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Investigating the Impact of Variation in Carbomer Homopolymer Type C (Carbopol® 980) Concentration on Diclofenac Sodium Gels' Microstructure and Skin Permeation

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PURPOSE

Most topical drug products deliver drugs to the local tissue with complex absorption dynamics. Historically, bioequivalence (BE) between a prospective generic product and the corresponding reference standard has been established using comparative clinical endpoint BE studies, which are often time consuming and expensive. Qualitative (Q1) and quantitative (Q2) differences in inactive ingredients can impact a product's physicochemical and structural (Q3) characteristics and performance. The aim of this study was to assess the impact of Q2 changes in carbomer homopolymer Type C (Carbopol® 980) on Q3 characteristics, *in vitro* drug release (IVRT) and *in vitro* skin permeation (IVPT) of the active ingredient from diclofenac sodium (DS) from topical gels.

METHOD(S)

Formulation development

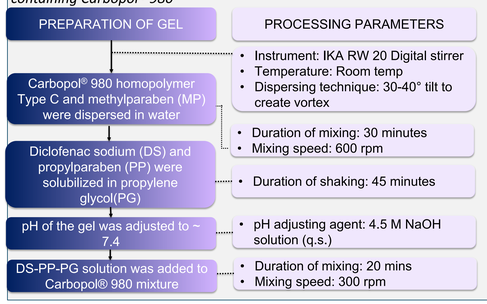
Gels of diclofenac sodium (0.5% w/w) were prepared using a manufacturing process after optimizing several parameters as depicted in Figure 1. The gels were formulated by varying the concentrations of Carbopol® 980, the main gelling agent as seen in Table 1. Formulation 1 (F1) containing 0.5% w/w of Carbopol® 980 was considered as the reference gel. The concentrations of Carbopol® 980 in the rest of formulations represent ± 10% (F3, F4) and ± 25% (F2, F5) quantitative differences compared to 0.5% w/w in the reference gel.

Table 1. Formulation composition of diclofenac sodium (DS) topical gels containing Carbopol® 980 (Propylene glycol: PG; Methylparaben: MP; Propylparaben: PP)

Formulation	Carbopol® 980 (% w/w)	Diclofenac Sodium (% w/w)	PG (% w/w)	MP (% w/w)	PP (% w/w)	4.5 M NaOH	Water (% w/w)
F2 (-25%)	0.375	0.5	15	0.1	0.03	q.s.	q.s. to 100
F3 (-10%)	0.45	0.5	15	0.1	0.03	q.s.	q.s. to 100
F1 (reference)	0.5	0.5	15	0.1	0.03	q.s.	q.s. to 100
F4 (+10%)	0.55	0.5	15	0.1	0.03	q.s.	q.s. to 100
F5 (+25%)	0.625	0.5	15	0.1	0.03	q.s.	q.s. to 100

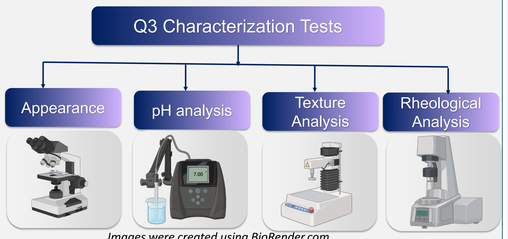
**Drug strength was selected based on the solubility of diclofenac in PG and water. The 0.5% concentration ensured that DS was completely dissolved in the gels.*

Figure 1. Manufacturing method of diclofenac sodium topical gels containing Carbopol® 980



Assessment of microstructural properties (Q3)

Visual appearance, optical microscopy, pH, texture analysis, specific gravity and rheological properties were assessed (n=3) to identify potential differences in Q3 properties between the modified gels compared to the reference gel.



Images were created using BioRender.com

Performance test

The reference gel and modified gels were assessed for in vitro drug release and in vitro skin permeation (Table 2) using vertical diffusion cells. Drug in the IVRT and IVPT receptor solution was quantified by High-Performance Liquid Chromatography-Ultraviolet (HPLC-UV).

Table 2. IVRT (top) and IVPT (bottom) study conditions

IVRT	
Gel formulation	F1, F2, F3, F4, F5
Receptor solution	Phosphate-buffered saline pH 7.4
Replicates per formulation	6 cells per formulation
Sampling volume	200 µL
Membrane	Versapor 0.45 µm
Sample time points	45 min, 1.5, 2.25, 3, 3.75 and 4.5 h
IVPT	
Gel formulation	F1, F2 and F5
Receptor solution	Phosphate-buffered saline pH 7.4
Donor and replicates	3 donors and 4 replicates per formulation
Sampling volume	Full receptor solution sampling
Skin	Dermatomed human skin
Sample time points	0, 0.5, 1, 2, 4, 6, 8, 12, 20 and 24 h

RESULT(S)

Q3 characterization tests

- **Visual and microscopic imaging** showed clear, crystal-free stable gels (F1-F5) (Figures 2 and 3).
- The **pH** of the gels was monitored, and the change was found to be minimal over 7 days (Table 3).
- **Specific gravity** was similar across all gels (Table 4).

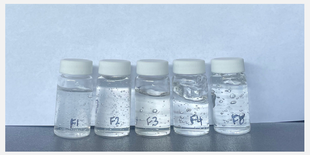


Figure 2. Diclofenac sodium (DS) topical gels F1-F5

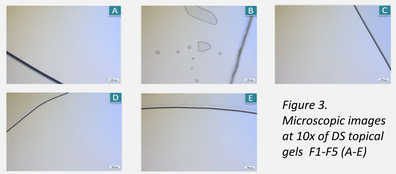


Figure 3. Microscopic images at 10x of DS topical gels F1-F5 (A-E)

Gel	pH measured in triplicate		Net increase in 7 days
	Day 1	Day 7	
F2	7.12 ± 0.00	7.13 ± 0.01	0.01
F3	7.19 ± 0.00	7.24 ± 0.00	0.05
F1	7.23 ± 0.00	7.31 ± 0.01	0.08
F4	7.24 ± 0.00	7.27 ± 0.01	0.03
F5	7.46 ± 0.01	7.48 ± 0.01	0.02

Table 3. pH measurement on day 1 and 7 after manufacturing (Mean ± SD, n = 3)

Gels	Specific Gravity
F2	1.02 ± 0.01
F3	1.01 ± 0.05
F1	1.02 ± 0.04
F4	1.01 ± 0.03
F5	1.00 ± 0.24

Table 4. Specific gravity of DS topical gels (Mean ± SD, n = 3)

- **Rheological study** results showed that all formulations depict non-Newtonian behavior:
  - Yield stress and viscosity increased with increasing concentration of Carbopol® 980 (Tables 5 and 6);
  - Gels with higher concentrations of Carbopol® 980 have higher storage modulus (Figure 4)
  - Gels with higher concentrations of Carbopol® 980 have higher crossover points, suggesting that they have stronger chemical or physical bonding making them more resistant to deformation (Figure 4)

Shear Rate (s^{-1})		Viscosity (Pa.s)				
		F2	F3	F1	F4	F5
Low shear	2	5.36 ± 0.29	10.71 ± 1.25	15.23 ± 0.38	26.68 ± 11.26	35.83 ± 13.66
Medium shear	45	0.52 ± 0.04	0.93 ± 0.10	1.28 ± 0.04	1.68 ± 0.03	2.30 ± 0.03
High shear	90	0.33 ± 0.02	0.59 ± 0.06	0.80 ± 0.02	1.04 ± 0.02	1.41 ± 0.02

Table 5. Viscosities of DS topical gels at different shear rates (Mean ± SD, n =3)

Yield Stress (Pa)	F2	F3	F1	F4	F5
	7.96 ± 0.35	16.46 ± 2.13	23.65 ± 0.61	33.34 ± 0.54	45.77 ± 4.72

Table 6. Yield stress of DS topical gels (Mean ± SD, n =3)

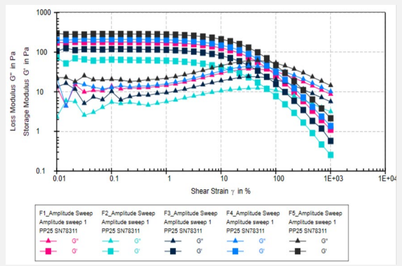


Figure 4. Amplitude sweep for F1-F5 Representative storage and Loss modulus v/s shear strain; (n = 3)

- **Texture analysis** showed that 1) Increasing Carbopol® 980 concentration decreased the adhesiveness; 2) Values of cohesiveness were comparable amongst the five formulations (Table 7)

Gel	Carbopol® 980 (% w/w)	Adhesiveness (g)	Hardness (g)	Cohesiveness (g)
F2	0.375	1.25 ± 0.21	1.1 ± 0.00	0.89 ± 0.01
F3	0.45	-7.63 ± 0.57	1.93 ± 0.61	0.87 ± 0.07
F1	0.5	-7.63 ± 0.29	1.8 ± 0.00	0.83 ± 0.01
F4	0.55	-11.6 ± 0.42	2.2 ± 0.00	0.84 ± 0.00
F5	0.625	-16.17 ± 0.25	2.8 ± 0.17	0.82 ± 0.01

Table 7. Texture profile analysis of DS topical gels (Mean ± SD, n = 3)

IVRT tests

- IVRT method was established by performing receptor solution selection, membrane screening, optimizing duration of study and sampling time points, and validated for interday and intraday precision. The method was found to reproducible with desired linearity (R2 > 0.95)

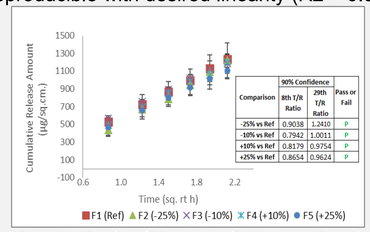


Figure 5. IVRT profiles of DS topical gels (F1-F5, Mean ± SD, n = 6)

- **IVRT** results demonstrated comparable release profiles between all gels (F1 vs F2, F1 vs F3, F1 vs F4 and F1 vs F5) (Figure 5).

IVPT tests

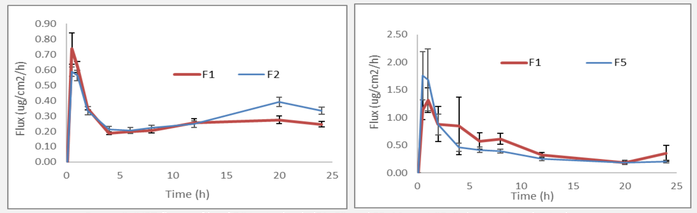


Figure 6. IVPT flux profile of DS topical gels (F1, F2 and F5, Mean ± SE, 3 donors, 4 replicates)

- **IVPT** results demonstrated comparable permeation profiles between F2 and F1, and between F5 and F1 (Figure 6).
- Dose-discrimination studies for confirming the selectivity of the IVPT method are planned for future evaluation.

CONCLUSION(S)

The current study suggests that changes in concentrations of Carbopol® 980 influenced Q3 attributes of diclofenac sodium topical gels which were observed as differences in texture and rheological profiles. Concentration changes of ± 25% in the gelling agent from the reference (0.5% w/w) influenced the Q3 properties of the gels more than the ± 10% change. However, these changes did not result in significant differences in in vitro release and skin permeation of diclofenac sodium from the topical gels. While not evaluated in this work, parallel research suggests that large differences in rheological and textural properties may impact sensorial perception. The impact of the changes in Q3 properties observed here on sensorial properties is not known.

FUNDING

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