PP-033

# NYSTATIN-LIDOCAINE LOZENGES: INNOVATION IN THE TREATMENT OF ORAL MUCOSITIS

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## Background

Oral mucositis (OM) is an inflammation that is reported as the most debilitating side effect in cancer patients. Pain is usually the most reported symptom as it can compromise oral intake of food and water, negatively affecting the QOL. Therefore, it is important to develop oral formulations that enhance therapy compliance, improve the administration and ensure the effectiveness of the drug.

Lozenges are solid products that act by slow dissolution and disintegration in the oral cavity. Are described as an effective alternative to mouthwashes.

Table 1- Advantages and disadvantages of lozenges.

| Advantages | Disavantages |
|---|---|
| ✓ Ease of administration (without vehicle) | × Children can mistakenly take it as candy |
| ✓ Palatability | |
| ✓ Extended time in the oral cavity | × Unequal distribution of drug within saliva |
| ✓ Geriatric and Paediatric friendly | |

## Purpose

The present work describes the development and stability studies of a formulation of nystatin and lidocaine lozenges for the treatment of oral mucositis.

## Materials

Lidocaine hydrochloride and gelatine were purchase from Acopharm®, sucrose and propylparaben were obtained from Fagron®, glycerin from DS Produtos Farmacêuticos®, arabic gum from Farma-Química SUR S.L®, methylparaben from Merck® and nystatin from Mycostatin® (Bristol-Myers Squibb®).

## Methods

Different excipients, such as gelatine, polyethylene glycol 1500, sucrose, glycerin (humectant), acacia (binder, bio adhesive properties) and parabens (preservatives) were tested to obtain suitable properties for the oral administration, storage, and therapeutic compliance.

Lozenge's production method: 1- weigh and place the excipients in a thermostatic bath at 70-75°C until a homogeneous mixture is obtained; 2- after cooling, blend in the active substances, homogenize and fill the mold (Fig. 1); 3- after solidification, pack and label (Fig 2).

Fig. 1- Filling molds during lozenge's production.


Fig. 2- Primary packaging and labeling.

Full pharmaceutical quality testing was carried out and included: organoleptic properties and pH evaluation at 37ºC (Mettler Toledo®) , disintegration (Erweka® ZT3) and dissolution tests (Sotax® AT7) for oral dosage forms (with artificial saliva at 37ºC), uniformity of mass and content and grittiness test. A drug-excipient compatibility study was performed by Differential Scanning Calorimetry (DSC from *Instruments,* New Castle, USA). The samples were weighed into aluminum cells and scanned at 25ºC to 270ºC (reference blank cell).

Appropriate stability-indicating analytical methodology (HPLC) was developed to quantify nystatin and lidocaine. The microbiological test was set according to the European Pharmacopoeia 8 (EP 8) specifications (category 3A).

## Results

The main results are listed in table 2. The final aspect obtained is in Fig. 3.

Table 2- Summary of the main results obtained with lidocaine and nystatin lozenges.

| Assay | Result |
|---|---|
| Colour | Pale yellow |
| Aspect | Homogeneous |
| Flavor | Slightly sweet |
| pH | 5,75±0,03 |
| Disintegration time | 17±2 min |
| Average weight | 3,938 ± 0,072 g |

Fig. 3- Final aspect of nystatin and lidocaine lozenges.

These lozenges have suitable content and mass uniformity. No incompatibilities were found between the drugs and the excipients (Fig. 4). After partial dissolution the lozenges had their texture unchanged (Fig. 5).

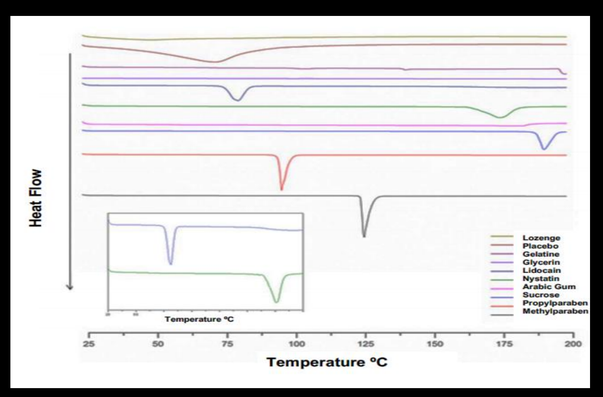


Fig. 4- DSC results.

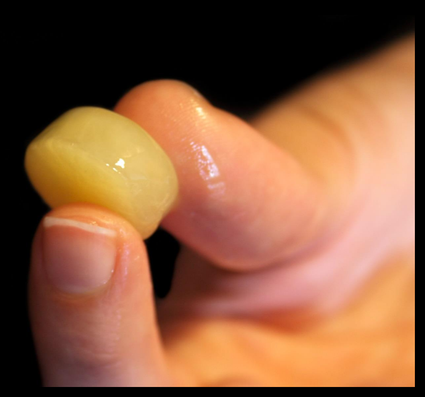

Fig. 5- Grittiness test.

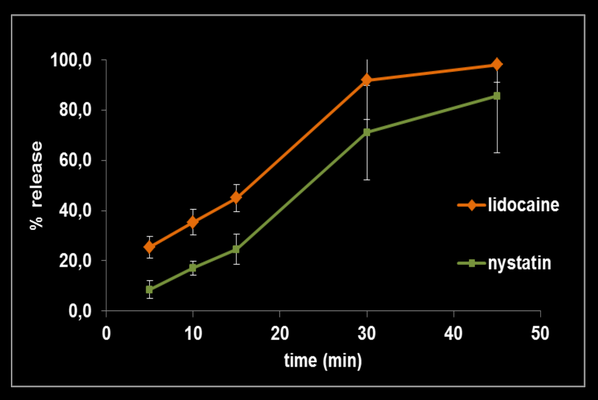


Fig. 6- Results obtained on the dissolution test with nystatin and lidocaine lozenges in artificial saliva.

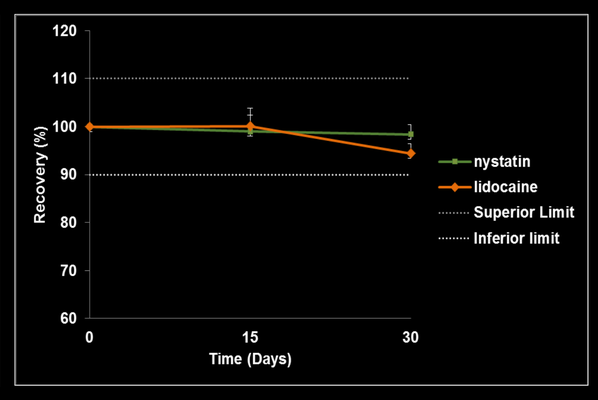


Fig. 7- Recovery percentage lidocaine and nystatin lots 1, 2 and 3 stored at 5 ± 3 ° C (mean ± SD, n = 3).

The nystatin and lidocaine lozenges maintained their physical, chemical (Fig. 7) and microbiological stablility for 30 days when stored at 2-8ºC and protected from humidity and light.

## Conclusions

- ✓ A stable formulation of soft nystatin-lidocaine lozenges was obtained, presenting suitable palatability, final pH and pharmaceutical characteristics such uniformity of mass and content, disintegration time and dissolution rate.
- ✓ They are stable for 30 days when stored between 2-8ºC and protected from light and humidity.
- ✓ They can be an effective alternative to mouthwashes for the treatment of oral mucositis due to their versatility, palatability and easier administration.
- ✓ Patients can control the retention time of the drugs in the oral cavity and consequently manage their pain treatment.
- ✓ Clinical application will validate the efficacy and optimum dosing frequency of the formulation.

## Bibliography

1. European Pharmacopoeia, 8th edition, 2014
2. Allen L V, City O. Troches and Lozenges. Secundum Artem. 4(2)
3. Wonnemann M, Helm I, Stauss-grabo M, Röttger-luer P, Tran C, Gmbh EA, et al. Lidocaine 8 mg Sore Throat Lozenges in the Treatment of Acute Pharyngitis. Arzneimittel- Forchung (Drug Res. 2007;57(11):689–97.).

No conflict of interest.