

## Supplementary material

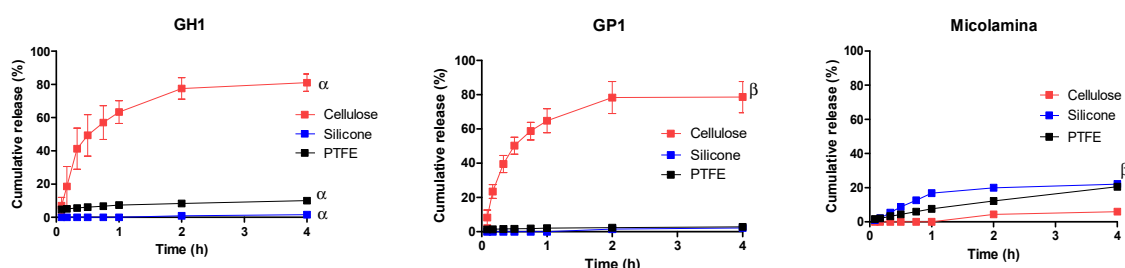
### New formulation-microporation combined approaches to deliver ciclopirox across human nail.

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#### S1. In vitro release test (IVRT) results

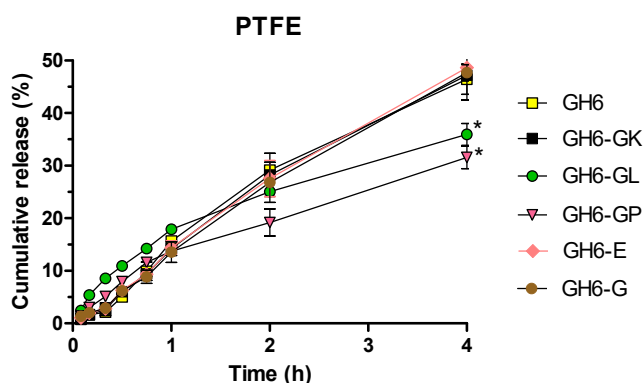
##### 1.a Preliminary IVRT: Membrane selection:

Figures S1 show CPO release from a gel (GH1), a thermogel (GP1) formulation and from Micolamina®, all containing 8% of drug, and across 3 different artificial membranes for 4 hours.



**Figure S1** – CPO cumulative *in vitro* percentual release (mean  $\pm$  SD, n=6) from GH1, GP1 and Micolamina® across cellulose, silicone and PTFE membranes. Results from one-way ANOVAs followed by Bonferroni's multiple comparison tests:  $\alpha$ : significantly ( $p < 0.05$ ) different percentage released across the three different membranes,  $\beta$ : significantly ( $p < 0.05$ ) different percentage released across cellulose and the other two membranes, but no differences found between silicone and PTFE membranes.

##### 1.b IVRT results corresponding to the second series of gel products (Table 3) based on GH6 formulae.



**Figure S2** - CPO cumulative amount (mean  $\pm$  SD, n=6) released from gels GH6, GH6-GK, GH6-GL, GH6-GP, GH6-E and GH6-G across PTFE membranes. GH6-GP and GH6GP (\*) donors provided a significantly ( $p < 0.05$ ) smaller percentage released compared to all other gels but no differences were found between these two (one-way ANOVAs followed by Bonferroni's multiple comparison tests).

## S2. Additional formulation properties and drug stability.

Table S1 shows the organoleptic characteristics, pH and CPO content (mean  $\pm$  SD) for the formulations. CPO content was determined immediately after preparation, and after 6 months storage at room temperature, and in all cases, the CPO loading was within the limit specified for topical formulations (90-110%).

Table S1 - Organoleptic characteristics, pH and CPO content (mean  $\pm$  SD) of the formulations. \* pH terminated using pH indicator paper (MQuant®-Merck).

Formulations	Consistency	Colour	Odor	pH	CPO content (%)	CPO content (%)
					T 0	T 6 months
<b>GH1</b>	Liquid	Colorless	Isopropanol residue	12.5 $\pm$ 0.02	98.37 $\pm$ 0.07	97.11 $\pm$ 0.2
<b>GH2</b>	Liquid	Slightly yellowish	Isopropanol residue	12.4 $\pm$ 0.03	108.18 $\pm$ 0.025	99.23 $\pm$ 0.13
<b>GH3</b>	Liquid	Slightly yellowish	Isopropanol residue	12.7 $\pm$ 0.04	100.37 $\pm$ 0.027	96.73 $\pm$ 0.12
<b>GH4</b>	Liquid	Colorless	Isopropanol residue	10.8 $\pm$ 0.01	104.83 $\pm$ 0.02	99.45 $\pm$ 0.18
<b>GH5</b>	Liquid	Colorless	Isopropanol residue	12.3 $\pm$ 0.07	106.1 $\pm$ 0.015	96.66 $\pm$ 0.92
<b>GH6</b>	Liquid	Slightly yellowish	Isopropanol residue	12.1 $\pm$ 0.05	101.36 $\pm$ 0.036	95.99 $\pm$ 0.12
<b>GH6-E</b>	Liquid	Colorless	Isopropanol residue	10.6 $\pm$ 0.01	100.65 $\pm$ 0.078	98.02 $\pm$ 0.18
<b>GH6-G</b>	Liquid	Colorless	Isopropanol residue	10.9 $\pm$ 0.02	102.10 $\pm$ 0.068	99.82 $\pm$ 0.14
<b>GH6-GK</b>	Liquid	Colorless	Isopropanol residue	12.5 $\pm$ 0.03	99.75 $\pm$ 0.087	95.10 $\pm$ 0.15
<b>GH6-GL</b>	Liquid	Colorless	Isopropanol residue	12.8 $\pm$ 0.01	99.95 $\pm$ 0.058	98.77 $\pm$ 0.24
<b>GH6-GP</b>	Liquid	Colorless	Isopropanol residue	12.3 $\pm$ 0.02	102.02 $\pm$ 0.074	97.15 $\pm$ 0.27
<b>GP1</b>	Slightly viscous liquid	Colorless	Isopropanol residue	11.1 $\pm$ 0.01	103.45 $\pm$ 0.11	101.19 $\pm$ 0.12

<b>GP2</b>	Slightly viscous liquid	Slightly yellowish	Isopropanol residue	$10.8 \pm 0.05$	$109.5 \pm 0.17$	$96.84 \pm 0.17$
<b>GP3</b>	Slightly viscous liquid	Slightly yellowish	Isopropanol residue	$12.3 \pm 0.02$	$107.88 \pm 0.035$	$104.00 \pm 0.92$
<b>GP4</b>	Slightly viscous liquid	Slightly yellowish	Isopropanol residue	$10.5 \pm 0.01$	$99.97 \pm 0.33$	$96.02 \pm 0.02$
<b>GP5</b>	Slightly viscous liquid	Slightly yellowish	Isopropanol residue	$12.9 \pm 0.01$	$100.01 \pm 0.04$	$95.00 \pm 0.16$
<b>MICOLAMINA</b>	Liquid	Slightly yellowish	Organic solvent residue	5*	$107.3 \pm 0.04$	$98.34 \pm 0.24$

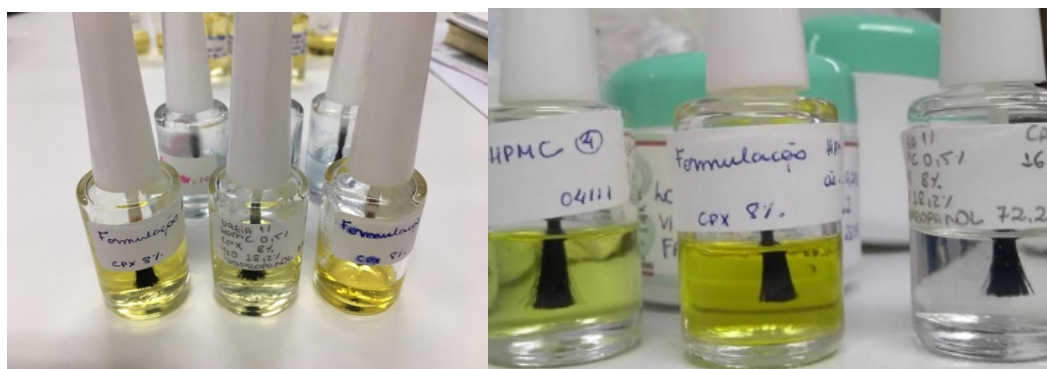


Top panel: Example of thermogel formulation without crystals (left panel) and with crystals (right panel)



Bottom panel: Example of thermogel formulation without crystals (left panel) and with crystals (right panel)

**Figure S3** - Absence of crystals was made by placing 2 drops of each formulation on a slide, covered with a coverslip and then observed through an optical microscope.



**Figure S4** – CPO formulations present the typical yellow colour (left panel) which may intensify 2-3 hour after preparation (right panel).