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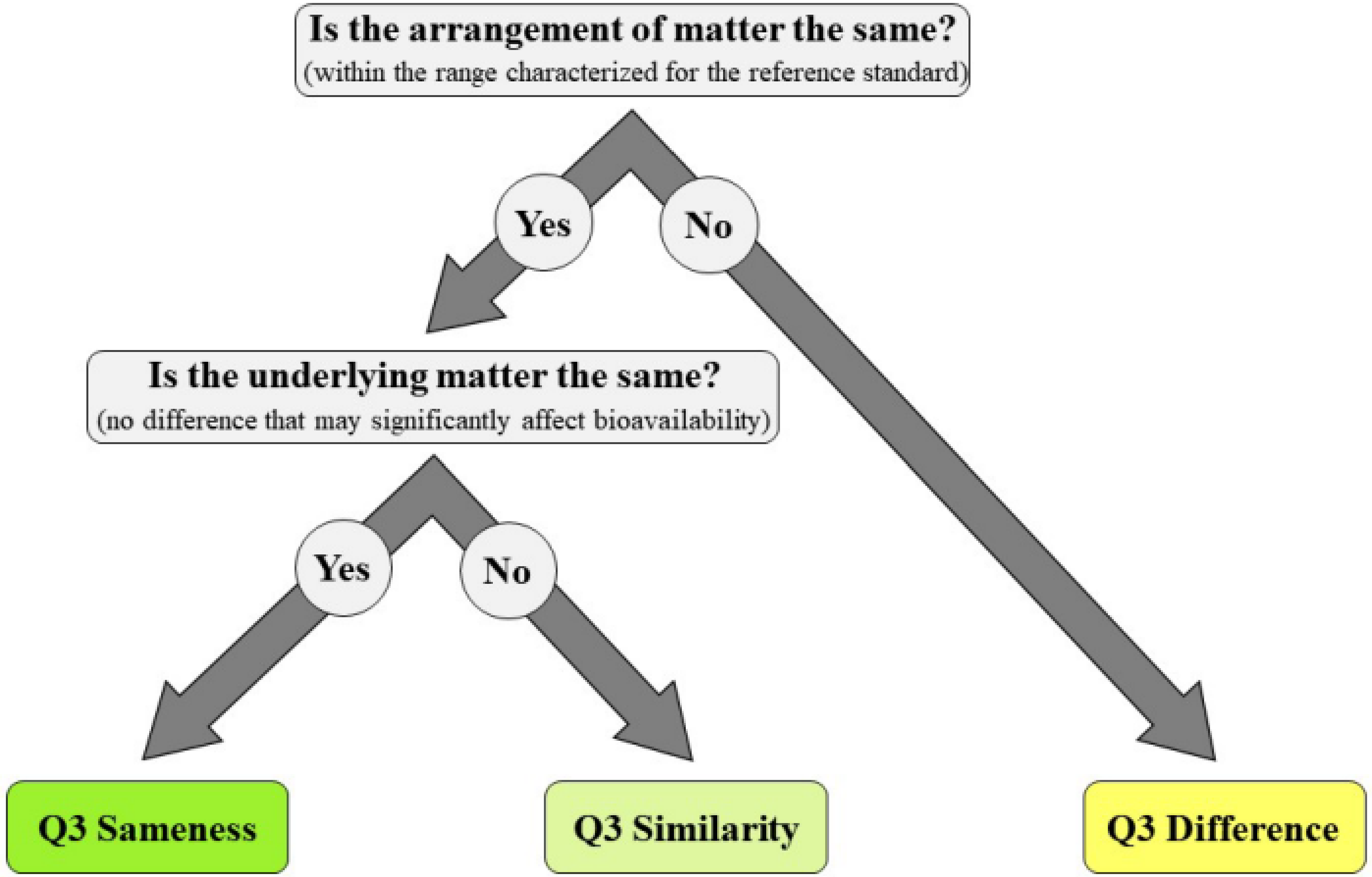
Development of Methods for Evaluation of Formulation Differences and their Impact on Therapeutic Equivalence: Broadening the Therapeutic Scope

Dr Yousuf Mohammed PhD


Is the arrangement of matter the same?
(within the range characterized for the reference standard)
Yes
No
Is the underlying matter the same?
(no difference that may significantly affect bioavailability)
Yes
No
Q3 Sameness
Q3 Similarity
Q3 Difference

Product quality and performance

- Product quality (Q3) and performance is related closely.
- New Q3 guidances recommend Q3 sameness and emphasize on Physical and structural similarity
- If we retrace the steps to regulatory recommendation, sensitive and discriminating Q3 tests are at the heart of the in vitro approach
- Hence, developing a battery to tests characterizing the physical, structural and microstructural attributes are imperative
- Sameness (within the range characterized for the reference standard) has the potential to guarantee therapeutic equivalence

The question then is,
what is covered in therapeutic equivalence ?

Broadening the therapeutic scope

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- Even before a topical product (in this case a generic product) is applied to the skin and owing to its skin penetration, exerts its therapeutic effect, it comes in contact with the patient by sensory means.
- The new age consumer (patient) sees beyond the “bitter pill logic”
- If a pill requires taste masking excipients for compliance, so do topical formulations.
- Generic products therefore, require to look and feel as elegant as the reference product

Therapeutic effects can also be perceived sensorially

- Patient skin can often be irritated and damaged
- Hence, a cooling product can start to provide its therapeutic effect, long before the drug penetrates the skin
- Similarly, the perception of grit (grittiness) can further irritate sensitive and sore skin and will therefore be therapeutically a negative experience, inducing “nocebo” effects and reducing compliance

Can we design Q3 tests that cover a larger area of therapeutic equivalence?

Sensorial attributes influencing therapeutic equivalence

List of attributes that can be perceived by patients during and after application of topical products on the skin

Attribute	Definition
Perceivability	The point at which the patient/subject perceives the product on the skin
Hardness	Force exerted to apply the product
Grittiness	Grainy or gritty feel of product due to suspended nature of the active or certain excipients
Cooling sensation	This sensation is perceived due to specific excipients incorporated in the product such as emulsifiers, emollients, fragrances
Absorption point	Number of rubs (rotations) needed for the product start to be absorbed by the skin
Spreadability	Ease of spreading product on skin
Slipperiness	Ease of sliding finger over the skin
Stickiness	Degree with which fingers adhere to the skin
Immediate white residue	White film formed on the skin immediately after the spreading of the product
Residual white residue	White film formed on the skin 1 minute after spreading the product
Velvety/soft film	Feeling of softness
Dry touch	Skin non-sticky, non-greasy and dull.
Immediate gloss on skin	Light intensity reflected on skin immediately after product spreading
Residual gloss on skin	Light intensity reflected on the skin 2 minutes after spreading the product
Immediate Oiliness	Sensation of oil on the skin during and immediately after the product spreading
Residual Oiliness	Sensation of oil on the skin 2 minutes after spreading the product
Immediate greasy film	Sensation of grease film, formed on the skin, immediately after the product spreading
Residual greasy film	Sensation of grease film, formed on the skin, 2 minutes after spreading the product

Sensorial attribute	Possible mechanism
Grittiness	This often means crystals present. Their size, aspect ratio and crystal habit have an effect on TE
Softness/hydration	Skin hydration enhances penetration
Greasiness (immediate and residual)	Increased viscosity can lead to reduced release. Also enhances occlusivity
Greasy fat film (instant and residual)	Occlusivity enhances hydration, affecting TE. May also reduce penetration of active by film formation
Slipperiness	May not cover the same area intended
Cooling sensation	Cooling due to alcohol content can lead to solubility differences
Firmness/Stickiness	Two products with different stickiness usually have different Zero shear viscosity affecting release
Spreadability	May not cover the same area intended
Quick drying	The evaporation rate affects drug solubility and can lead to drug crystallisation upon evaporation
Speed of absorption	Directly related to the absorption of the vehicle which carries the API.

Grittiness

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- One of the reasons for grittiness is inconsistences in the product
- This can often mean presence of crystals or lumps
- Crystal size, aspect ratio and crystal habit have an effect on TE
- Grittiness can also increase irritancy when the product is used on already irritated skin

Softness/hydration

- It is known that skin hydration enhances penetration
- Skin hydration via occlusion can also temporarily alter the barrier properties of the stratum corneum to allow for an enhanced flux of both hydrophilic and hydrophobic drugs
- Emollients and surfactants used to improve the skin feel can have penetration enhancing effects

Cooling sensation

- Cooling due to alcohol content can lead to differences in solubility of active
- Cooling can reduce itchiness and irritation and compliment the efficacy of API in certain skin conditions where surface evaporation/cooling has a soothing effect

Greasiness (immediate and residual)

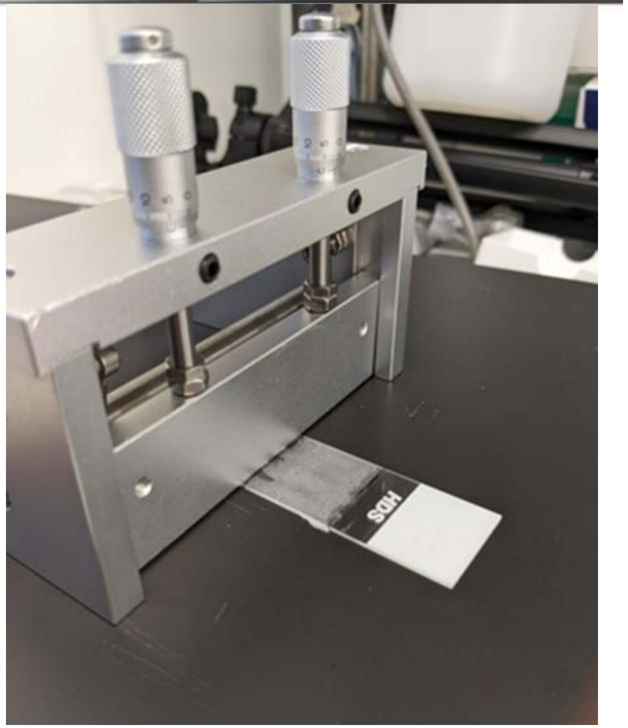
- Increased viscosity can lead to reduced release
- Enhanced occlusivity can improve penetration
- Less wash-off effect as the product is water resistant can lead to higher time on the skin

$Q3^+$ tests – Procedures and modifications

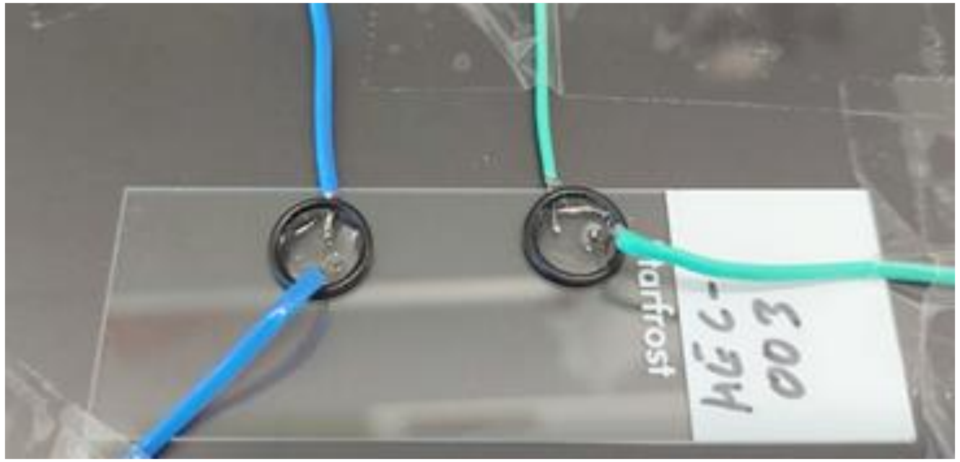
Measurement of volatile loss from gels and creams

Experimental conditions

- **Gels and creams : Q1 and Q2** variants
- **Replicates: 3**
- A known amount of product was placed on glass slides to measure volatile loss
- The experiments were undertaken at 25°C and 32°C and loss was measured over a duration of 1 hour
- Methods have also been developed under in use conditions where the product is spread evenly using a micrometre applicator



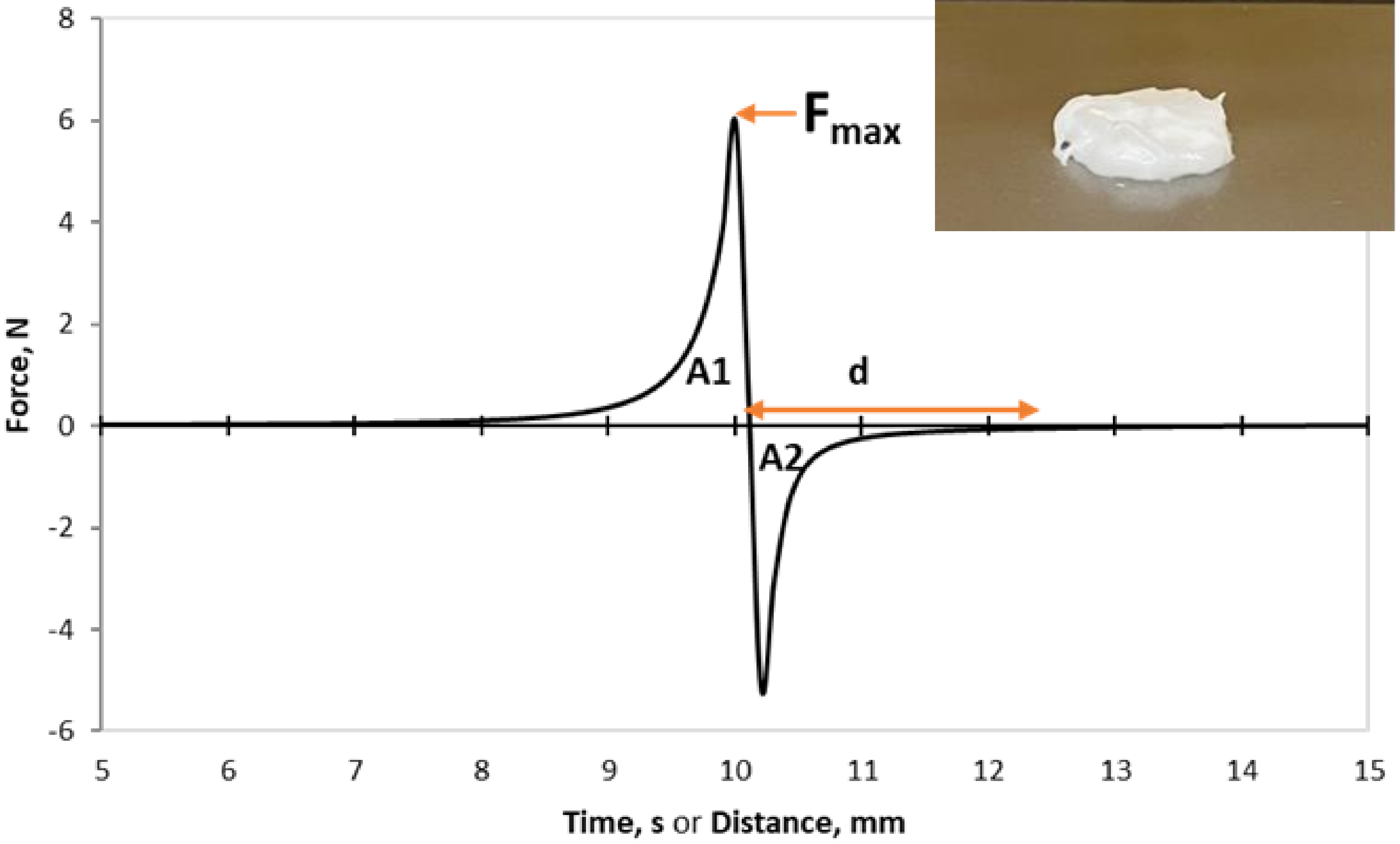
Investigating mechanism of cooling (evaporation)-Thermocouples



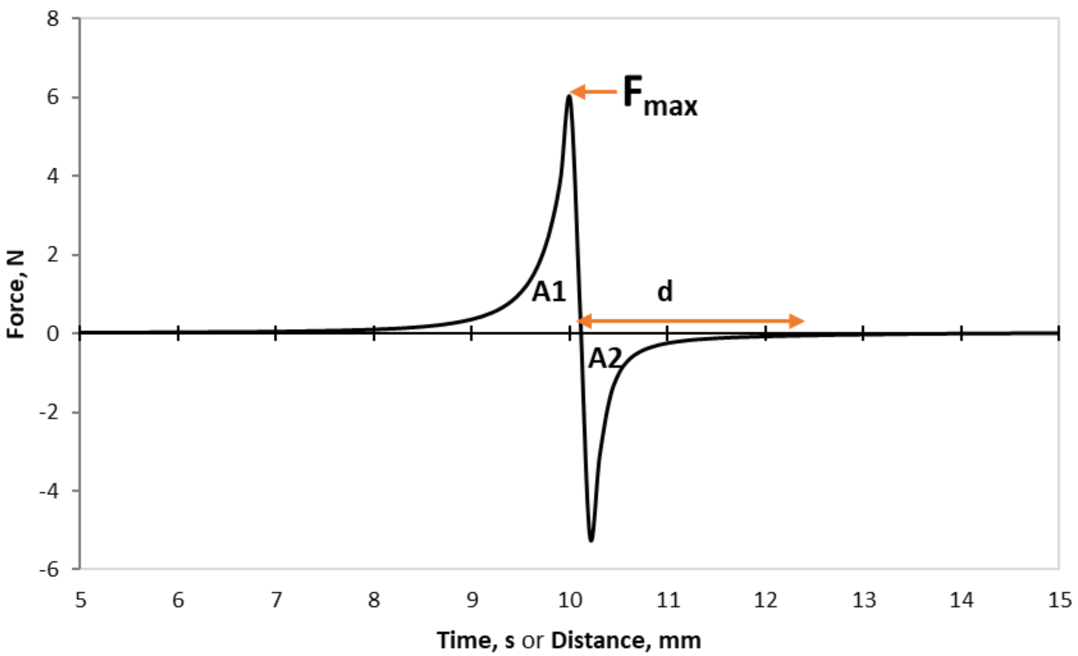
- Experiments were performed in triplicate.
- A thermocouple probe was affixed at the bottom (T2) and the other probe on the top surface of the gel (T1)

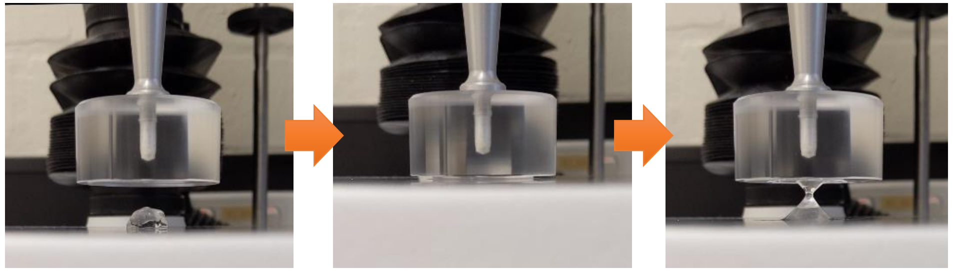
Q3 – Product texture and consistency

- Texture analysis



Texture profile analysis with compression test:





- ***Firmness***: Maximum force required for compression to 500µm gap
- ***Spreadability***: Magnitude of shear-work required in first cycle of compression (area *A1*)
- ***Adhesiveness***: Magnitude of work required to withdraw probe to original height after first compression (Area *A2*)
- ***Stringiness/tailing***: Distance to which product remains adhered to the probe during withdrawal after first compression (distance *d*)

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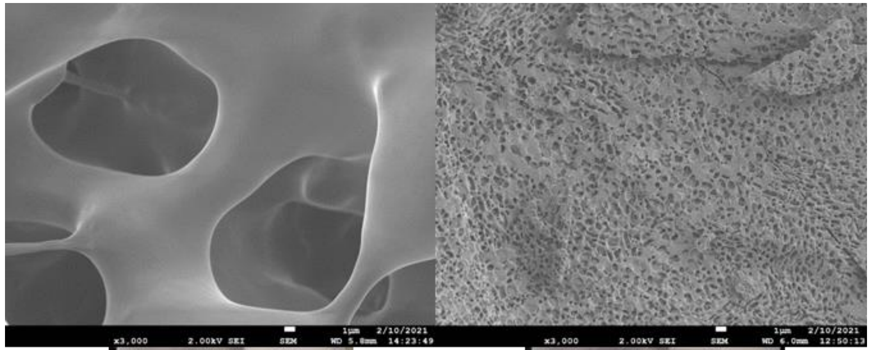
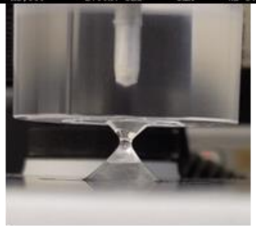
Texture profile analysis: Effect of CBP concentration

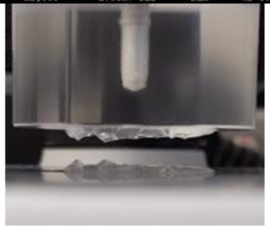
- The increasing CBP concentration formed consistently **firmer** and more adhesive gels that required more work to **spread**.
- The work required to withdraw the probe (adhesiveness), can be related to **stickiness** (with which sample adheres to the probe) and the force required to overcome internal cohesive strength of the structure.
- With increasing CBP from 0.5-1.0%, stringiness of the gels was reduced due to the increasing cohesive strength (more solid-like structure).
- The stringiness in F009, may likely be due to the surface tension of the sample rather than stretching of the network.
- With a highly porous and weaker gel network, F002 was relatively less firmer and adhesive that can be easily spread, but formed most stringy gel
- And at higher CBP concentrations, formation of less stringy and compact network increased the firmness and adhesive force values

Gels	CBP, %	PG, %	CBP/H_2O fraction	Firmness, N	Work of shear/ Spreadability, N.s	Adhesiveness, N.s	Stringiness, mm
F009	**0.1**	15	0.12	0.13±00	0.02±00	0.10±00	4.6±0.06
F002	**0.25**	15	0.30	0.81±0.05	0.23±0.01	0.33±0.01	8.3±0.2
F001	**0.5**	15	0.59	2.28±0.20	0.73±0.04	0.67±0.04	5.9±0.5
F003	**0.65**	15	0.77	3.23±0.07	1.04±0.02	0.75±0.1	4.7±0.7
F010	**1.0**	15	1.21	4.37±0.08	1.39±0.02	0.92±0.08	4.6±0.3





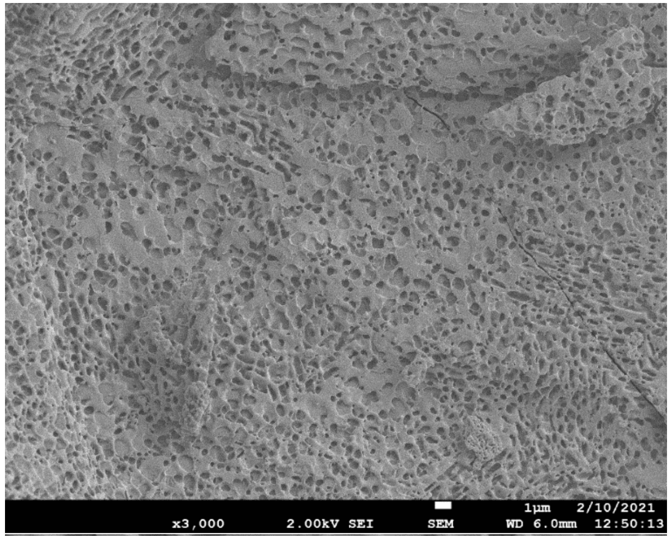
CBP 0.25%

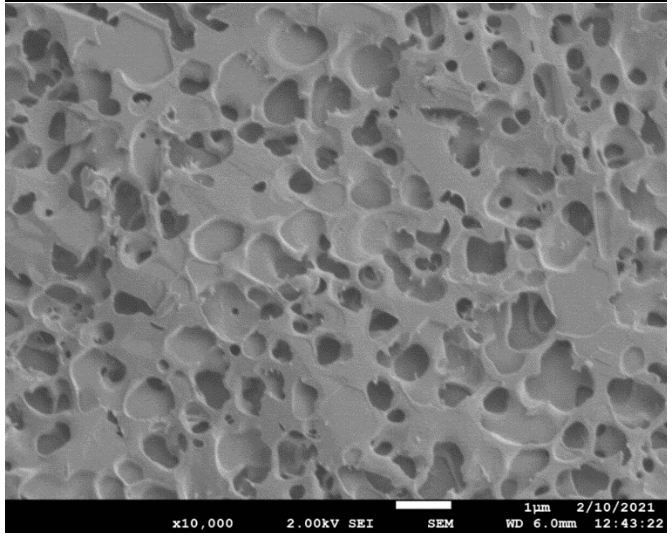


CBP 0.5%

Effect of sublimation time-temp combinations in F014

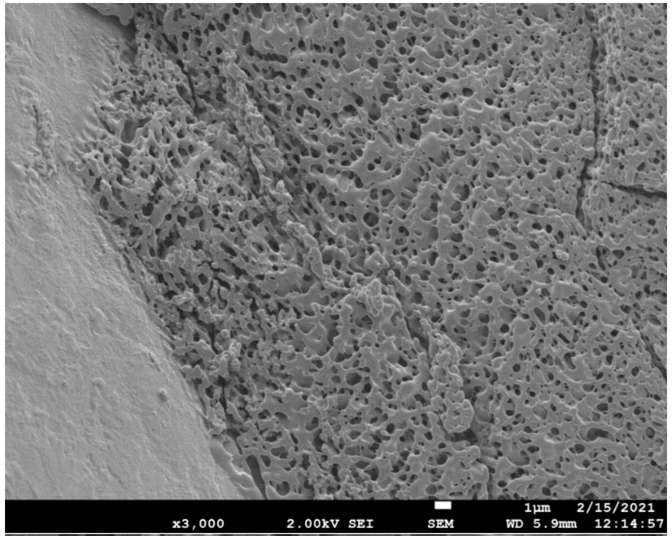
-105°C/30min

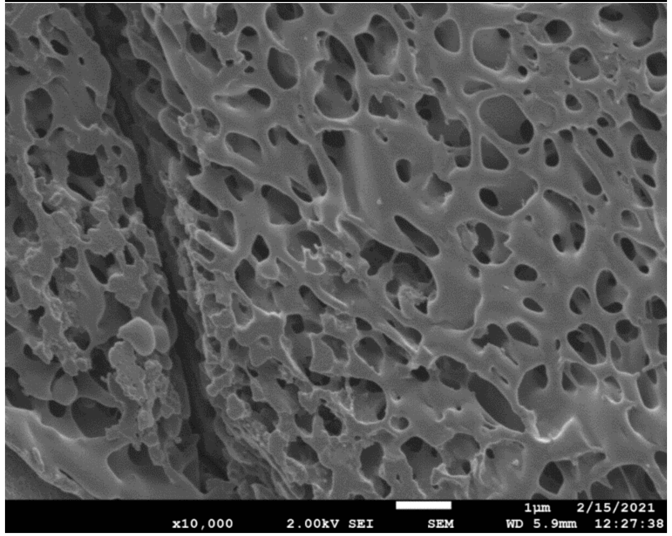




Network was partially sublimated
Pore size, shape and density were clearly identifiable

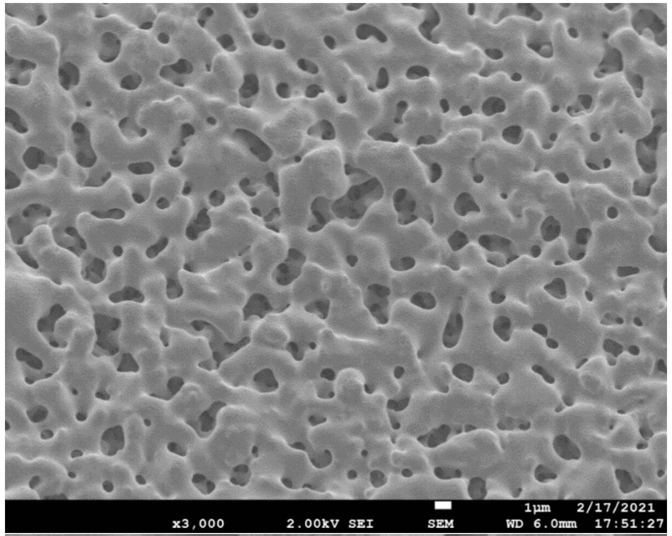
-105°C/60min

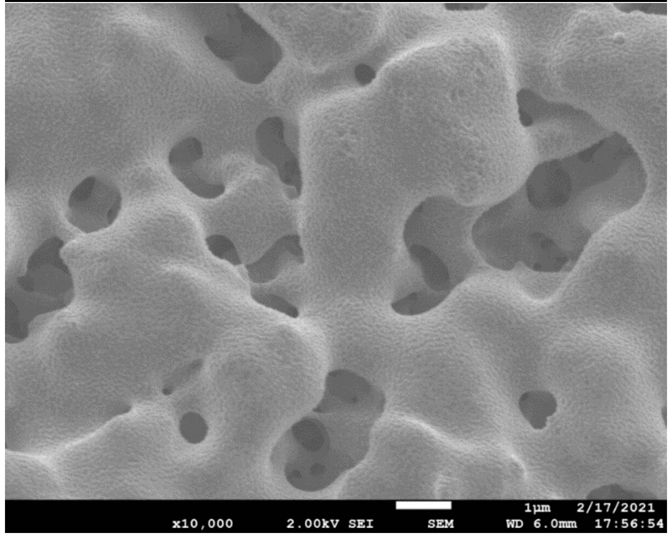




Pores were fully sublimated
Thickness of network linkages was seen to be increased

-85°C/30min

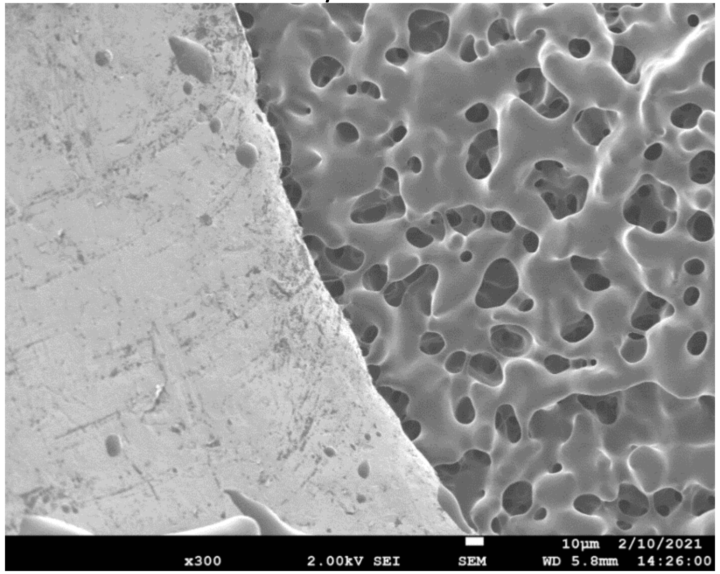


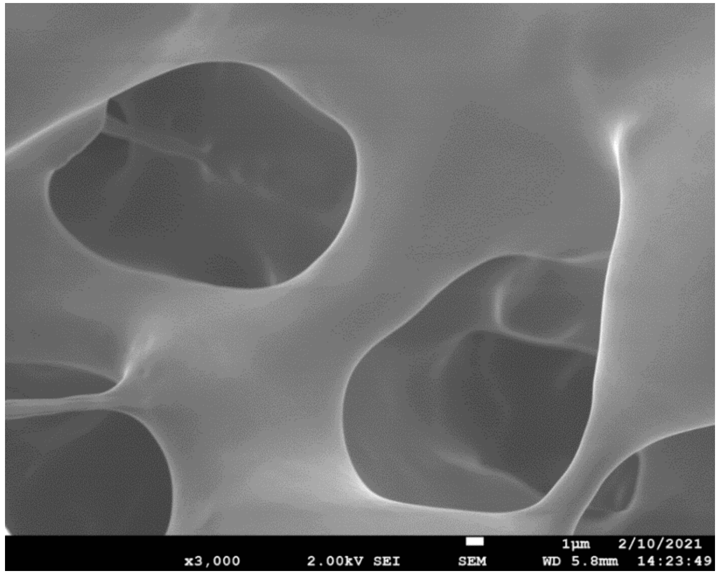


Extensive sublimation
PG in gel appeared to migrate on top layer surrounding the linkages

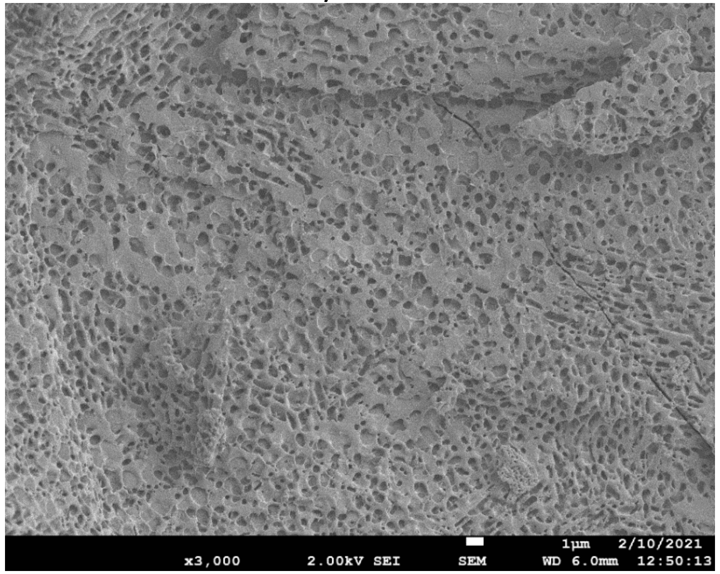
Effect of polymer concentration on gel microstructure

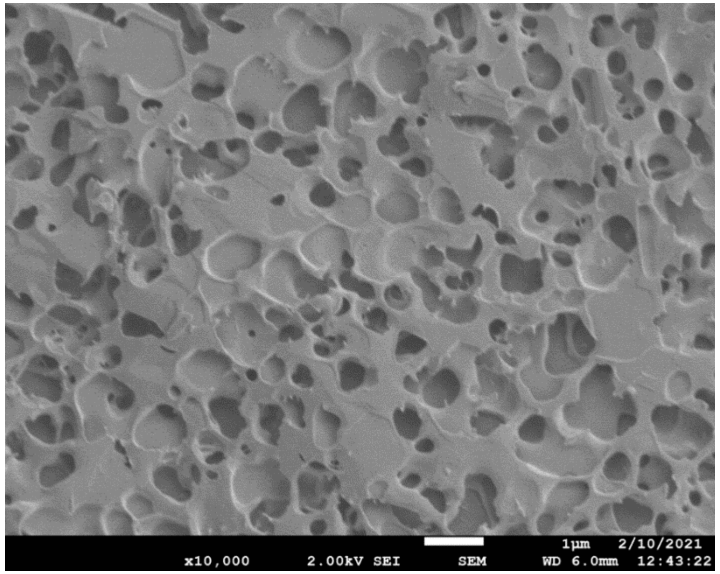
F002: 0.25% CBP, 15% PG
Sublimation: -105°C/30min





F014: 0.5% CBP, 25% PG
Sublimation: -105°C/30min





- At 0.25% CBP, highly porous gel network with larger pore size is formed
- At 0.5% CBP, microstructure is characterized with compact network with small pores of less than 1 um and high pore density

Considerations to further optimize the process

- Examining the effect of PG at specific sublimation conditions using additional control samples with and without PG
- Employment of high-pressure freezing (HPF) of samples to minimize gradient of freezing from edge to centre and pore expansion

Q3 attributes – Rheological assessment

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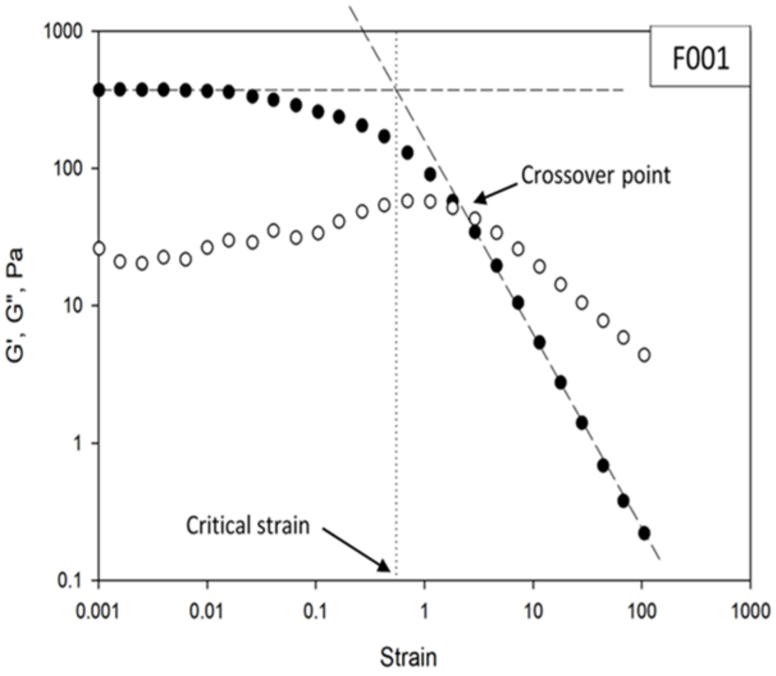
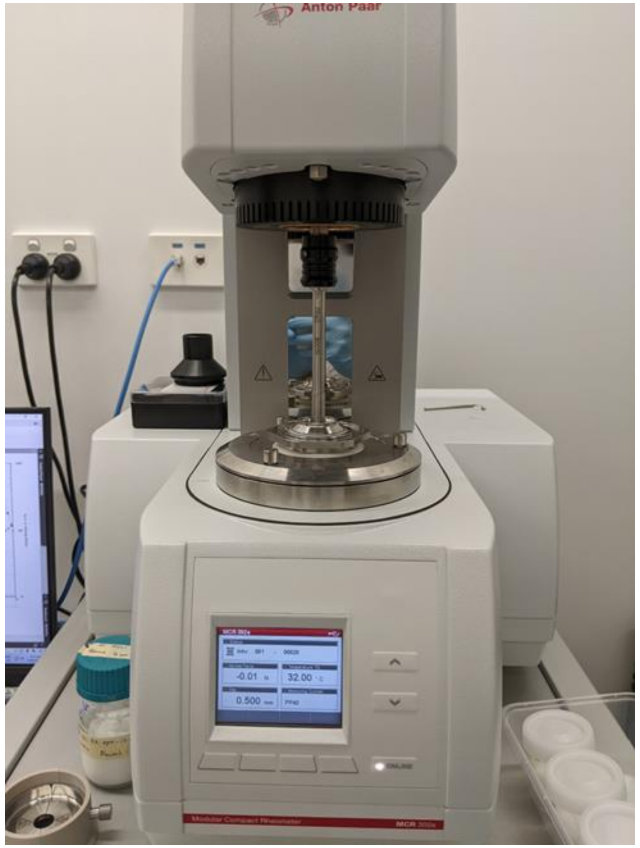
- Oscillatory rheology – strain sweep, temperature sweep
- Rotational rheology – thixotropy, appropriate model application, optimisation of gap

Geometry: **40 mm parallel**
Controlled strain: **0.001 to 100%**
Frequency: **1 Hz**
Gap: **500 µm, 100 µm, 50 µm, 25 µm**
Temperature: **23-32 °C**





Rheological parameters measured

- Viscosity - positive relationships between sensory tackiness and stickiness and negative relationships between spreadability and oiliness.
- Storage and loss modulus (G') and (G")
- Tan -G′ is greater than G″ this shows that the sample is a viscoelastic solid ($\tan\delta < 1$) whereas when G′′>G′, samples are more viscous than elastic
- Viscoelastic region (LVR)
- Zero shear ($\eta 0$)– related to first product pick-up i.e. when the user first encounters the product's inherent strength
- Infinite shear viscosity ($\eta\ \infty$) - is a measure of the friction and related to in use product behaviour while rubbing the product into the skin and just before it disappears.
- Yield stress - good measure to understand the spreadability and ease of application.
- Temperature sweep to changes in the critical rheological parameters between a specified temperature range to simulate temperatures that can be achieved while use of the product on the skin by rubbing.

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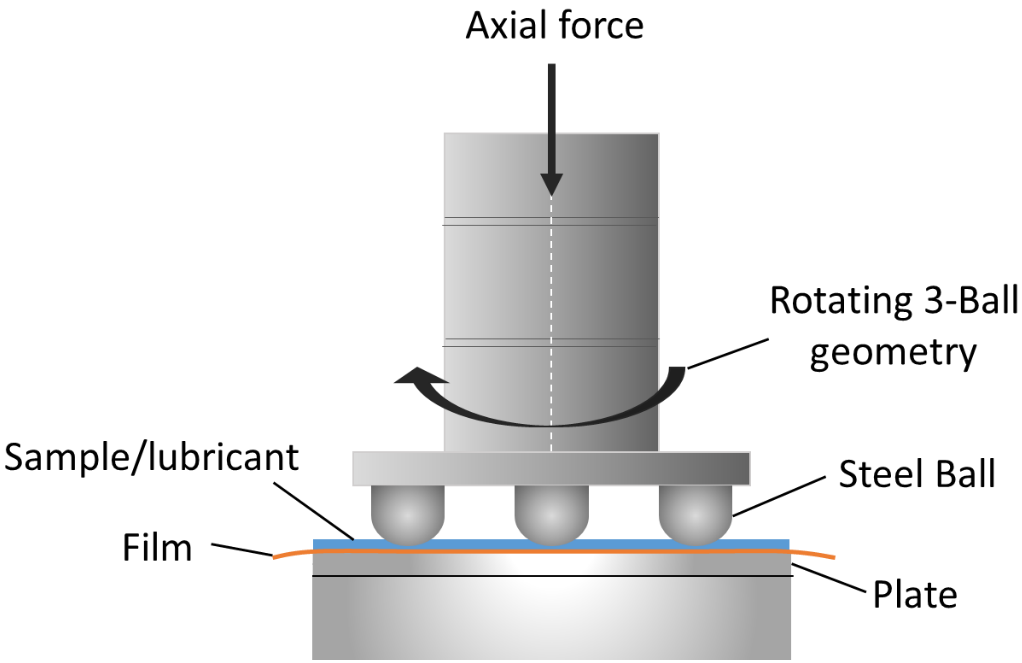
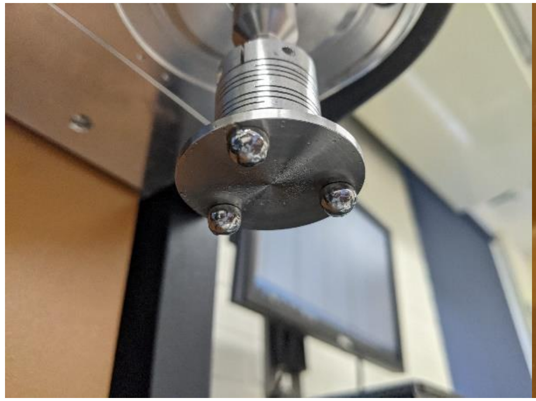
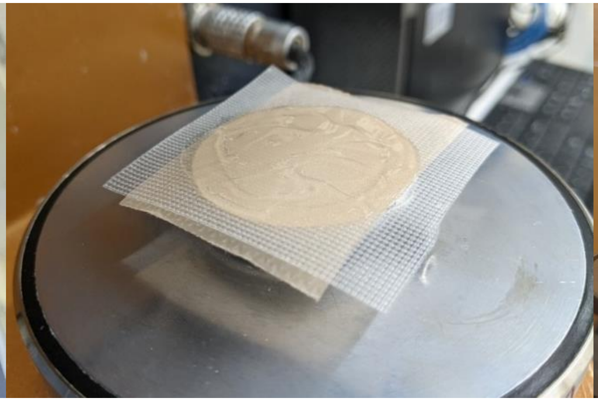
Tribology flow sweep for assessment of lubrication property

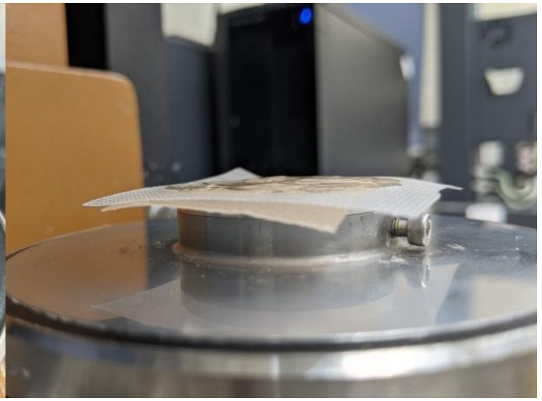


Flow sweep method:

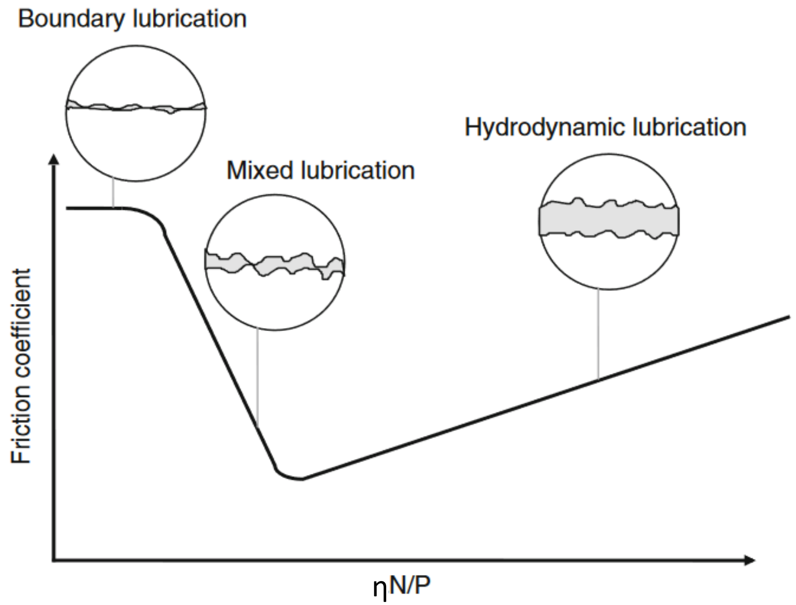
- Geometry: 3-ball on plate
- Sample: 0.4 mL to form thin film after even spread
- Axial/load force: Set to 4.5 N, sufficient to generate friction up to hydrodynamic region without damaging the film substrate
- Geometry sliding velocity: 0.1-100 rad/s

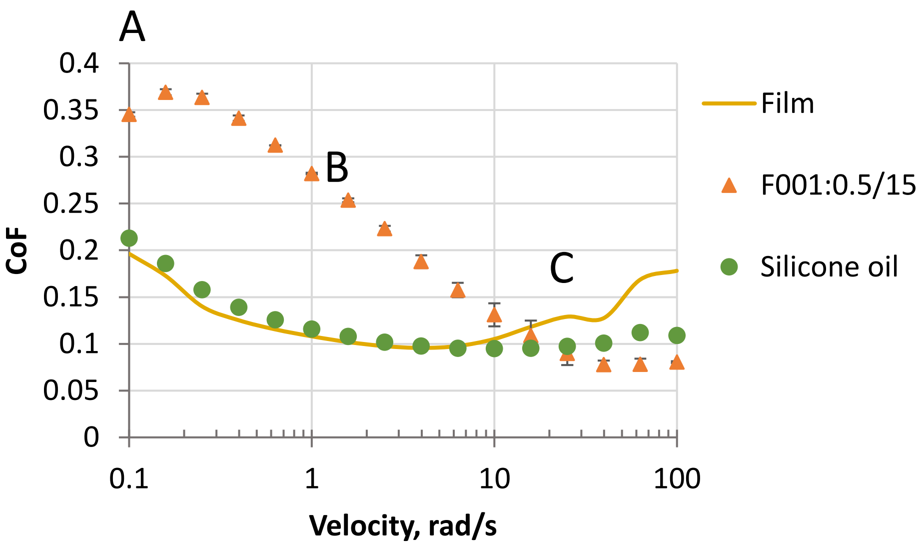






Schematic of Stribeck curve:





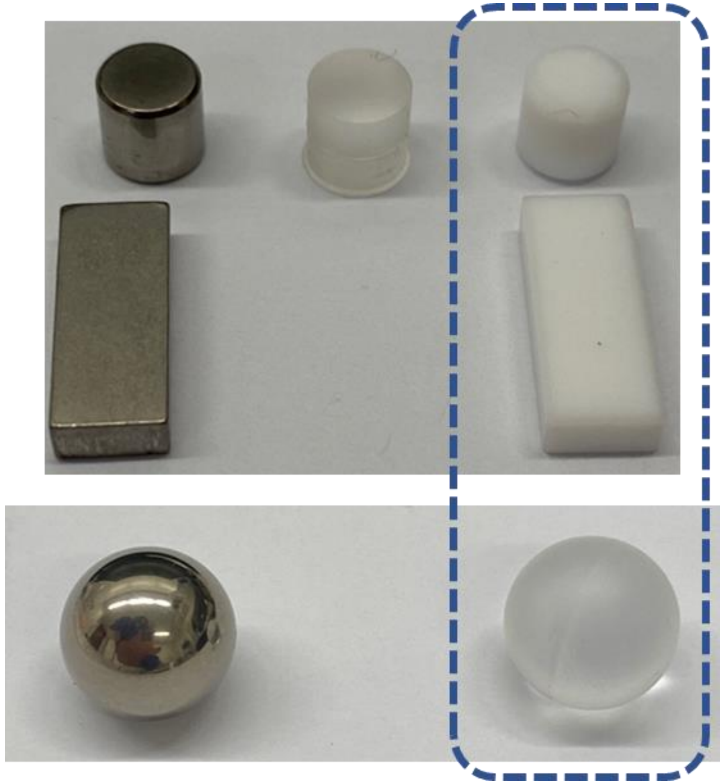
- The **Stribeck curve** is an overall view of friction variation in the entire range of lubrication, including the hydrodynamic (full film), mixed, and boundary lubrication regimes
- (A) Boundary lubrication regime: Friction mainly due to rubbing of surfaces with some boundary layers
- (C) Full-film/hydrodynamic lubrication regime: Friction mainly caused by viscous dissipation
- (B) Mixed lubrication regime: Summation of the friction due to viscous shear and that due to contact and sliding in the boundary lubrication

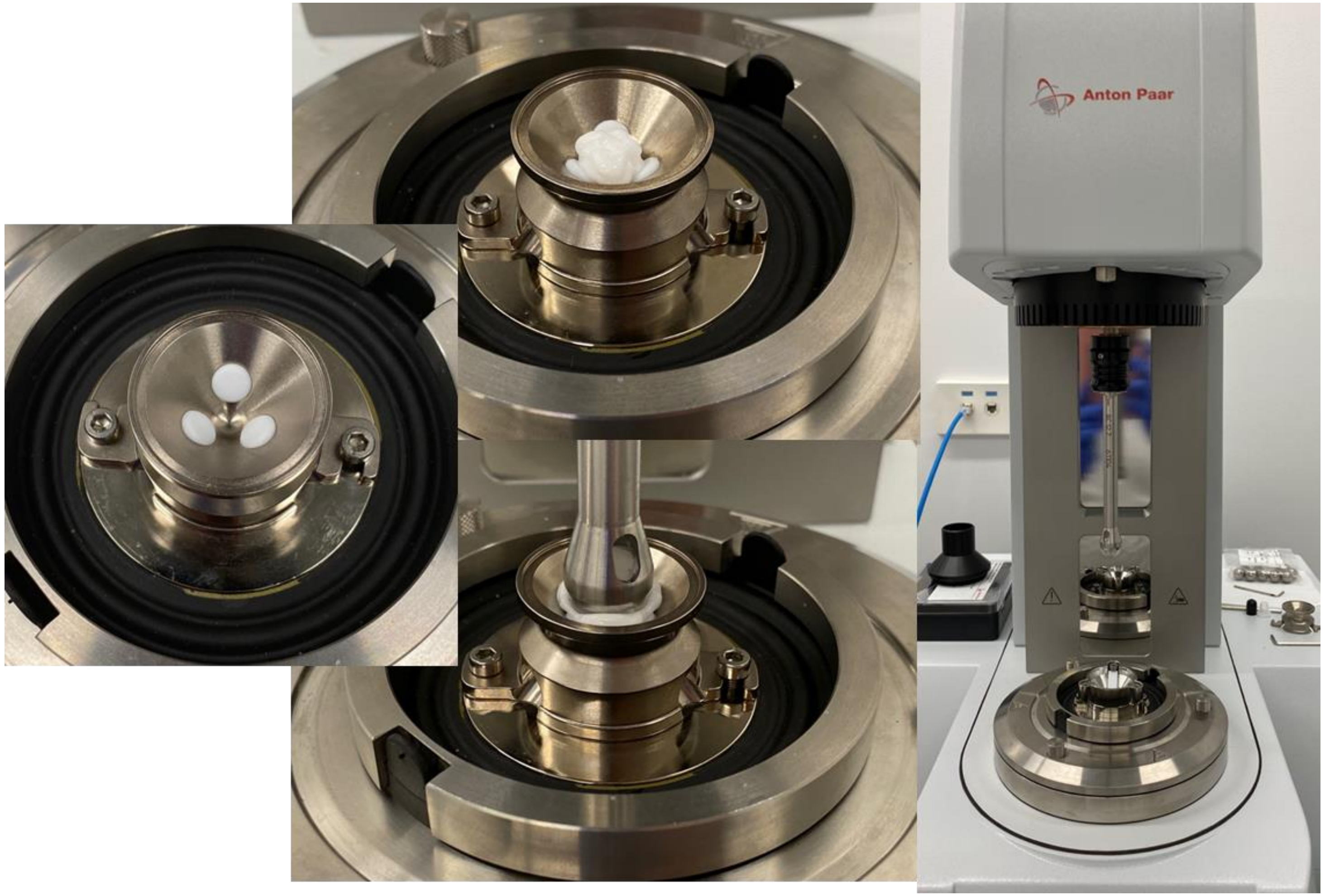
Q3 Characterization techniques – Tribology

- **Tribology – method development; Sample volume, applied force, holding time/sliding speed will be optimised**

  - Glass ball (12.7 mm of diameter; 0.55 µm of surface roughness) and
  - PDMS pins (6 mm of diameter and high; 0.17 µm of surface roughness)

→ Represent human finger and skin for friction measurement





Cooling sensation In vitro FLIR experimental set up

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- Model: FLIR T840
- Thermal sensitivity: <30 mK at 30°C (42° lens)
- Resolution: 464×348 (161,472 pixels)
- Accuracy: ±2°C (±3.6°F) or ±2% of reading
- Emissivity: 0.98

Experimental Details and Set up

- Formulations used: gels F001 and F004
- 100 µL formulation applied inside a O ring placed on excised human skin
- This set up was placed on a heat pad to maintain surface temperature of approximately 32˚C.
- Thermal images was captured at 0, 1, 2, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 mins

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Statistical grouping and correlation of rheological, textural, and tribological attributes of gels

Considerations

- Correlation between the attributes from different analyses
- Similarity between the formulations and role of components
- Order of formulations in a specific parameter signifying respective sensory attribute

Dosage form	Sensory attributes	Classification as per Senses	Instrumental technique	Q3 attributes
Gels	Odour	Smell	Gas chromatography/e-nose	Evaporation of volatiles
	Colour	Visual	Spectrophotometer/Visual assessment	Uniformity and consistency
	Grittiness/ Texture	Hybrid	Microscopy/Tribometer	Particle size and hardness, crystal habit and aspect ratio, coefficient of friction
	Quick drying	Touch	Gravimetric/TEWL measurement/Corneometer	Evaporation of volatiles and drying, Hydration
	Speed of absorption	Touch	Time for absorption	Infinite shear viscosity/?
	Greasiness (non-greasy)	Touch	Sebumeter/Tribometer	Coefficient of friction
	Stringiness	Hybrid	Rheometer/Texture analyser/Tribometer	Viscosity, yield stress, coefficient of friction
	Cooling sensation	Touch	Infrared camera and thermocouple/Gravimetric/ TEWL measurement/TiVi/ Corneometer	Evaporation of volatiles and drying, Hydration
	Firmness/Stickiness	Hybrid	Texture analyser/Rheometer	Zero shear viscosity, adhesiveness and yield stress
	Spreadability	Touch	Rheometer	Zero shear viscosity, Yield stress

Touch | Visual | Hearing | Smell | Hybrid

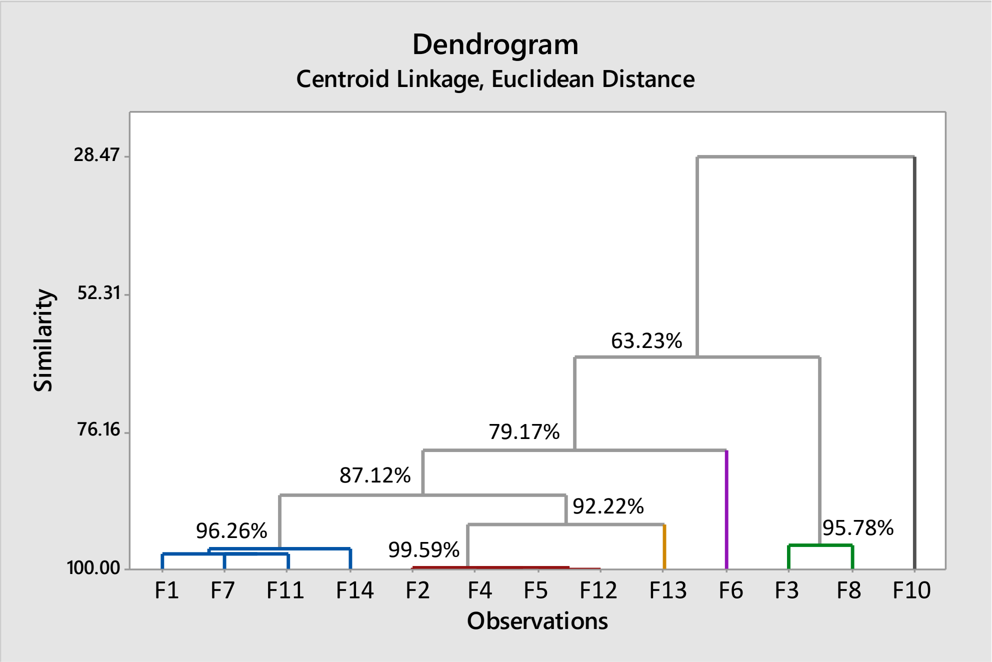
Handling of the product	Application phase	Residual film properties
1) Immediate Cooling sensation 2) Firmness 3) Adhesiveness /Stickiness 4) Stringiness	1) Spreadability 2) Slipperiness 3) Grittiness 4) Evaporative cooling sensation	1) Rate of absorption & drying 2) Residual stickiness 3) Residual greasiness 4) Residual film

Pearson correlation between the material attributes

		Rotational rheology				Oscillatory rheology			TPA		
		Zero-shear viscosity η_0	Yield stress τ_y	Infinite-shear viscosity η_∞	Consistency index K	Plateau elastic modulus G'_p	Yield stress τ_y	Plateau loss tangent $Tan\delta_p$	Firmness	Work of shear	Adhesiveness
Rotational rheology	τ_y	0.959 ***									
	η_∞	0.919 ***	0.934 ***								
	K	0.960 ***	0.998 ***	0.942 ***							
Oscillatory rheology	G'_p	0.780 ***	0.873 ***	0.738 ***	0.870 ***						
	τ_y	0.857 ***	0.947 ***	0.833 ***	0.943 ***	0.968 ***					
	$Tan\delta_p$	-0.430 ***	-0.486 ***	-0.328 **	-0.470 ***	-0.723 ***	-0.620 ***				
TPA	Firmness	0.838 ***	0.911 ***	0.801 ***	0.907 ***	0.945 ***	0.954 ***	-0.730 ***			
	Work of shear	0.837 ***	0.917 ***	0.802 ***	0.913 ***	0.950 ***	0.965 ***	-0.709 ***	0.997 ***		
	Adhesiveness	0.692 ***	0.772 ***	0.657 ***	0.772 ***	0.896 ***	0.865 ***	-0.774 ***	0.935 ***	0.934 ***	
	Stringiness	-0.552 ***	-0.596 ***	-0.494 ***	-0.581 ***	-0.555 ***	-0.597 ***	0.272 *	-0.505 ***	-0.498 ***	-0.274 *

*** $p<0.01$; ** $p<0.05$; * $p<0.1$

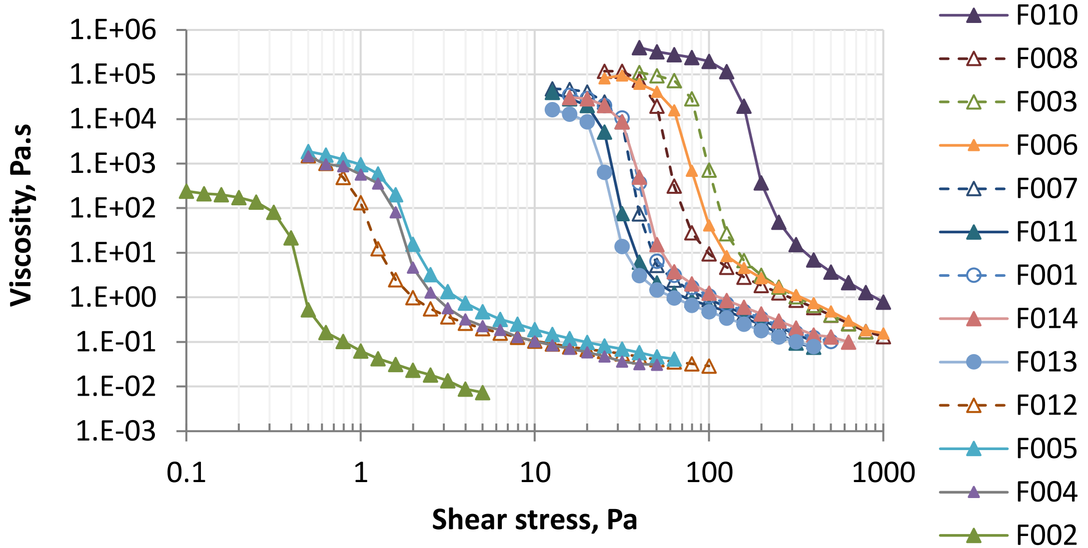
Clustering of zero-shear viscosity (η_0) observations



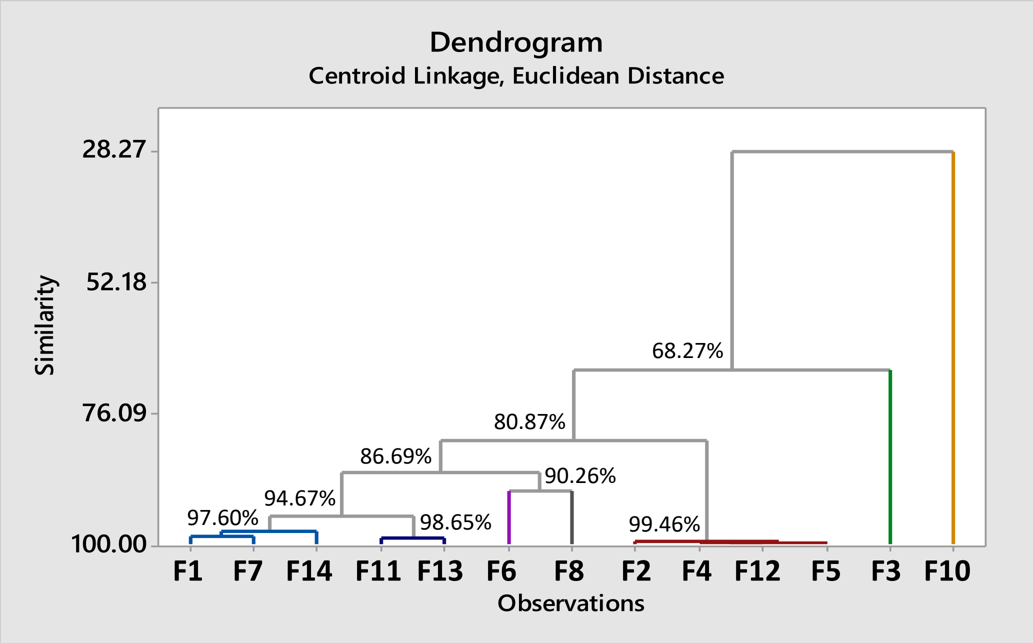
Formulation	CBP, %	PG, %	Ethanol, %	η_0	ANOVA Grouping (p<0.05)						Clustering (≥95% similarity)
F010	1.0	15	--	407409	A						C1
F008	0.5	50	--	224916		B					C2
F003	0.65	15	--	218582		B					
F006	0.5	35	--	125598			C				C3
F007	0.5	15	20	81902			C	D			C4
F011	0.5	15	35	77858			C	D			
F001	0.5	15	--	68880			C	D			
F014	0.5	25	--	57609				D	E		
F013	0.5	15	10	33655				D	E	F	C5
F012	0.5	15	50	2407					E	F	C6
F005	0.25	35	--	2390					E	F	
F004	0.25	25	--	1706					E	F	
F002	0.25	15	--	319						F	

Zero-shear viscosity: Consistency (Firmness, spreadability, adhesiveness)

- Combined effect of polymer and PG concentrations



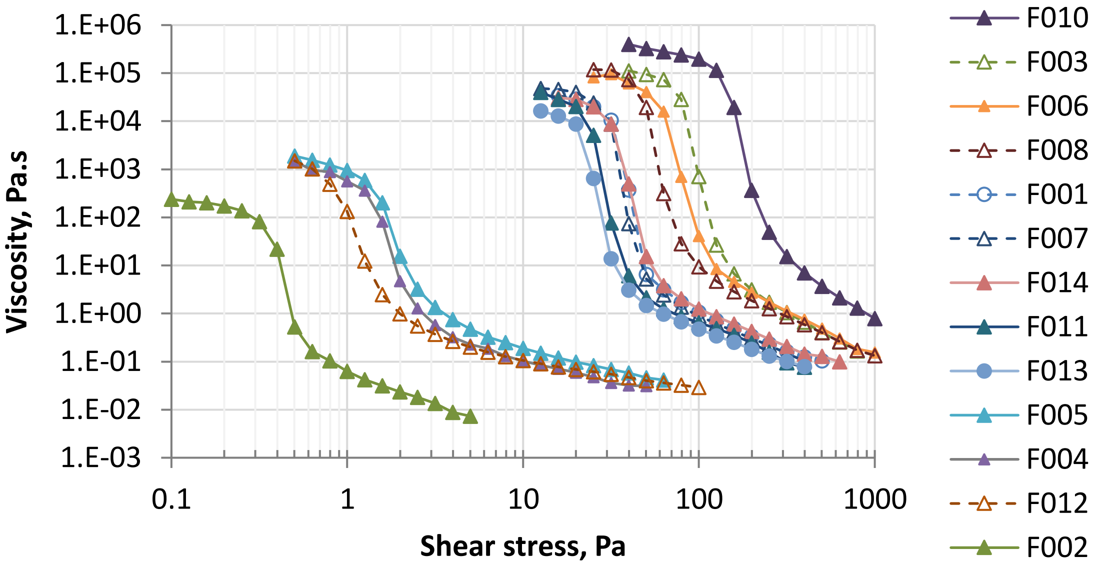
Clustering of yield stress (τ_y) observations



Formulation	CBP, %	PG, %	Ethanol, %	τ_y	ANOVA Grouping (p<0.05)							Clustering (≥95% similarity)
F010	1.0	15	--	139.33	A							C1
F003	0.65	15	--	76.59		B						C2
F006	0.5	35	--	56.88			C					C3
F008	0.5	50	--	45.86				D				C4
F001	0.5	15	--	31.78					E			C5
F007	0.5	15	20	31.39					E			
F014	0.5	25	--	29.52					E	F		
F011	0.5	15	35	22.85					E	F		C6
F013	0.5	15	10	21.56						F		
F005	0.25	35	--	1.39							G	C7
F004	0.25	25	--	1.21							G	
F012	0.5	15	50	0.96							G	
F002	0.25	15	--	0.32							G	

Yield stress: Firmness, spreadability, adhesiveness & stringiness (cohesive strength), consistency

- Dominating effect of higher polymer concentration followed by PG content



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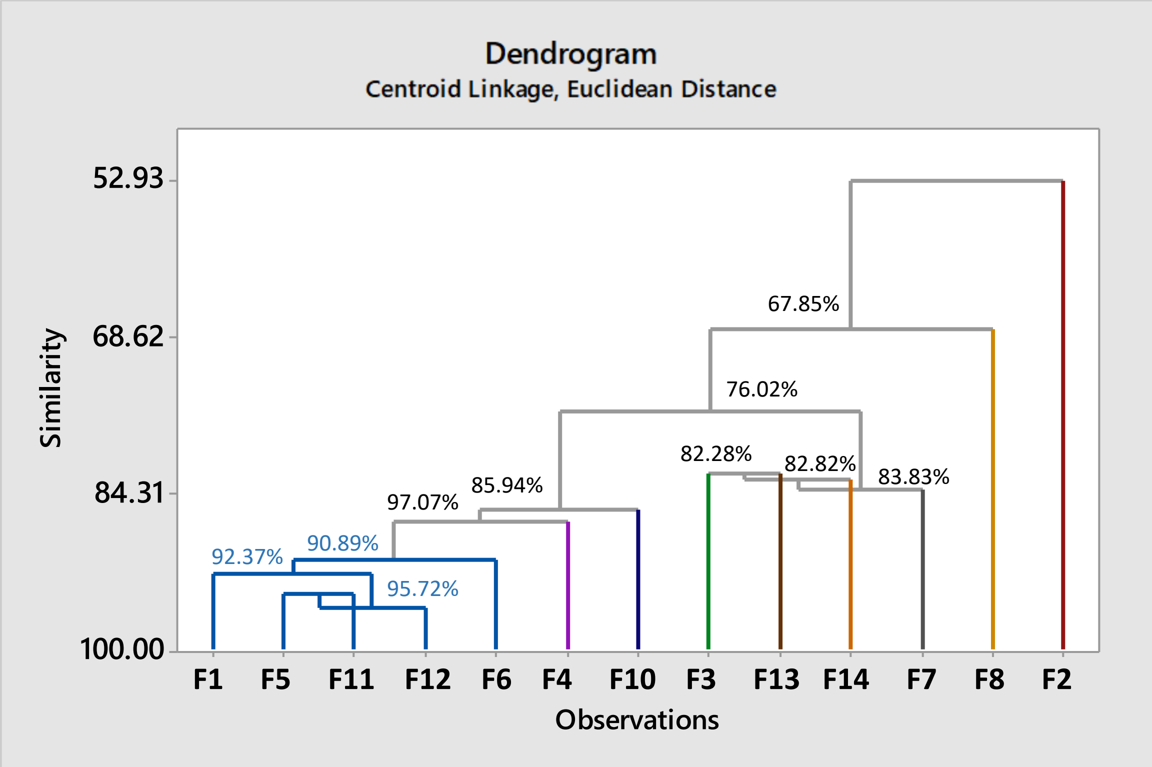
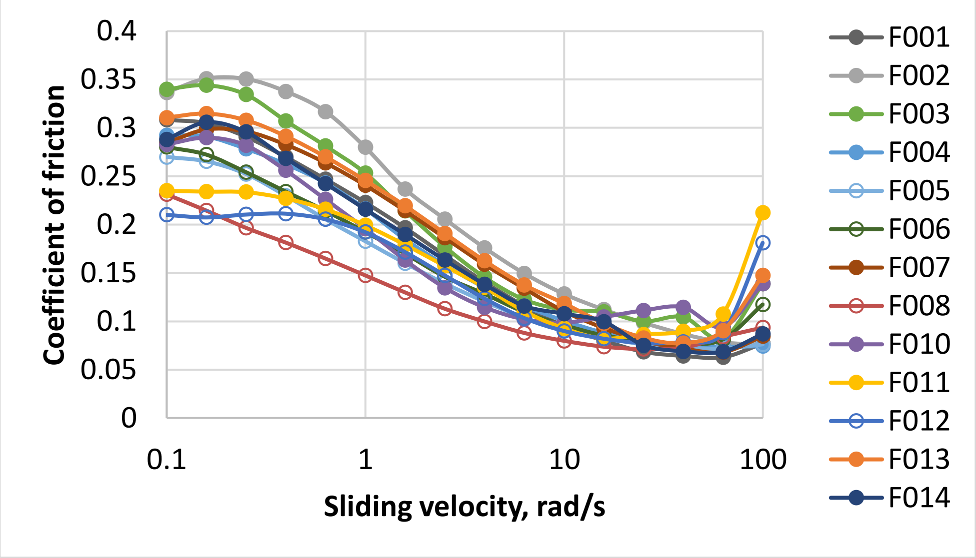
Cof measures at 10 rad/s

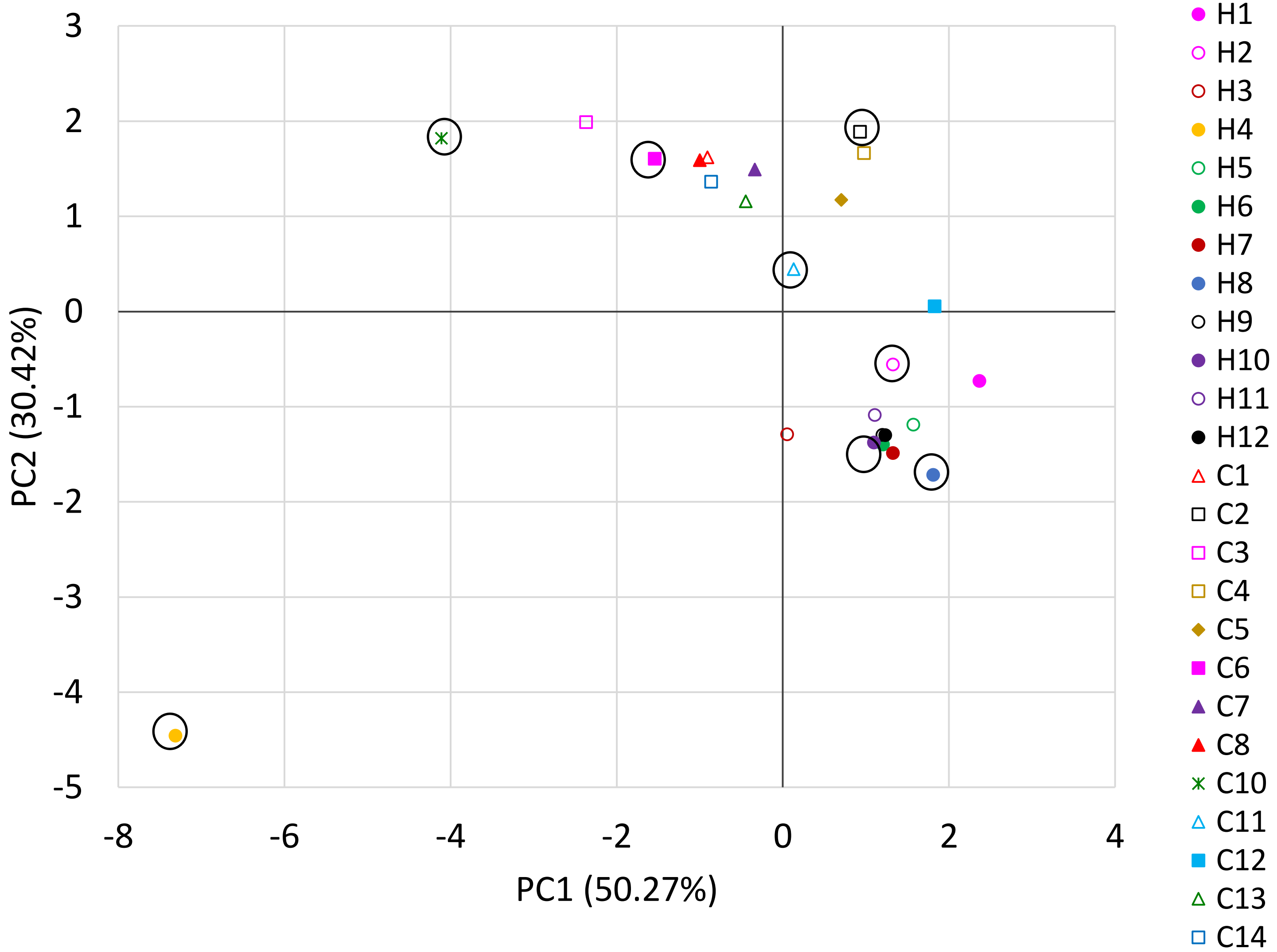


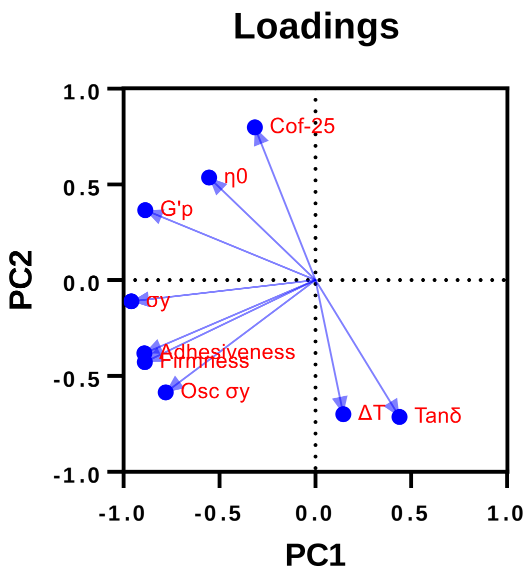
Formulation	CBP, %	PG, %	Ethanol, %	CoF at 10 rad/s	ANOVA Grouping (p<0.05)							Clustering (≥90% similarity)
F002	0.25	15	--	0.128	A							C1
F013	0.5	15	10	0.119	A	B						C2
F003	0.65	15	--	0.112		B	C					C3
F007	0.5	15	20	0.110		B	C	D				C4
F014	0.5	25	--	0.108		B	C	D	E			C5
F004	0.25	25	--	0.101			C	D	E	F		C6
F010	1.0	15	--	0.099			C	D	E	F		C7
F006	0.5	35	--	0.096				D	E	F		
F001	0.5	15	--	0.095					E	F	G	
F011	0.5	15	35	0.093					E	F	G	C8
F005	0.25	35	--	0.091						F	G	
F012	0.5	15	50	0.090						F	G	
F008	0.5	50	--	0.080							G	C9



- *Friction profile in mixed region*: Truncation of the curves with shear dissipation
- Formulations followed quite similar order

PCA of all gel formulations

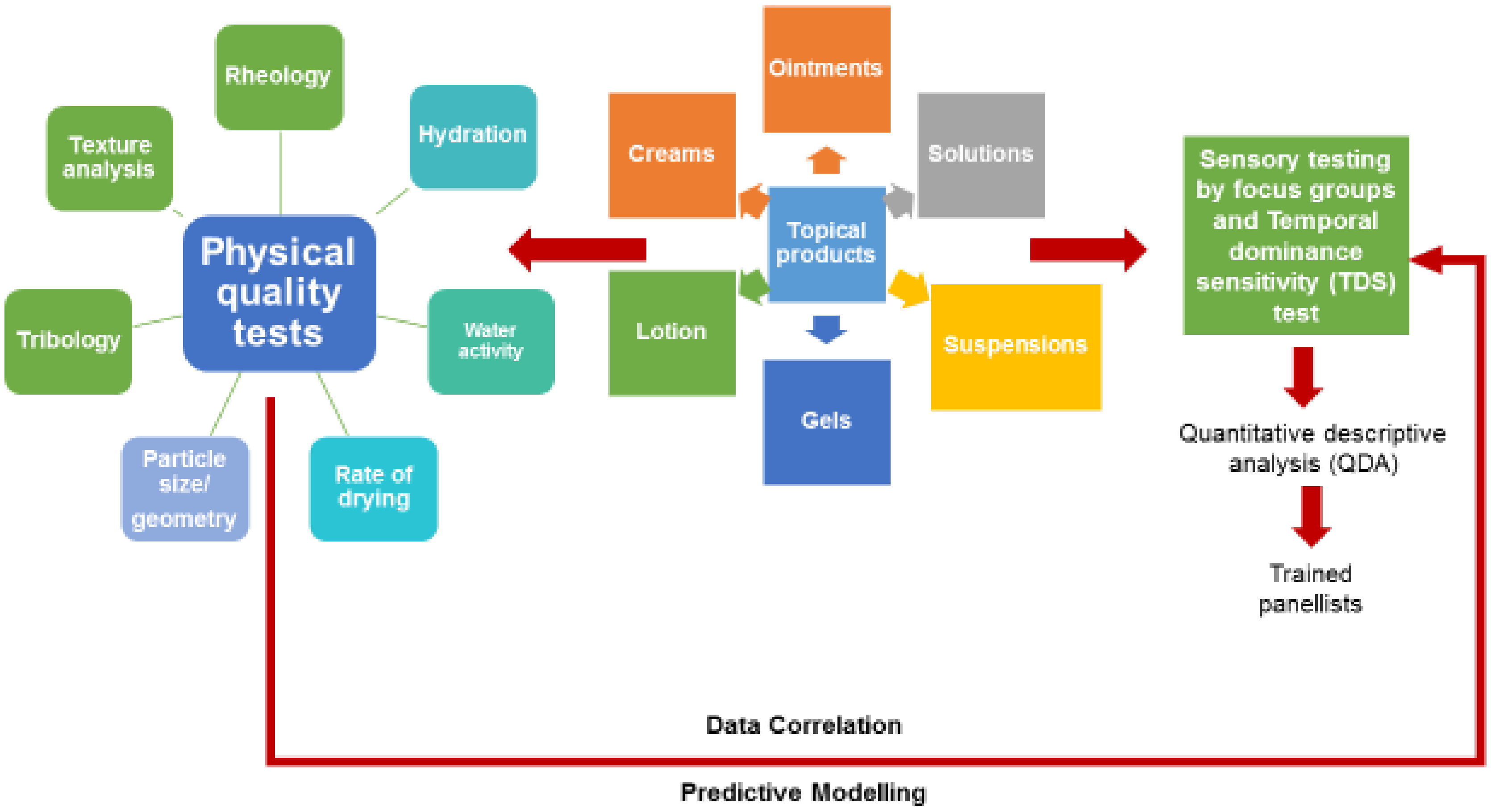




- PCA performed on gels, considering the textural, rheological, tribological, and cooling sensation attributes to find similarity and grouping between the formulations
- PCA allows to simplify the scattering on two newly generated principal components out of considered attributes

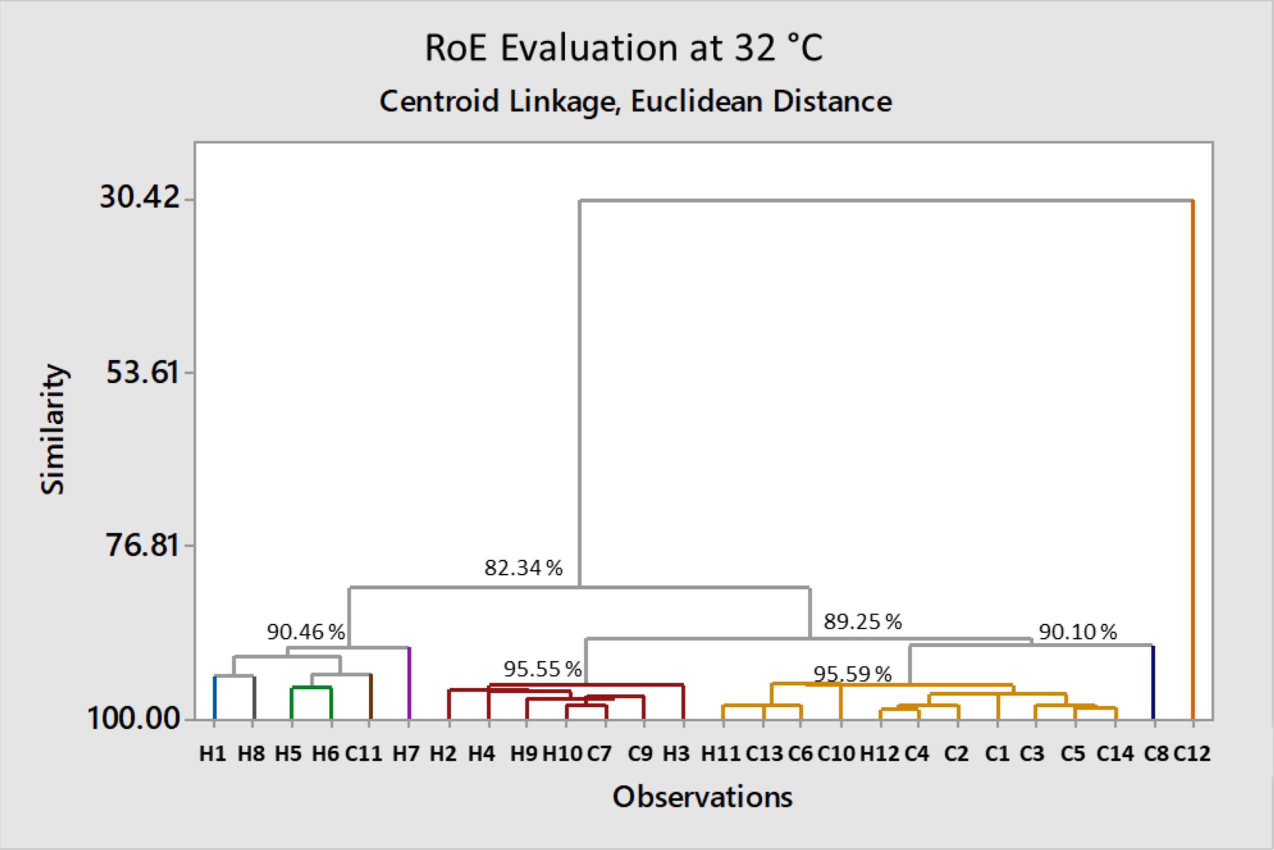
Correlations between Q3 and sensory attributes

Overall Approach



Case study
Gel Cooling Sensation
Sensory Evaluation - In Vivo Volunteers

Gels: Over all Clustering



	Zero-shear viscosity η_0	Yield stress τ_y	Consistency index K	Plateau elastic modulus G'_p	Plateau loss tangent $Tan\delta_p$	Cooling sensation (ΔT)
HEC	-0.044 *	-0.176 *	-0.198 *	-0.234 *	0.495 *	0.23 *
CBP	-0.25 *	-0.24 *	-0.242 *	-0.421 *	0.681 ***	0.721 ****

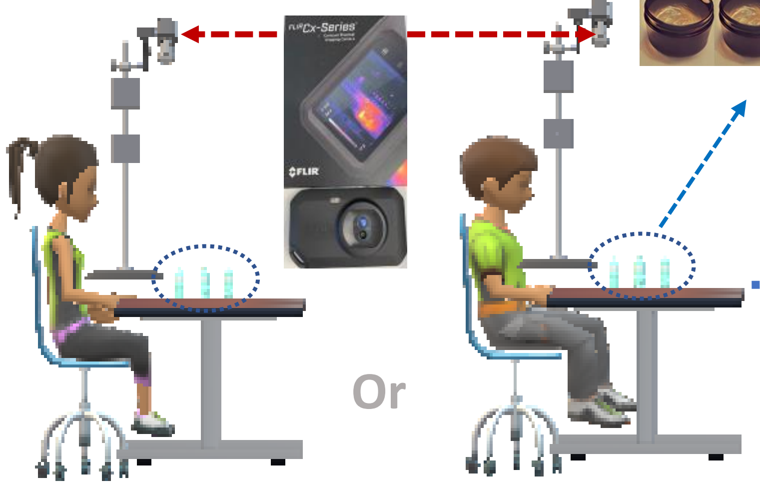
**** p<0.01; *** p<0.05; ** p<0.1; * p>0.1

Formulation	Polymer, %	PG, %	Ethanol/iso-propanol, %	Mean temp diff (°C)
CBP12	0.5	15	50	25.23045
HEC01	1	15	20	14.34028
HEC08	2.2	15	50	13.28011
HEC07	2.2	15	45	12.985
HEC05	2.2	15	25	12.18227
HEC06	2.2	15	30	11.43415
CBP11	0.5	15	35	10.68753
HEC03	3	15	20	9.958432
HEC02	2.2	15	20	9.311328
CBP09	0.1	15	--	9.082201
HEC09	2.2	20	20	8.769099
CBP07	0.5	15	20	8.513817
HEC04	5	15	20	8.424113
HEC10	2.2	30	20	8.120083
HEC11	2.2	40	20	6.866832
CBP10	1	15	--	6.778394
CBP13	0.5	15	10	6.746772
CBP06	0.5	35	--	6.335894
CBP01	0.5	15	--	5.880307
CBP02	0.25	15	--	5.653175
HEC12	2.2	50	20	5.46889
CBP04	0.25	25	--	5.300702
CBP03	0.65	15	--	4.859788
CBP14	0.5	25	--	4.652692
CBP05	0.25	35	--	4.480218
CBP08	0.5	50	--	3.02541

Setting up the vivo test

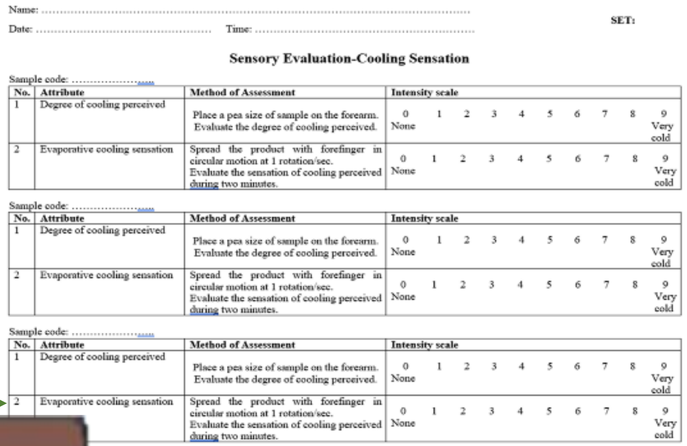
3 coded gel samples (2+1)

FLIR-Thermal camera



Trained panellists

- Positive displacement pipettes used for sample volume uniformity
- Rubbing alcohol and cotton pads applied to clean the determined skin area prior to evaluate gel cooling sensation



Name: ....
SET:
Date: .... Time: ....

Sensory Evaluation-Cooling Sensation

Sample code: ....

No.	Attribute	Method of Assessment	Intensity scale
1	Degree of cooling perceived	Place a pea size of sample on the forearm. Evaluate the degree of cooling perceived.	0 None 1 2 3 4 5 6 7 8 9 Very cold
2	Evaporative cooling sensation	Spread the product with forefinger in circular motion at 1 rotation/sec. Evaluate the sensation of cooling perceived during two minutes.	0 None 1 2 3 4 5 6 7 8 9 Very cold

Sample code: ....

No.	Attribute	Method of Assessment	Intensity scale
1	Degree of cooling perceived	Place a pea size of sample on the forearm. Evaluate the degree of cooling perceived.	0 None 1 2 3 4 5 6 7 8 9 Very cold
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Sample code: ....

No.	Attribute	Method of Assessment	Intensity scale
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2	Evaporative cooling sensation	Spread the product with forefinger in circular motion at 1 rotation/sec. Evaluate the sensation of cooling perceived during two minutes.	0 None 1 2 3 4 5 6 7 8 9 Very cold

Immediate cooling sensation:

Place a pea size of sample on the forearm.

Evaluate the degree of cooling perceived for the **first 15 s**

Evaporative cooling sensation:

Spread the product with forefinger in circular motion at 1 rotation/sec.

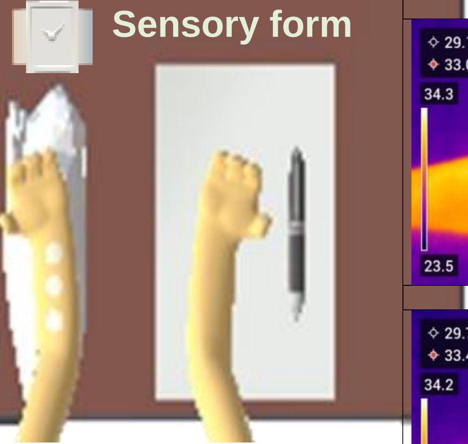
Evaluate the sensation of cooling perceived during **2 min**

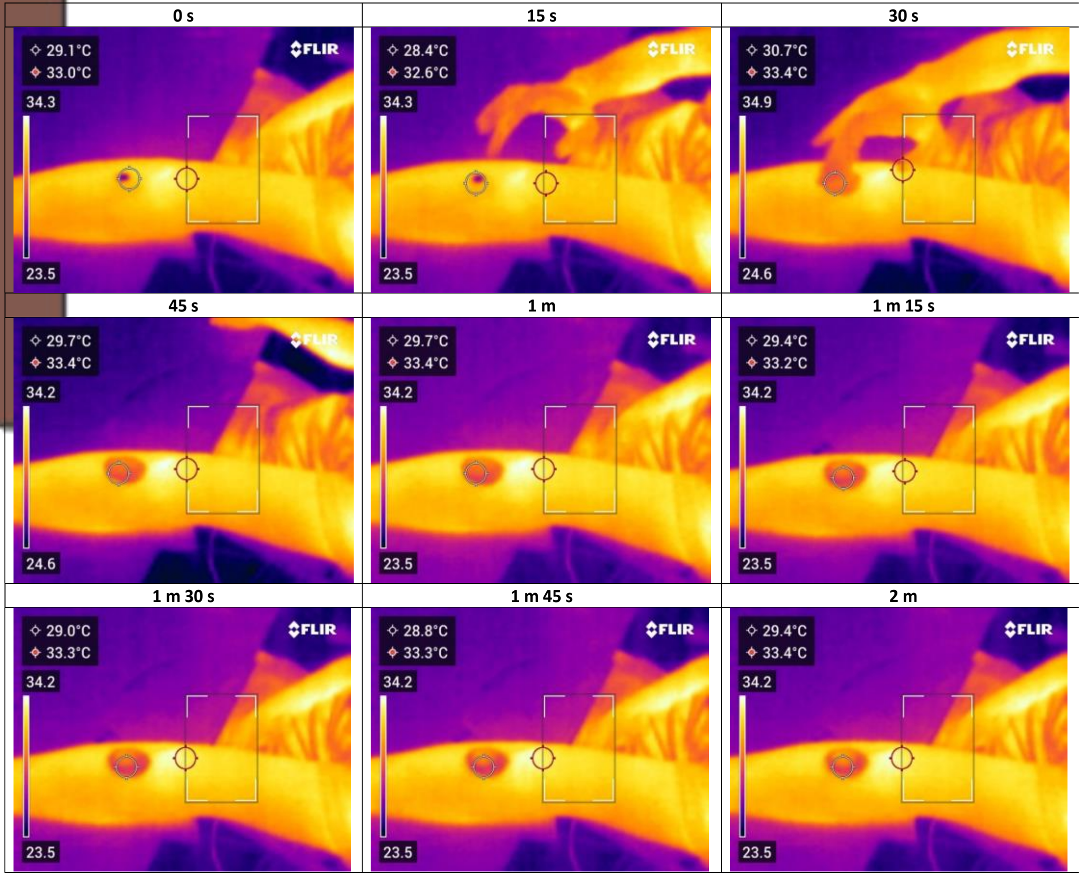
Stopwatch

At one time slot, one coded sample was applied at pea size to a marked **area (12.5 cm²)** of forearm skin

3 different areas were determined for 3 coded samples

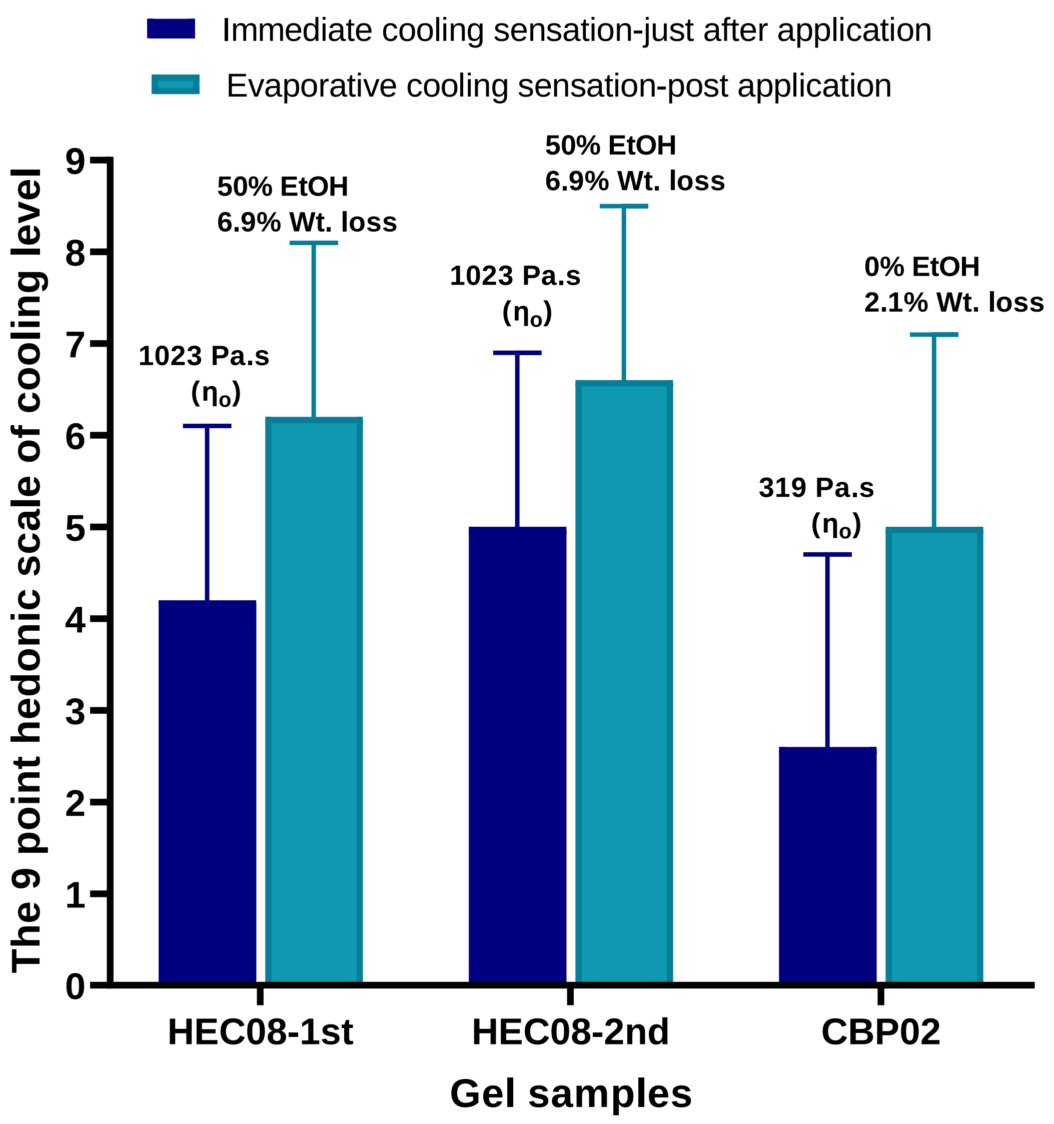
Sensory form





Pictures were captured every 15 s by FLIR thermal camera to record the temperature of the treated and untreated skin area with the gel sample

Sensory evaluation of cooling sensation in vivo

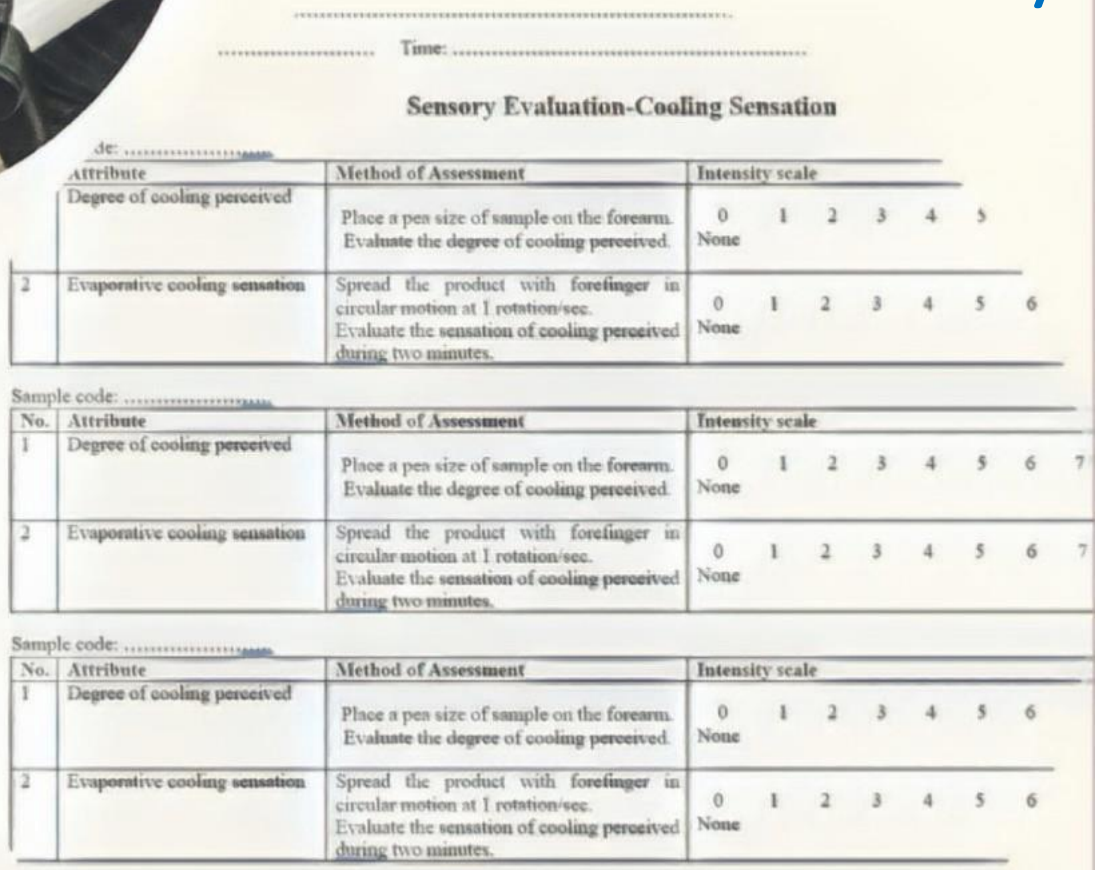


- Cooling sensation appears to be the result of both – solvent evaporation and differences in inherent sample temperature
- Evaporative cooling effect is seen prominent with high ethanol content in the samples
- That followed by the high polymer containing variants – having high elasticity that possibly slows down the heat transfer

FLIR Cx-Series Compact Thermal Imaging Camera

Compared with

The 9-point Hedonic Scale for Sensory evaluation



.... Time: ....

Sensory Evaluation-Cooling Sensation

...de: ....

No.	Attribute	Method of Assessment	Intensity scale
	Degree of cooling perceived	Place a pea size of sample on the forearm. Evaluate the degree of cooling perceived.	0 None 1 2 3 4 5
2	Evaporative cooling sensation	Spread the product with forefinger in circular motion at 1 rotation/sec. Evaluate the sensation of cooling perceived during two minutes.	0 None 1 2 3 4 5 6

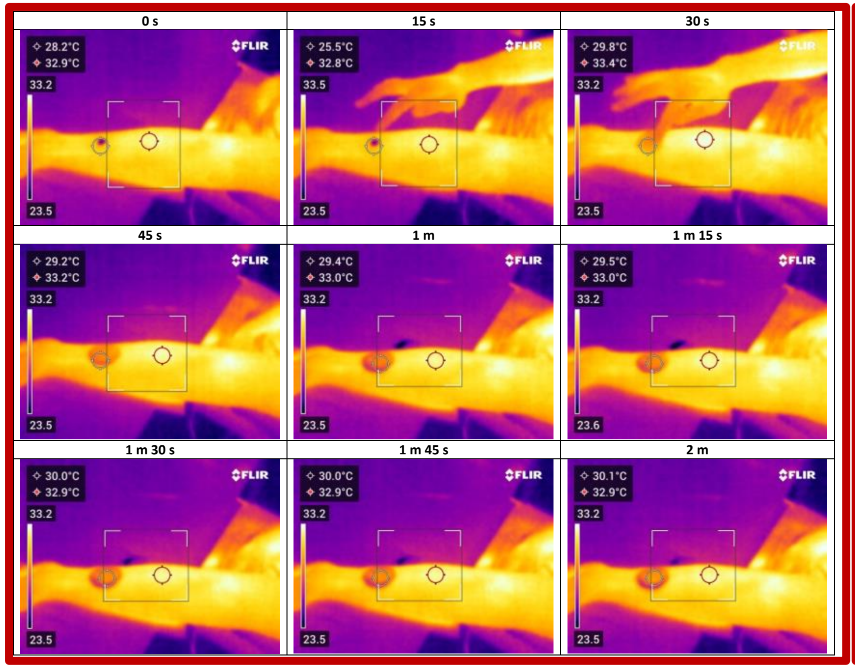
Sample code: ....

No.	Attribute	Method of Assessment	Intensity scale
1	Degree of cooling perceived	Place a pea size of sample on the forearm. Evaluate the degree of cooling perceived.	0 None 1 2 3 4 5 6 7
2	Evaporative cooling sensation	Spread the product with forefinger in circular motion at 1 rotation/sec. Evaluate the sensation of cooling perceived during two minutes.	0 None 1 2 3 4 5 6 7

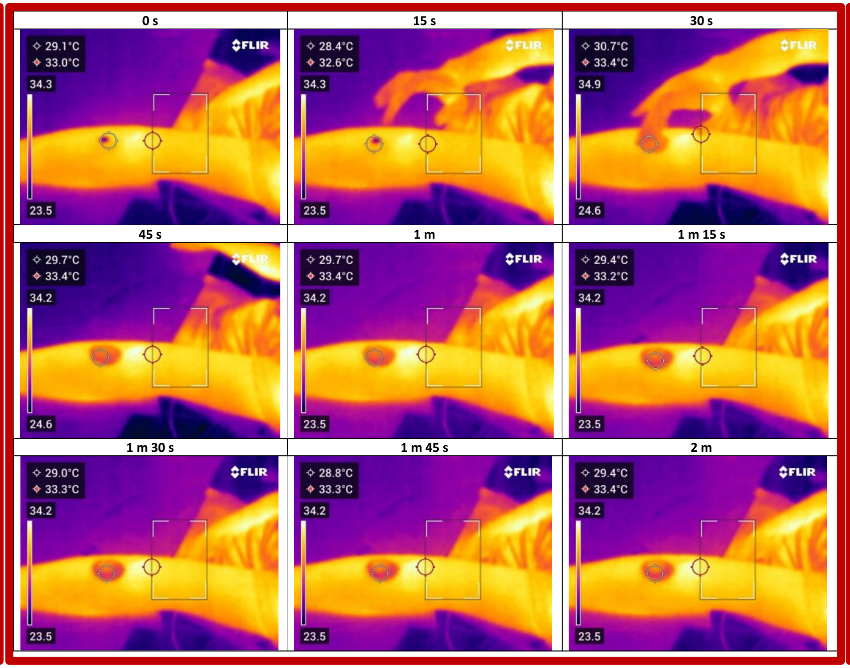
Sample code: ....

No.	Attribute	Method of Assessment	Intensity scale
1	Degree of cooling perceived	Place a pea size of sample on the forearm. Evaluate the degree of cooling perceived.	0 None 1 2 3 4 5 6
2	Evaporative cooling sensation	Spread the product with forefinger in circular motion at 1 rotation/sec. Evaluate the sensation of cooling perceived during two minutes.	0 None 1 2 3 4 5 6

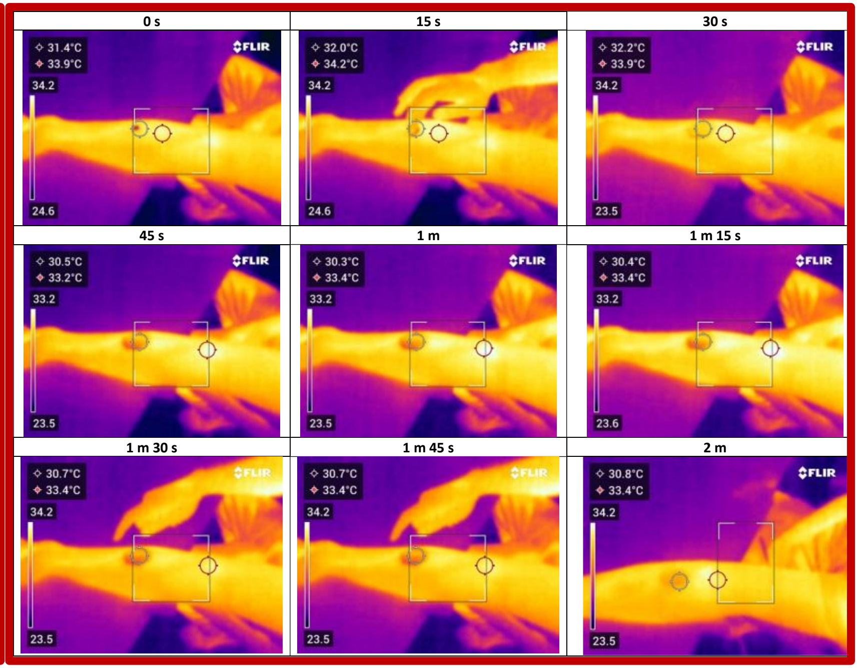
Captured Pictures & Skin Temperature Recorded by The FLIR Thermal Camera



HEC08-1st



HEC08-2nd

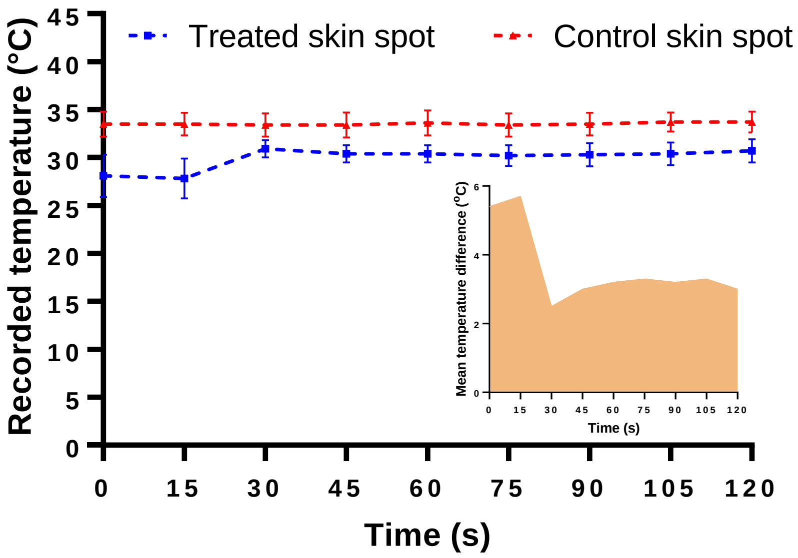


CBP02

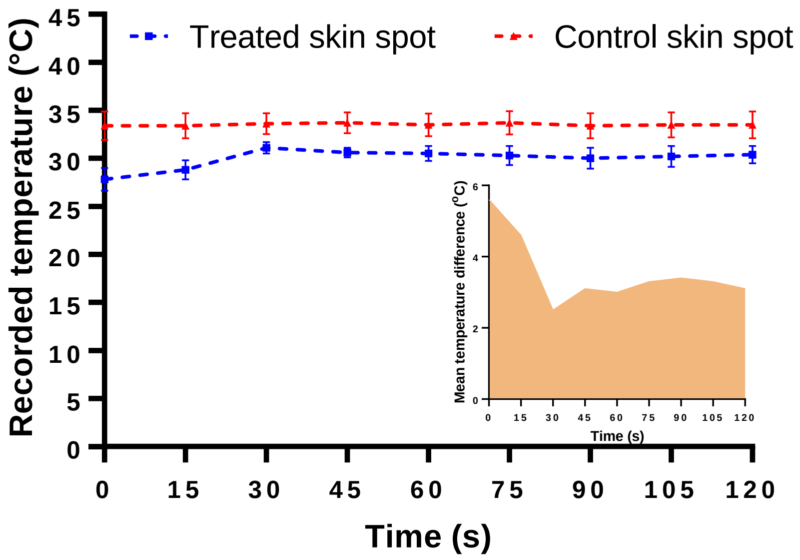
Temperature difference of skin recorded by the FLUX thermal camera

Gel samples	Time (s)	Skin temperature (^oC)		
		Treated skin spot	Control skin spot	Mean Temp. difference
HEC08-1st	0	28.1 ± 2.2	33.5 ± 1.3	5.4
	15	27.8 ± 2.1	33.5 ± 1.2	5.7
	30	30.9 ± 0.9	33.4 ± 1.2	2.5
	45	30.4 ± 0.9	33.4 ± 1.3	3.0
	60	30.4 ± 0.9	33.6 ± 1.3	3.2
	75	30.2 ± 1.1	33.4 ± 1.2	3.3
	90	30.3 ± 1.2	33.5 ± 1.2	3.2
	105	30.4 ± 1.2	33.7 ± 1.0	3.3
	120	30.7 ± 1.2	33.7 ± 1.1	3.0
HEC08-2nd	0	27.8 ± 1.2	33.4 ± 1.5	5.6
	15	28.8 ± 1.0	33.4 ± 1.3	4.6
	30	31.1 ± 0.6	33.6 ± 1.1	2.5
	45	30.6 ± 0.5	33.7 ± 1.1	3.1
	60	30.5 ± 0.8	33.5 ± 1.2	3.0
	75	30.3 ± 1.0	33.7 ± 1.2	3.3
	90	30.0 ± 1.1	33.4 ± 1.3	3.4
	105	30.2 ± 1.1	33.5 ± 1.3	3.3
	120	30.4 ± 0.9	33.5 ± 1.4	3.1
CBP02	0	30.1 ± 1.4	33.9 ± 1.3	3.8
	15	31.0 ± 1.6	33.9 ± 1.4	2.9
	30	31.8 ± 1.3	33.6 ± 1.4	1.8
	45	31.1 ± 1.4	33.3 ± 1.4	2.2
	60	31.1 ± 1.1	33.5 ± 1.2	2.4
	75	30.9 ± 1.2	33.4 ± 1.2	2.6
	90	30.9 ± 1.3	33.3 ± 1.3	2.4
	105	30.7 ± 1.1	33.7 ± 1.3	3.0
	120	31.1 ± 0.7	33.4 ± 1.4	2.3

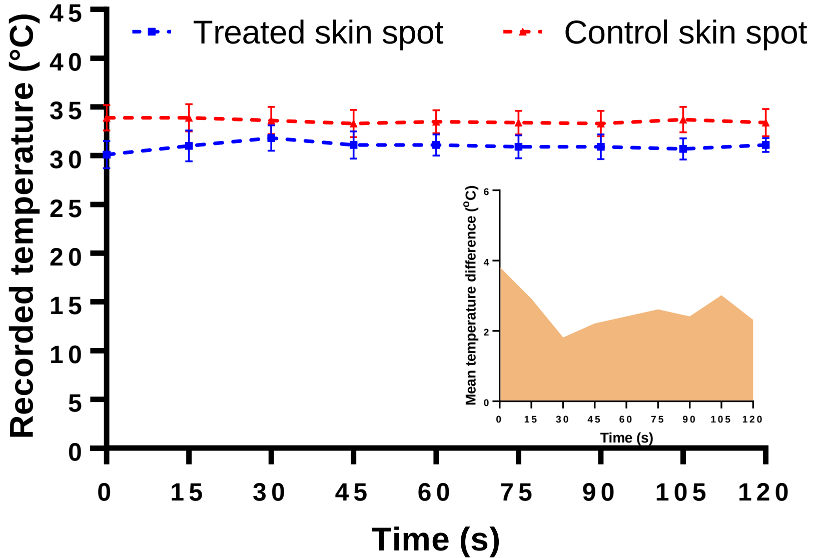
HEC08-1st



HEC08-2nd



CBP02



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