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The Systematic Influence of Changes in Manufacturing Process Variables on the Microstructure and Performance of Topical Emulsions

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PURPOSE

Products that are qualitatively (Q1) and quantitatively (Q2) identical may differ in microstructure due to differences in the manufacturing process. Microstructural differences in topical products could significantly impact the bioavailability of the active pharmaceutical ingredient (API) from topical dosage forms. We sought to elucidate how variations in specific manufacturing parameters may impact the microstructural properties of the resulting creams.

OBJECTIVE(S)

The aim of this study was to investigate the effect of manufacturing process variables on the microstructural arrangement of matter (Q3) of topical oil in water (O/W) emulsions, and the impact of these microstructural differences on their performance.

METHOD(S)

Preparation of Creams:

Seven custom-made Q1 and Q2 identical emulsion formulations (designated F1 through F7) were prepared with systematic alterations in the homogenization speed (F1-F4) measured as revolutions per minute (rpm), and/or the duration of homogenization (F5-F6) and F7 with no cooling protocol, as shown in Table 2 .

Table 1: Composition of emulsion

Ingredients	Quantity (% w/w)
Cetostearyl alcohol	7
Mineral oil	12
Cremophor® A25	1.5
Cremophor® A6	1.5
Propylene glycol	8
Water purified	70

Table 2: Process variables used to manufacture formulations (F1-F7)

Formulation code	Homogenization speed (rpm)	Homogenization time (minutes)
F1	500	20
F2	1000	20
F3	3000	20
F4	5000	20
F5	3000	10
F6	3000	40
F7*	3000	20

*A controlled cooling protocol (ramping from 80 °C to 25 °C in 25 min) was followed for all the emulsions, except F7 which was allowed to cool to room temperature in an uncontrolled manner.

Characterization of Creams:

1. **Appearance**: Nile Red, a hydrophobic dye, was incorporated in the oil phase to facilitate microscopic visualization of the globules. The visual appearance of each emulsion was characterized quantitatively using a hand-held PCE-CSM1 colorimeter.
2. **Globule Size**: The globule sizes were evaluated for each emulsion by confocal microscopy using a Zeiss LSM 510.
3. ***In Vitro* Permeation Test (IVPT):** The *in vitro* permeation of the Nile Red (as a model hydrophobic compound) was evaluated using vertical Franz diffusion apparatus with porcine skin to study the rate and extent of skin permeation from each emulsion.
4. **Texture Analysis**: Texture analysis was conducted in compression mode using a TA-XT2i Texture Analyzer equipped with a TA-3 acrylate cylindrical probe.
5. **Rheology:** Rheological characterization was performed using a TA HR2 rheometer equipped with 25 mm parallel plate. The experiments were conducted at 32 °C and the temperature was controlled using a Peltier stage

The relationships between the quality and performance attributes were assessed.

RESULT(S)

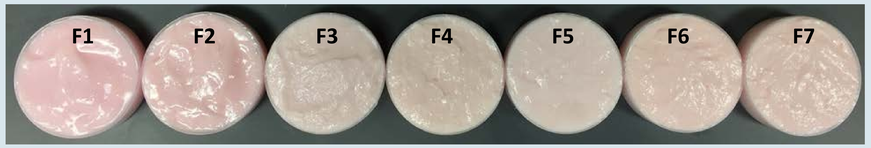


Figure 1: Appearance of seven custom-made creams that are Q1/Q2 identical

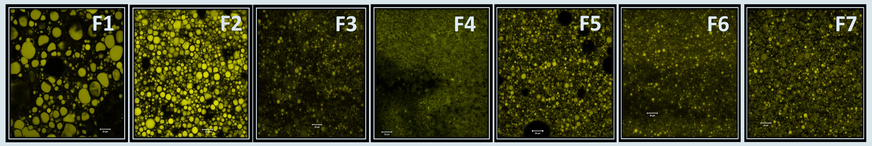


Figure 2: Images of seven creams at 40X magnification using a Zeiss LSM 510 confocal microscope.

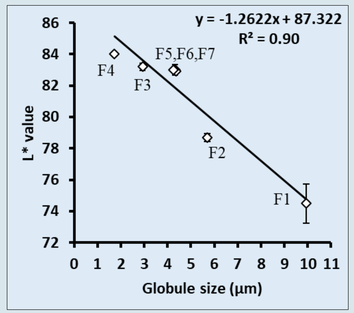


Figure 3: Relationship between lightness of creams (L) and globule size of seven creams (n=3; Shown as Mean ± Standard Deviation (SD)).

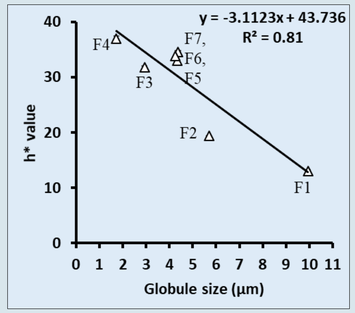


Figure 4: Relationship between hue values (h) and globule size of seven creams (n=3 ; Shown as Mean ± SD).

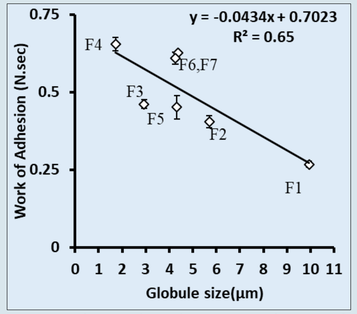


Figure 5: Relationship between the work of adhesion and globule size of seven creams (n=3 ; Shown as Mean ± SD).

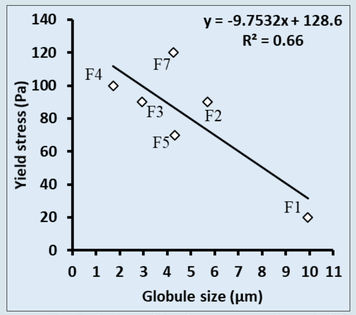
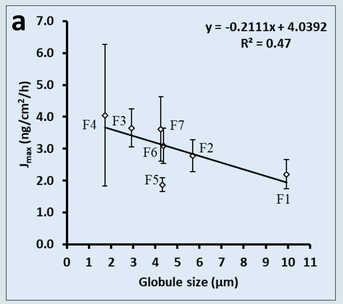


Figure 6: Relationship between the yield stress and globule size of seven creams (n=3).



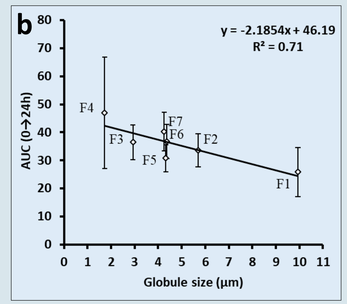


Figure 7: (a) Relationship between IVPT average maximum flux (J_{max}) and average globule size of seven creams; **(b)** Relationship between IVPT average total cumulative permeation (area under the curve; AUC) and globule size of seven creams (n = 4; Shown as Mean ± SD).

CONCLUSIONS

This study illustrated that systematic variations in manufacturing parameters of an emulsion can progressively influence the resulting Q3 attributes. For example,

1. The results showed that variations in homogenization speed and duration can alter the visual appearance of a cream, which may influence patients' perception of product quality.
2. The results suggested that manufacturing variations may impact the bioavailability of hydrophobic drugs from topical emulsions, even when the composition (Q1 and Q2) is identical. Of particular interest, this study elucidated a potential mechanistic basis for topical bioavailability whereby relatively larger globules (with a relatively smaller surface area) tended to decrease the average J_{max} and AUC for permeation of a model hydrophobic compound into and through the skin.

Our limited results are suggestive of a possible mechanism whereby changes in manufacturing could potentially alter the quality attributes, and correspondingly, the rate and extent of bioavailability for a hydrophobic compound dosed in a topical emulsion.

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