ABSTRACT SUMMARY
Microbial infections, like oral candidiasis, represent the most common drawback of certain immunosuppressant and antibiotic systemic treatments. Oral candidiasis are often treated with topical formulations like antifungal oral gels. In order to increase patient compliance, above all in children, chewing gums are considered as an alternative buccal dosage form for antifungal drugs. The main disadvantages are the low antifungal drug release from gums due to the high affinity of the antifungal drugs (i.e. miconazole, MCN) for the gum matrix thus the need for frequent administrations. The aim of this research project is to encapsulate MCN in mucoadhesive microparticles and to incorporate them into chewing gums in order to increase MCN release from gums and to prolong MCN activity.

INTRODUCTION
Oral candidiasis represents a frequent disease both in adult and in paediatric patients, as consequence of different systemic treatments (antibiotics and immunosuppressants) and steroids by inhalation.

Oral candidiasis is commonly treated with different antifungal drugs, like imidazoles, formulated as systemic and topical dosage forms. Recent studies demonstrated that Miconazole (MCN) loaded chewing-gums were as effective as oral gels showing better compliance for paediatric patients. The problems are the long treatment time needed for the complete recovery from the infection with respect to systemic administration and the uncomfortable dosage regimen (4 times daily) caused by the MCN poor release from gum matrix [1]. MCN loaded mucoadhesive microparticles incorporated into chewing-gums could represent a good strategy to improve MCN local effect, increasing and sustaining MCN release from gums through the release of the undamaged MCN loaded microparticles into the mouth. The goal of this work is to incorporate MCN loaded mucoadhesive microparticles into chewing gums in order to reduce the MCN amount pro dose maintaining the therapeutic effect over 4 hours.

EXPERIMENTAL METHODS
Different microparticle batches were prepared in order to exploit the MCN best release profile and to realize microparticles with suitable mucoadhesive features: a) alginate microparticles; b) chitosan coated alginate microparticles; c) chitosan microparticles with a gelatine core and d) chitosan microparticles [2]. All batches were prepared using a mechanical instrument based on the nozzle vibration technique (Encapsulator Buchi 350 pro), using both standard and concentric nozzles. The suitable process parameters like polymer concentration, nozzle diameter and nozzle vibration frequency were selected by a design of experiment (Statgraphics Centurion) with the aim of obtaining microparticles with diameter lower than 200 µm. MCN loaded microparticles were evaluated in terms of dimensions (dynamic light scattering) and MCN encapsulation efficiency (HPLC) [3]. In vitro
release tests were performed in artificial saliva, pH 5.4, at 37°C [4].

Micro particles loaded chewing-gums were prepared by softening the gum base and incorporating freeze dried microparticles before cooling. All formulations were submitted to an in vitro release test using chewing machine in artificial saliva as release medium.

RESULTS AND DISCUSSION

Despite of good dimensions obtained (142 µm), alginate microparticles were discarded because of the poor MCN release after 4 hours (20.81±3.4%) (Fig.1). Chitosan coating of alginate microparticles significantly reduced MCN loading (6.21%) (Table 1); consequently, in vitro release tests were not performed on these microparticle batches.

\[
\text{Table 1. MCN content and Encapsulation Efficiency (EE %) for microparticle batches.}
\]

<table>
<thead>
<tr>
<th>Batch</th>
<th>Theoretical drug content (mg MCN / mg MS)</th>
<th>Actual drug content (mg MCN / mg MS)</th>
<th>EE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alginate</td>
<td>0.2</td>
<td>0.095±0.018</td>
<td>46.53±10.2</td>
</tr>
<tr>
<td>Alginate/ Chitosan</td>
<td>0.2</td>
<td>0.099±0.004</td>
<td>6.21±1.7</td>
</tr>
<tr>
<td>Gelatine/ Chitosan</td>
<td>0.2</td>
<td>0.102±0.016</td>
<td>50.73±7.9</td>
</tr>
<tr>
<td>Chitosan</td>
<td>0.2</td>
<td>0.101±0.021</td>
<td>50.34±7.2</td>
</tr>
</tbody>
</table>

\[\text{In vitro release study of final chewing-gum formulations demonstrated: i) the rapid release of undamaged microparticles from gum matrix (5' chewing) and ii) an improved release of MCN from chitosan microparticles with respect to the release of MCN incorporated as such into chewing gum matrix.}\]

CONCLUSIONS

Chitosan microparticles demonstrated to be suitable in increasing the release rate of hydrophobic drugs from chewing gums.

REFERENCES