

Topical Ketamine (2%) - Amitriptyline (1%) Gel: Which Poloxamer 407 (P407) Concentration Should Be Chosen?

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Introduction

Background: Request for the formulation of a topical gel indicated for the symptomatic treatment of neuropathic pain refractory to standard therapy, to be packaged in a tube

- Formulation:** ketamine hydrochloride 2% w/V and amitriptyline hydrochloride 1% w/V: synergistic actions combining efficacy and tolerability
- Gelling agent selected:** Poloxamer P407 (P407), a thermogelling agent (liquid at low temperature and **gelled at room temperature from 18% P407**): allows packaging in a tube in liquid form (after refrigeration) and cutaneous application in gel form (at room temperature)



Objective: To determine the optimal P407 concentration to achieve a gelation temperature (Tgel) < 20°C and to investigate the factors likely to affect it

Materials and Methods

- Analysis of inter-batch variability of P407:** Formulation of gels using **3 batches of P407**
- Analysis of the impact of P407 concentration:** Formulation of 3 gels (from 3 batches of P407) at **20%, 22.5% and 25%** P407 (n=1) without API, and 2 gels with API at 22.5% and 25% P407 (2 batches of P407, n=3)
- Analysis of the impact of active pharmaceutical ingredients (API):** Comparison of gels formulated at **22.5% and 25% P407 + API** (n=3)
- Analysis of the impact of the dispersion process:** Formulation of gels at **25% P407 without API** (n=1): 1st gel not homogenized, 2nd gel homogenized with the Ultra-Turrax (UT) for 1 min (speed 2), and 3rd gel for 5 min (speed 3); in parallel, homogenization with a paddle stirrer for 1 min for a 1st gel and 5 min for a 2nd gel
- Equipment:** RM200 CP-4000 PLUS LAMY RHEOLOGY rheometer, cone-plate geometry, diameter: 20mm, angle: 1.98°, measurements acquired for 3min/°C, temperature ramps from 15°C to 25°C

→ Viscosity measurement and comparison of Tgel

Results

1- Impact of batch and P407 concentration?

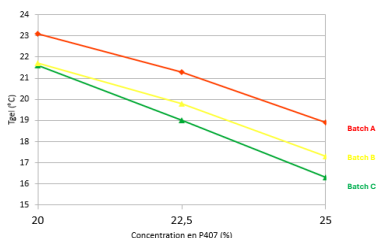


Figure 1: Graph showing Tgel (°C) as a function of P407 concentration (20%, 22.5% and 25%) for 3 different batches of P407

	Batch A	Batch B	Batch C
20%	23,1 °C	21,6°C	21,7°C
22,5%	21,3°C	19°C	19,8°C
25%	18,9°C	16,3°C	17,3°C

Table I: Tgel as a function of P407 percentage and batch

20%	22.5%	25%
22.1 +/- 0.8°C (CV = 3.6%)	20 +/- 1.1 °C (CV = 5.5%)	17.5 +/- 1.3 °C (CV = 7.6%)

Table II: Mean Tgel of the P407 batches used at 3 different concentrations



Figure 2: Gel appearance at 20%, 22.5% and 25% P407+API (left to right)

Batch and P407 concentration affect Tgel:
the higher the concentration,
the lower the Tgel

2- Impact of APIs?

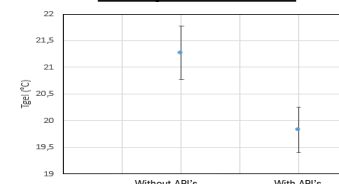


Figure 3: Graph showing Tgel of gels formulated at 22.5% P407 +/- API

Tgel (22.5% P407) = 21.3 +/- 0.5 °C
Tgel (22.5% P407 + API) = 19.8 +/- 0.4 °C
Mean Tgel at 25% P407 (batches A and B + API) = 16.9 (+/- 1.7 °C)

Influence of API on Tgel at a P407 concentration of 22.5%:
decrease in Tgel with the addition of APIs

3- Dispersion process

a) Impact of the UT?

	No UT	1 min, S2	5 min, S3
25%	18.6 °C	18.7°C	18.8°C

Table III: Comparison of Tgel for 3 gels formulated at 25% P407 homogenized with or without the UT (varying duration and speed)

b) Impact of the paddle stirrer?

Tgel = 18.5 °C regardless
of the homogenization duration

No influence of the homogenization process on Tgel,
regardless of the speed or duration applied

Discussion - Conclusion

- Tgel depends on P407 concentration and appears to decrease with the addition of APIs
- Inter-batch variability was observed (CV > 5%)

→ to confirm these trends: further repetitions and statistical testing are needed

- Formulations at 22.5% and 25%: ideal texture for use at 20°C (Tgel < 20°C)



At 25%, the high viscosity could complicate the process steps
as well as cutaneous application



- ❖ Use a P407 concentration between 22.5% and 25% to obtain a Tgel < 20°C
- ❖ **Stability study and scale-up to confirm the concentration to be selected**
- ❖ **Measure the viscosity of each new batch of P407**
- ❖ **Raise staff awareness of the process**