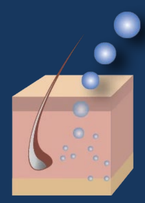

OPTIMIZATION OF MANUFACTURING METHOD FOR DEVELOPMENT OF CRYSTAL-FREE DICLOFENAC TOPICAL GELS

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BACKGROUND

- Topical semisolid products: drugs in **dissolved** or **suspended** forms
  - Dissolved drug → Readily available for absorption
  - Suspended drug → Must dissolve first before it can be absorbed
- Drug's physical state affects → Bioavailability
- **Study Aim:** Develop a crystal-free diclofenac sodium gel
- **Formulation Challenges:**
  - Diclofenac sodium: pH-dependent solubility (pH > 7)
  - Gelling agent (Carbopol® 980): acidic → promotes crystallization

METHODS AND MATERIALS

❑ **Gel Preparation & Optimization**

- Diclofenac sodium gels (**Table 1**) were prepared by optimizing key manufacturing process parameters (**Figure 2**):
  - Gelling agent addition speed
  - Stirring rate
  - Solubilization time
  - Stirrer type

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
Water	Q. S 100% w/w

Table 1. Formulation composition of diclofenac sodium gel, 0.5% w/w

- Manufacturing Process Overview (**Figure 3**)

1. Gelling agent dispersed in water
2. Drug and preservatives solubilized separately in propylene glycol
3. Gel dispersion neutralized with sodium hydroxide → gel base
4. Drug solution incorporated into gel base

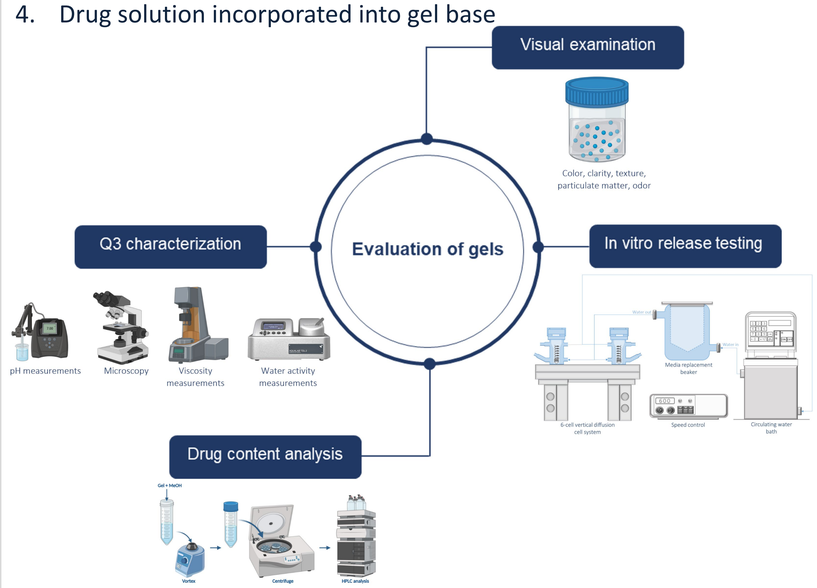


Figure 1. Evaluation of diclofenac sodium gels, 0.5% w/w

GRAPHICAL ABSTRACT

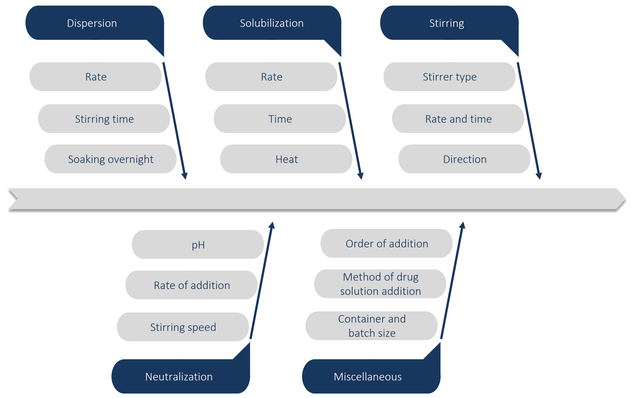


Figure 2. Cause and effect diagram showing the various manufacturing process parameters that may contribute to crystallization of diclofenac sodium in the final dosage form (gel)

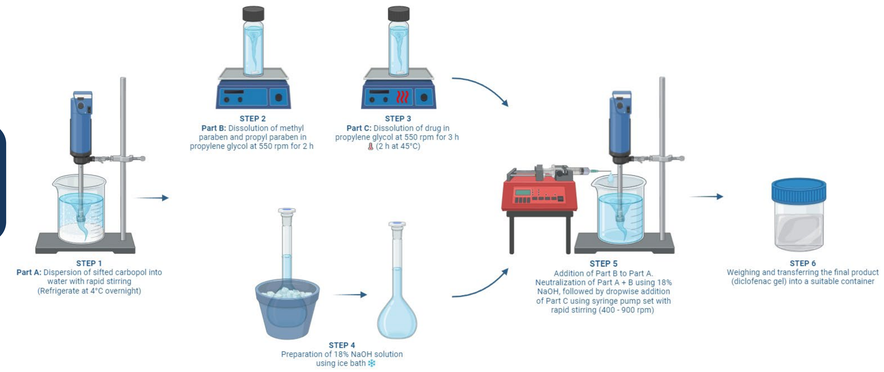


Figure 3. Schematic representation of the manufacturing process used to prepare diclofenac sodium topical gels

RESULTS

Optimization of manufacturing process parameters to develop crystal-free diclofenac sodium gels:

- Neutralization: Adjusting the pH to 7.3-7.5 → prevented drug crystal formation
- Solubilization: Heat ensured complete solubilization of drug → crystal-free clear gels
- Dispersion: Slow addition of the gelling agent and medium stirring → clump-free dispersions
- Stirring: A paddle-type stirrer with bidirectional mixing helped avoid drug crystallization
- Miscellaneous: Controlled, slow addition of the drug, Appropriate container and batch size → crystal-free clear gels

Non-optimized gels showing diclofenac sodium crystals:

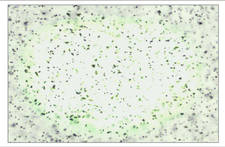
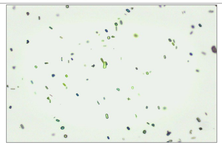
Manufacturing conditions (see Figure 3)	Representative micrographs of final gels
Neutralization (STEP 5): Drug solution added at pH < 7	
Addition of the drug (STEP 5): Unregulated addition of drug solution	
Solubilization (STEP 3): Drug dissolved in propylene glycol without heat	
Stirring (STEP 5) Non-uniform mixing due to axial blade stirrer and larger batch size	

Table 2. Representative microscopic images of non-optimized gels (100x) using a Nikon Eclipse E200 microscope

Crystal-free clear gels after optimization of manufacturing process parameters:

Figure 4 Representative images of the optimized diclofenac sodium gel (400x)

RESULTS

Table 3. Characterization of optimized diclofenac sodium gel (data are presented as Mean ± SD, n=3)

Parameter	Observation
pH	7.50 ± 0.01
Water activity	
25°C	0.96 ± 0.0003
32°C	0.96 ± 0.0011
Visual description	
Color	Colorless
Clear/ opaque	Clear
Texture	Smooth
Odor	Chemical odor
Particulate matter	None
Microscopy	
Phase states	Single
Undissolved API	None
Air bubbles	Very few on Day 1, None by Day 10
Drug content (%)	98.44 ± 2.49
Zero-shear viscosity (Pa.s)	2636 ± 413
In vitro release rate (μg/cm²/h)	79.53 ± 2.95

CONCLUSION

The physical state of the drug substance in a topical semisolid product can significantly influence drug permeation and bioavailability. In this study, key manufacturing parameters affecting the physical state of diclofenac sodium in gels were identified and optimized. Under these optimized conditions, a clear gel with fully dissolved diclofenac sodium was developed, which will be used for further evaluation.

ACKNOWLEDGMENTS

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