

# Development and characterization of thermosensitive mucoadhesive gels based on lidocaine and chlorhexidine for the treatment of oral mucositis



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### Introduction

Oncology treatments cause numerous side effects both in paediatric and adult patients, including severe oral mucositis (SOM) [1]. Mucositis is an inflammation of the oral mucosa that results in pain, ulceration and bleeding. The incidence of SOM is associated with the chemotherapy regimen used, the duration of treatment and the dose of the administered drugs. The oral mucosa is particularly susceptible to chemotherapy-induced damage, causing ulceration, bacterial, fungal and viral infections (primarily caused by *Candida albicans* and *Herpes simplex*) and difficulty or inability to eat, drink or swallow. Despite its clinical relevance, SOM is scarcely studied, with no established 'gold standard' for its prevention or effective treatment [2].

# Aim of the work

The aim of the work was to develop a possible topic and versatile treatment for oral mucositis in both paediatric and adult patients:

a thermosensitive and mucoadhesive oral gel able to reduce not only severe pain associated with mucosal injuries (lidocaine), but also oral bacterial, fungal and viral infections (chlorhexidine), as well as promoting the regeneration of the damaged tissue (hyaluronic acid).

# **Gels formulation**







- Lidocaine HCl 2 % (LID) Chlorhexidine 0.20 % (CHX) Poloxamer 407 20 % or 25 % (thermosensitive polymer) (P407)
- Sodium Hyaluronate 0.25 % or 0.5% (mucoadhesive polymer) (Na-Jalu) HydroxyPropylMethylCellulose 0.25 % or 0.5 % (mucoadhesive polymer) (HPMC)

#### **Selected gels**

in terms of pH, Gelation Temperature and Gelation time:

**3L:** 2% LID; 0.20% CHX; 25% P407; 0.25% Na-Jalu

5L:2% LID; 0.20% CHX; 20% P407; 0.25% HPMC

6L: 2% LID; 0.20% CHX; 20% P407; 0.50% HPMC

# Methods

•Gelation Temperature: tube-inverting method in the range 24-38°C at a ramp rate of 1°C/min

•Gelation time: at 37°C. The sample was stirred by a magnetic bar at 300 rpm up to stopping. •Residence time: 2.5mL of gel on a patient of the patient of the sample was stirred by a magnetic bar at 300 rpm up to stopping.

a petri dish containing a mucin-agar support. The petri dish was fixed on a 45°C inclined heated plate onto which a flow of 1.5mL/min of simulated saliva was dripped.

•Drugs release: D-Tube Dialyzer Midi with 2,5mL of gel equipped with a permeable dialysis membrane immersed in 40 mL of simulated Saliva (SS), under

stirring (200 rpm) inside a thermostatic bath at 37°C. 3 mL samples were withdrawn at 15', 30', 60', 90' and 120' and assayed by HPLC.

•Drugs permeation: Franz diffusion cells with 2.5 mL of gel on a cellulose acetate membrane soaked in a lipid mixture mimicking the buccal membrane. 0.5 mL samples were withdrawn at 15', 30', 60', 90' and 120' and assayed by HPLC.

#### Conclusions

- The promising in-vitro properties of the developed thermosensitive gels were highlighted.
- Slight variations depending on the different mucoadhesive polymer used were observed.
- Formulations with HPMC (5L and 6L) were preferable especially in terms of spreadability, residence time and drug release, compared to those containing Na-Jalu (3L), nevertheless its good overall performances.

# **Results & Discussion**

# pH, Gelation Temperature and Time

Target: Tolerable pH (between 5.6 and 7.0)

Gelation Temperature > 28°C

<ul> <li>Gelation time &lt; 60 sec</li> </ul>			
Gel	рН	Temperature	time
3L	6.0	29-30°C	0:30 min
5L	6.0	33-34°C	0:50 min
6L	5.8	31-32°C	0:30 min

# **Deformation test**

To test how the action of the tongue may influence gel mucoadhesion and residence time and its amount on the application site







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obtain with a of Good adhesiveness (0.28N-0.38N) and debonding distance between 4mm and



Formulations demonstrated to be easily spreadable with good values of firmness, stickness and work of shear

<u>Target</u>: to formulations suitable degree adhesiveness to the oral mucosa ensuring the gel remains in situ 8mm were noted



#### **Release studies**

CHX: complete release (100%) within 60' for series 5 and 6, and within 120' for series 3 LID: release average values just above 50% in all tested formulations



#### **HPLC** method

- Hitachi LaChrom Elite HPLC system
- Column: Phenomenex Luna 5 µm C18(2) 100 Å, LC Column 150 x 4.6 mm T: 40°C

LID

CHY

4,73 2,33

60

-

time, min

11.53

3,52

120

7,00 2,78

- Flow: 1.0 mL/min
- λ: 254 nm

100,00 90:00

80,00

70,00

60,00 % permeated

50,00

40.00

30,00

20,00

10,00

0,00

0.00

0

Mobile phase: Phosphate buffer solution pH 3.5; ACN

Gel 6L

3,00 1,83

30

1,23 1,09

15

Gradient method



References [1] Pulito, C. et al. Oral mucositis: the hidden side of cancer therapy, J Exp Clin Cancer Res 39, 210 (2020). [1] Foldo, C. et al. Oran Houses and Hutters and Hutt Thermosensitive Oral Gel Based on Poloxamer 407. Materials 2021, 14(16), 4522.

with Na-Jalu