DEVELOPMENT OF IN VITRO RELEASE TESTING AND IN VITRO PERMEATION TESTING METHODS TO STUDY THE IMPACT OF QUANTITATIVE DIFFERENCES IN CARBOMER ON THE PERFORMANCE OF DICLOFENAC SODIUM TOPICAL GELS

Seeprarani Rath[1], Mengmeng Niu[2], Priyanka Ghosh[2], Bozena Michniak-Kohn[1]

[1]Center for Dermal Research, Rutgers, the State University of New Jersey, Piscataway, NJ 08854, USA

[2]Division of Therapeutic Performance I, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA

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PURPOSE

- Differences in formulation and manufacturing process may influence the physicochemical and structural (Q3) properties of topical products.
- Changes in Q3 properties may affect drug product performance.
- Current study aim:
  - To develop and validate a discriminatory in vitro release test (IVRT) method and an in vitro permeation test (IVPT) method
  - To assess the impact of quantitative differences in carbomer on the performance of diclofenac sodium gels.

METHODS

Gel Manufacturing

- Five diclofenac sodium gels, 0.5% w/w containing propylene glycol, methylparaben, propylparaben, sodium hydroxide and water were prepared by varying the amount of gelling agent, carbomer homopolymer type C (Carbopol® 980). The Manufacturing process is shown in Figure 1.

Formulations:

- Reference: The reference formulation contained 0.5% w/w Carbopol® 980 (Table 1)
- Modified: Four modified formulations contained 0.55%w/w (reference+10%), 0.45%w/w (reference-10%), 0.625%w/w (reference+25%) and 0.375%w/w (reference-25%) of Carbopol® 980

Ingredients	Quantity (%w/w)
Diclofenac sodium	0.5
Carbopol® 980	0.5
Propylene Glycol	15
Methylparaben	0.1
Propylparaben	0.03
Sodium Hydroxide 18% w/v	Q. S to pH 7.3-7.5
Water	Q. S 100% w/w

Table 1. Formulation composition of diclofenac sodium gel, 0.5% w/w (reference formulation)

Q3 Characterization:

- Appearance, color, texture, presence of particulate matter and air bubbles, and odor were assessed visually.
- pH Measurement - Determined at room temperature using Mettler Toledo pH meter.
- Water Activity (aw) - Measured at 32°C using an Aqualab TDL2 water activity meter.
- Microstructure Analysis - Examined under a Nikon Eclipse E200 microscope equipped with an Excelis HD digital camera (1080p) using brightfield and cross-polarized light.
- Drug Content Determination - Drug extracted from the gel with methanol and quantified using a validated High-performance liquid chromatography (HPLC).
- Rheological Evaluation - Conducted at 20°C using a DHR-2 rheometer (TA Instruments) fitted with a 40 mm, 1° cone on an advanced Peltier plate.

Performance Studies

- **IVRT and IVPT studies were performed** using vertical diffusion cells (Logan Instruments) in accordance with the relevant FDA guidances [1,2].
- **Study Design:** The receptor solution, dose amount, study duration and sampling intervals were carefully chosen, and the parameters are summarized in **Table 2**.
- **IVRT Method Development**
  - **Receptor solution selection:** drug solubility was tested in the receptor solution
  - **Membrane inertness:** drug binding to the membrane was tested at at 32 ± 1 °C
- **IVRT Method Validation:** evaluation of linearity, precision, and reproducibility across 3 IVRT runs were conducted using the reference formulation
- **IVPT Sensitivity Testing:** The reference formulation was tested against a marketed formulation (Voltaren® topical gel) to confirm the sensitivity of the IVPT method
- **Pivotal IVRT and IVPT** studies were performed for all five formulations

Carbopol® 980 variation up to ± 25% appears to have no significant impact on in vitro performance of the diclofenac sodium gels used in this study

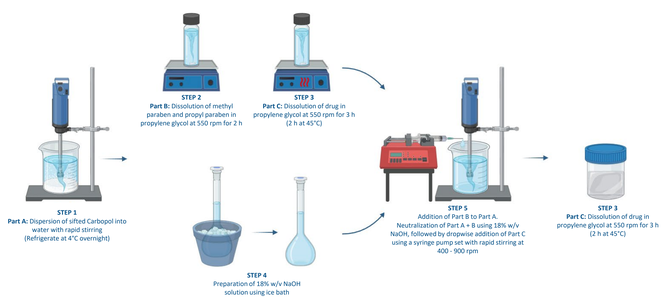


Figure 1. Schematic representation of the manufacturing process for diclofenac sodium gels

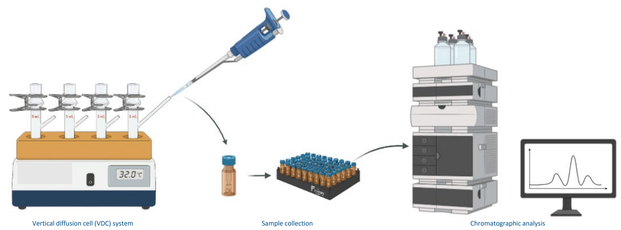


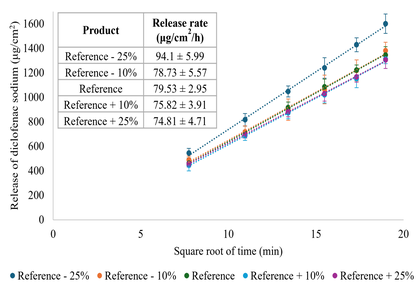
Figure 2. Schematic representation of the IVRT and IVPT setup

Performance test	In vitro release testing (IVRT)	In vitro permeation testing (IVPT)
Equipment	Vertical diffusion cell (VDC) system (Logan Instruments, NJ)	Vertical diffusion cell (VDC) system (Logan Instruments, NJ)
Membrane	PES (Millipore Express®), 0.45 µm, 13 mm, hydrophilic	Dermatomed (500 µm) human cadaver skin samples (stored at - 80 °C with TEWL < 10-15 g/m^2/h
Diffusional area	0.64 cm^2	0.64 cm^2
System temperature	32 ± 1 °C (using heat block)	32 ± 1 °C (using heat block)
VDC volume	5 mL	5 mL
Receptor medium	Phosphate buffer saline (PBS) pH 7.4	Phosphate buffer saline (PBS) pH 7.4
Dose	1000 mg	15 mg/cm^2
Duration	6 h	48 h
Sampling times	1, 2, 3, 4, 5, 6 h	0, 8, 12, 16, 20, 24, 30, 36, 42, 48 h
Sampling volume	200 µL	500 µg/cm^2/hL
Chromatographic system	Agilent 1100 series system	Agilent 1100 series system

Table 2. Summary of IVRT and IVPT study conditions

Q3 Parameter	Reference - 25%	Reference - 10%	Reference	Reference + 10%	Reference + 25%
pH	7.49 ± 0.01	7.37 ± 0.03	7.50 ± 0.01	7.31 ± 0.02	7.55 ± 0.03
Water activity readings					
25°C	0.9721 ± 0.0002	0.9568 ± 0.0003	0.9613 ± 0.0003	0.9607 ± 0.0012	0.9628 ± 0.0010
32°C	0.9618 ± 0.0018	0.9553 ± 0.0023	0.9552 ± 0.0010	0.9536 ± 0.0002	0.9535 ± 0.0006
Visual description					
Color	Colorless	Colorless	Colorless	Colorless	Colorless
Clear/ opaque	Clear	Clear	Clear	Clear	Clear
Texture	Smooth	Smooth	Smooth	Smooth	Smooth
Odor	Chemical odor	Chemical odor	Chemical odor	Chemical odor	Chemical odor
Particulate matter	None	None	None	None	None
Air bubbles	Very few on Day 1	Very few on Day 1	Very few on Day 1	Very few on Day 1	Very few on Day 1
	None by Day 10	None by Day 10	None by Day 10	None by Day 10	None by Day 10
Microscopy					
Phase states	Single	Single	Single	Single	Single
Undissolved API	None	None	None	None	None
Drug content (%)	102.75 ± 1.36	95.84 ± 0.90	98.44 ± 2.49	97.7 ± 0.92	98.81 ± 2.04
Zero-shear viscosity (Pa.s)	901.33 ± 151.67	1874 ± 100.04	2636.33 ± 413.49	3605 ± 509.82	4257.33 ± 620.52

Table 3. Q3 properties of diclofenac sodium gels containing different amounts of Carbopol® 980 (data are presented as Mean ± SD, n=3)



Product	Release rate (µg/cm^2/h)
Reference - 25%	94.1 ± 5.99
Reference - 10%	78.73 ± 5.57
Reference	79.53 ± 2.95
Reference + 10%	75.82 ± 3.91
Reference + 25%	74.81 ± 4.71

Figure 3. IVRT profiles of diclofenac sodium gels; insert table: release rate of diclofenac sodium from the five diclofenac sodium gels (data are presented as Mean ± SD, n = 6)

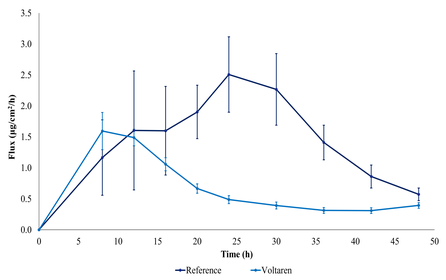


Figure 4. IVPT sensitivity testing: comparative flux profiles for reference diclofenac gel vs. marketed formulation (Voltaren®) (data are presented as Mean ± SE, 3 donors, 3 replicates per donor)

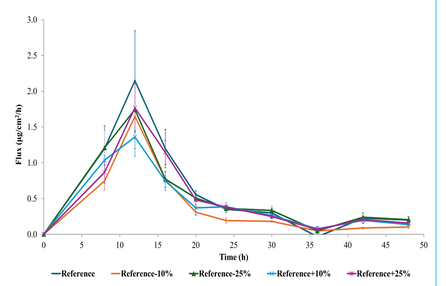


Figure 4. IVPT flux profiles for diclofenac sodium gels (data are presented as Mean ± SE, 3 donors, 3 replicates per donor)

RESULTS

Q3 Properties

- The measured Q3 properties were similar across the five gels **except rheology**.
- Microscopy: Diclofenac sodium was fully dissolved in all gels.
- Rheology: Zero-shear viscosity increased with increasing carbomer concentration (Table 3).

IVRT Method Development

- Receptor solution selection: Diclofenac sodium solubility in phosphate buffer saline pH 7.4 = 7.05 ± 0.29 mg/mL (n = 3), which is above 10x of the maximum drug concentration in the IVRT receptor solution at 6 hours.
- Membrane inertness: drug binding was negligible at 32 ± 1 °C, for 6 h
- Method was linear, precise, and reproducible with an average R^2 = 0.9989, intra-run coefficients of variance (% CV) = 5.53% and inter-run CV = 4.45% (n=6).

IVRT Results (Figure 3, Table 4)

- Diclofenac sodium release rates were comparable across all gels.
- Gel with 0.375% w/w carbomer (reference–25%) showed higher release rate compared to other gels.
- 90% confident interval (CI) values were within 75–133.33%, indicating no statistical difference in the diclofenac sodium release rates for the modified gels compared to the reference gel.

Comparison	90% Confidence Interval	
	Lower Limit	Upper Limit
Reference vs Reference - 25%	111.69	126.47
Reference vs Reference - 10%	92.43	105.88
Reference vs Reference + 10%	91.09	100.73
Reference vs Reference + 25%	88.33	99.78

Table 4. Comparison of release rates across the four modified gels vs. reference gel

IVPT Sensitivity (Figure 4)

- Flux profiles for the marketed formulation (Voltaren®) and reference gel were visibly different from each other in all 3 donors illustrating the IVPT method is sensitive to formulation differences.

IVPT Results (Figure 5)

- Permeation and flux profiles were similar across all gels. No significant differences observed in permeation or flux for the modified gels compared to the reference gel.

CONCLUSIONS

- Validated IVRT and IVPT methods were developed for diclofenac sodium topical gels.
- All modified gels showed similar Q3 properties to the reference gels, except rheology.
- In vitro release rates and flux profiles of diclofenac sodium were comparable across all five gels.
- Altering Carbopol® 980 concentration (±25%) did not significantly impact the in vitro performance of the diclofenac sodium gels used in this study.

REFERENCES

1. Draft Guidance for Industry: In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs https://www.fda.gov/media/162476/download
2. Draft Guidance: In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs https://www.fda.gov/media/162475/download

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CONTACT INFORMATION: seepra.rath@rutgers.edu