenac®.

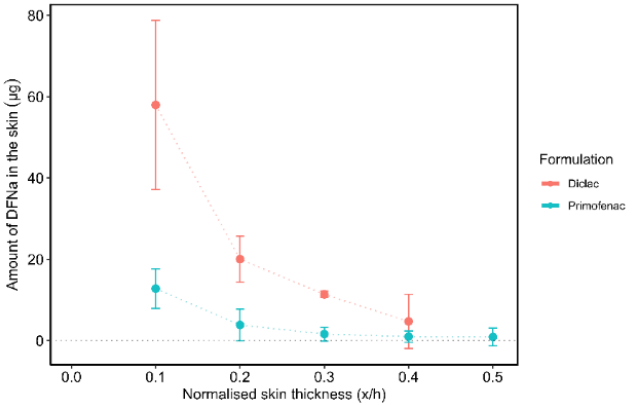
Diclac® Lipogel 10 mg/g	Primofenac® Emulsion gel 1%
DFNa	DFNa
RRR-α-tocopherol	cetyl alcohol
carbomer 980 NF	methyl-4-hydroxuybenzoate
decyl oleate	propyl-4-hydroxybenzoate
2-octyldodecanol	isopropyl alcohol
Lecithin	glycerol
ammonium hydroxide 10%	polyacrylic acid (Carbomer)
disodium edetate	medium-chain triglycerides
perfume oil 'Vert de Creme'	macrogol cetostearyl ether
isopropyl alcohol	purified water
purified water	



IVPT Data



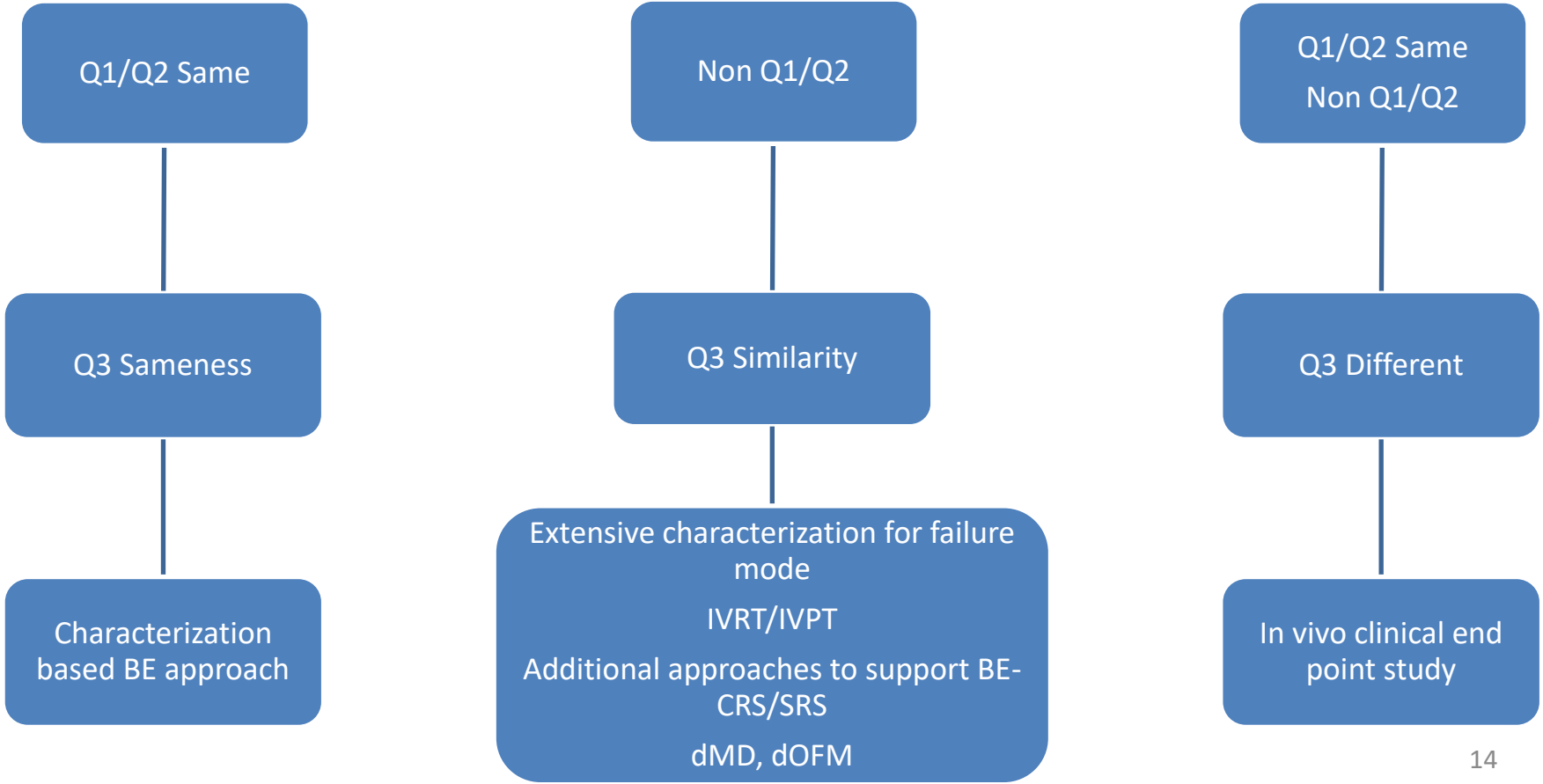
CRS Data



Tape Stripping Data

Iliopoulos, F. et al. Dermal Delivery of Diclofenac Sodium—In Vitro and In Vivo Studies. Pharmaceutics **2022**, 14, 2106.

BE Approaches



Conclusion

- Thorough characterization of components, composition, and physicochemical and structural characteristics in topical complex products is critical to their clinical performance.
- Characterization based approach for Q1/Q2/Q3 matching relative to refence formulation
- Q3 characterization of the reference product is critical to the product performance and Q3 same/ similar test product could mitigate the known failure modes for BE.
- Multiple studies including in vitro and/or in vivo tests of product performance may be conducted to support the BE evaluation for non Q1/Q2 formulation.

Thank you!