Redefining Ketoprofen: Nanoemulsion for Future Melanoma Therapeutics

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Introduction

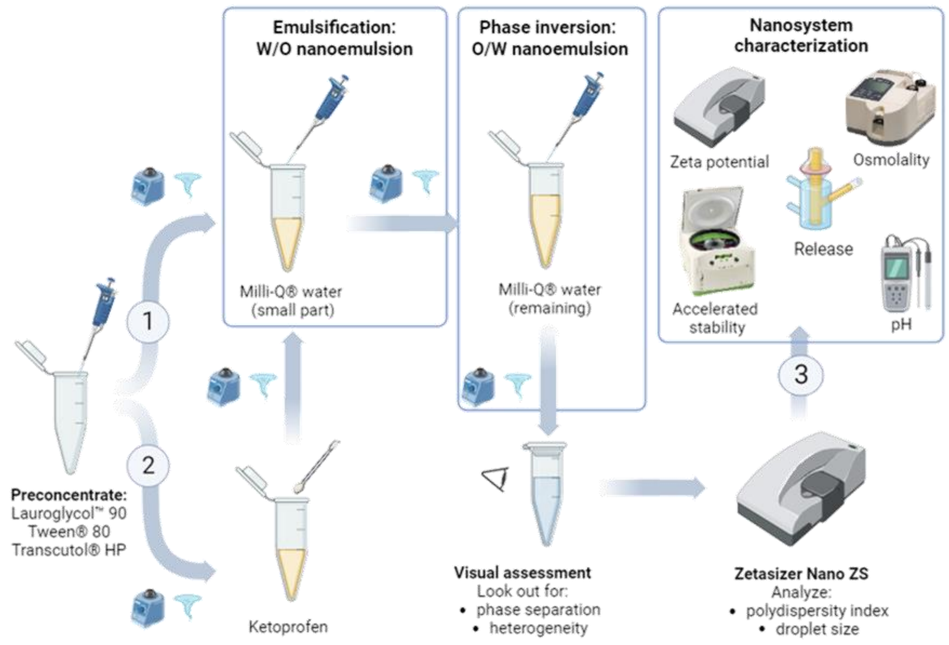
WHAT are we treating?
- Melanoma is the rarest but **deadliest** skin cancer
- 320.000+ new diagnosis and 57.000+ deaths worldwide (2020)[1]

WHY are current treatments not enough?
- Targeted therapies and immunotherapies have been developed
- Many patients are **not responsive** or develop **secondary resistance**[2,3]

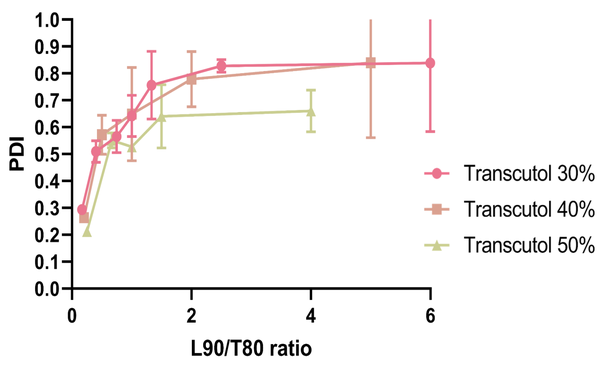
Our approach
- Ketoprofen (NSAID) has described **anti-proliferactive activity** on melanoma cell lines[4,5]
- However, it is **pratically insoluble** (0,0213 mg/mL)[6]

Our objective
- Incorporation of KET in an **oil-in-water nanoemulsion** to increase dosage in formulation
- Characterization of the nanosystem

Materials and Methods



Results

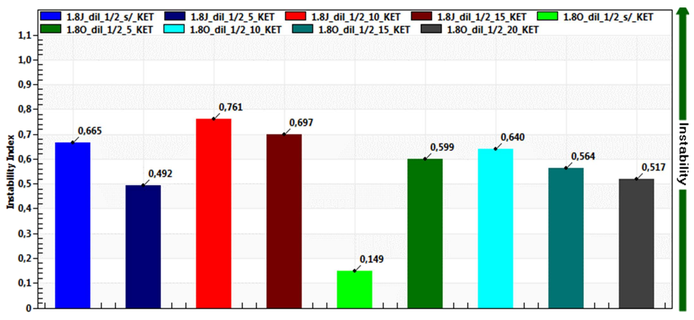


Graphic 1. Relationship between polydispersity index (PDI) and the Lauroglycol™ 90/Tween® 80 ratio in the seventeen nanoemulsions prepared in phase 1.

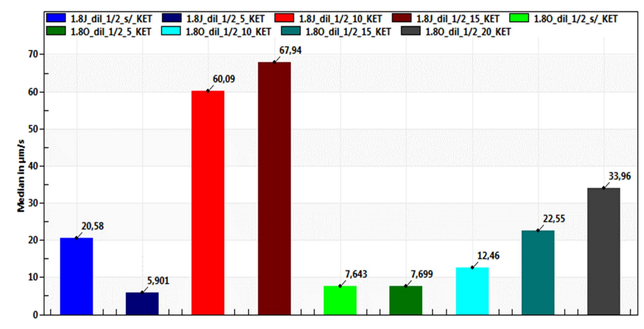
Formulations with:
- **PDI < 0,300**
- **Droplet size between 100 and 200 nm**

were selected for phase 2 assays (solubility testing)

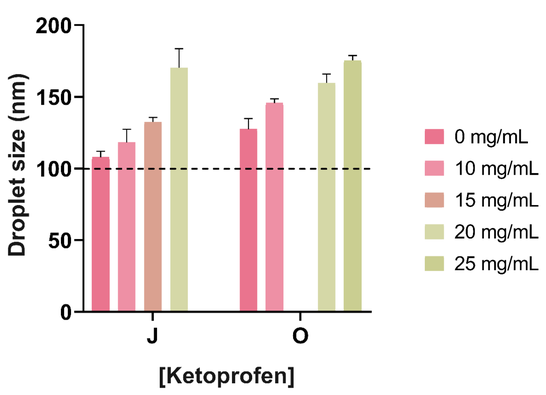
The same criteria was used to determine whether KET was solubilized or not.



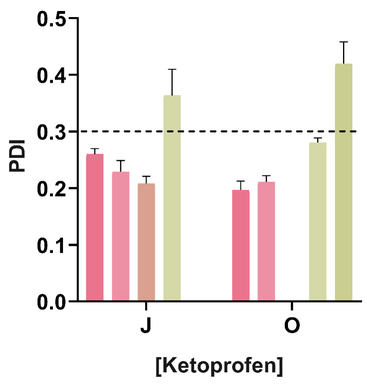
Graphic 4. Instability index of the formulations after accelerated stability conditions, using different ketoprofen concentrations. Incorporation of the drug might destabilize the system, but this effect is not concentration-dependent.



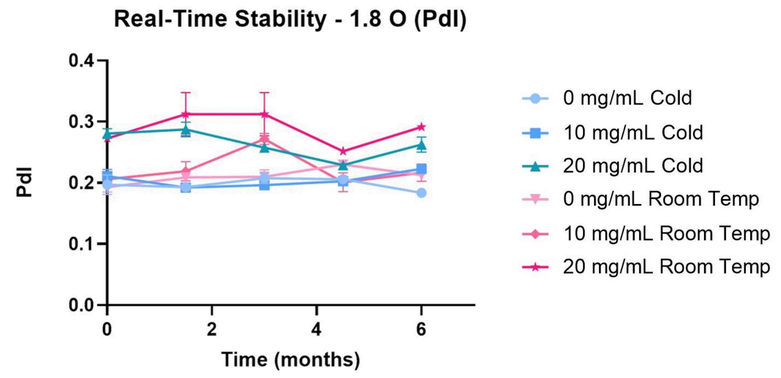
Graphic 5. Sedimentation speed of the formulations using different ketoprofen concentrations. Globally, increased drug concentration leads to a higher sedimentation speed.



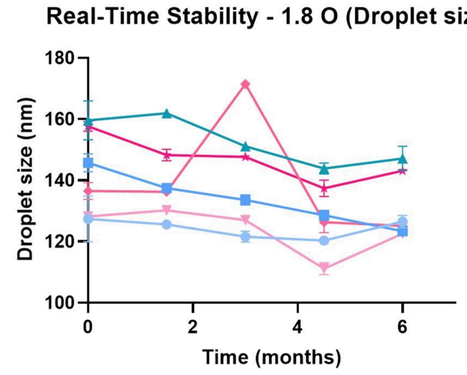
Graphic 2. Mean droplet size (nm) of nanoemulsions with different ketoprofen concentrations (mg/mL).



Graphic 3. Mean polydispersity index of nanoemulsions with different ketoprofen concentrations (mg/mL).



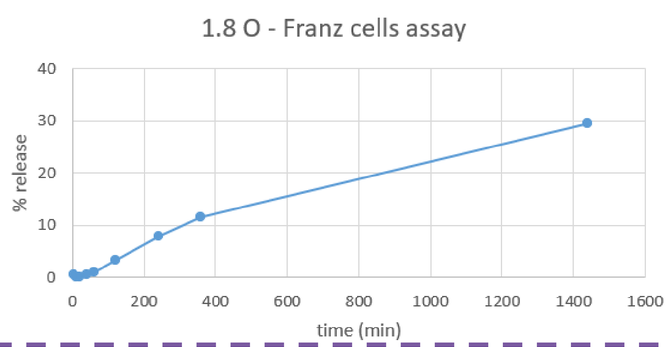
Graphic 6. Polidispersity index measurements for formulation 1.8 O, using different concentrations and temperatures, during 6 months.



Graphic 7. Droplet size measurements for formulation 1.8 O, using different concentrations and temperatures, during 6 months.

Formulation	pH	Zeta potential	Osmolality
1.8 J	6 ± 0,5	-10,7 mV	2354,2 mmol/kg
1.8 O	6 ± 0,5	-8,68 mV	2257,4 mmol/kg

Table 1. Results of different nanosystem characterization assays.



Graphic 8. Franz cells assay measurements for formulation 1.8 O. Samples were taken at 5, 10, 20, 40, 60, 120, 240, 360 and 1440 minutes, using 6 cells. Receptor medium was PBS pH 5.5.

Discussion and Conclusion

1. SCREENING
- Formulations with **higher %Transcutol® HP** (solubilizer and co-emulsifier) had a **lower PDI**;
- Nanoemulsions with **similar but also high** quantities of Tween® 80 (emulsifier) and Transcutol® HP had a **lower PDI**;

2. SOLUBILITY
- Formulation 1.8 J → **15 – 20 mg/mL** [KET] → **700x** solubility enhancement (compared to water)
- Formulation 1.8O → **20 – 25 mg/mL** [KET] → **930x** solubility enhancement (compared to water)

3. CHARACTERIZATION
- Formulations might be **suitable for topical application**.
- **Stability is not compromised** with increased drug loaded concentration and does not seem to be worsened with time.

- We were able to develop nanoemulsions with high ketoprofen strength, which could lead to **high bioavailability upon administration**.
- Viscosity, ex vivo drug permeation, and in vitro citotoxicity will further be assessed.

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