Insulin-loaded gellan microcapsules coated with resistant starch/pectin films: Morphology and mucoadhesive properties.

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ABSTRACT SUMMARY
Gellan gum microcapsules coated with films of resistant starch and pectin intended to oral administration of insulin were developed. Scanning electronic microscopy (SEM) analyzes show that coated particles have a smooth surface and a continuous internal structure of matrix systems. From “ex vivo” bioadhesion test can be concluded that microcapsules interact with the biological membrane mucus, which suggests its use as mucoadhesive polymeric carrier.

INTRODUCTION
Type I diabetic patients are treated with daily subcutaneous injection of insulin and the parenteral route of drug administration is painful, uncomfortable and has serious effects. Furthermore, this route often leads to decrease of patient adherence to treatment. The development of noninvasive route for insulin administration is necessary and the oral route represents a revolution, since is safer, comfortable and mimicking the physiologic dynamics of endogenous insulin via hepatic metabolism. However, insulin is a peptide susceptible to enzymatic degradation in acid pH of the stomach and shows low intestinal permeability. The use of gellan gum for obtaining microcapsules is an important strategy for protection against the adverse conditions of the GIT upper portions. Besides, the mucoadhesive properties of this polysaccharide can improve the interaction with biological membrane and so the permeability of the drug. On the other hand, colon specific delivery is favorable, since the colon provides a microenvironment with a pH closer to neutrality, reduced proteolytic activity and longer transit time. Colonic delivery can be achieved with coating of particles with biopolymers, as resistant starch obtained by retrogradation process. Therefore, the aim of this work was to prepare microcapsules of gellan gum coated with resistant starch/pectin and characterize them by SEM and “ex vivo” bioadhesion test.

EXPERIMENTAL METHODS
Microcapsules were prepared by ionotropic gelation. Gellan gum aqueous dispersions (1.5, 2.0 and 2.5\%) were mixed with insulin (0.5\%) and dropwised into aluminium cation solution (5\%) through 27-gauze flat-tipped needle, under stirring, which was kept for 30 min. Microcapsules were isolated by filtration, washed with distilled water and dried in oven-dryer at 30°C. Samples were labeled as 15, 20 and 25 respective to polymer concentration.

For filmogenic dispersion preparing, high amylose aqueous dispersion (5\%) was autoclaved (120°C/120 min), mixed with pectin dispersion (1:1) and subsequently submitted to retrogradation process by alternating thermal cycles (4°C and 30°C) for 16 days (two days at each temperature). Microcapsules were immersed in this dispersion containing PVA (0.01M) under magnetic stirring for 15 min, isolated by filtration and dried at 30 °C for 24 h.

The surface morphology of the microcapsules was studied by scanning electron microscopy (SEM) in JEOL JSM-7500F equipment.

Mucoadhesive properties were determined on a TA-XT2 Plus Texture Analyzer (Stable Micro Systems). Sections of pig gastrointestinal
mucosa (4cm²) were fixed on metallic holder and the microcapsules were attached to the cylindrical probe (10 mm) by using a double-face tape. The probe was moved down at constant speed (10mm min⁻¹) with a predetermined compressive force of 0.5 N until reach the mucosa. Sample was introduced 1 mm depth from the mucosa surface and the contact time was 60 s without the application of force during the contact. The probe was moved up at 20 mm min⁻¹ and the maximum detachment force (F_md) (N) and work of adhesion (W_a) (N.s), was calculated from area under the curve of force/time plots by Texture Exponent Lite software.

RESULTS AND DISCUSSION

In general, SEM micrographs indicate that microcapsules were approximately spherical in shape (Figures 1A, D and G). Some pores presented on the surface of 15 sample (Figure 1B) can be attributed to low polymer concentration that allow the formation of looser three-dimensional structure, whereas 20 sample has a more irregular surface with the presence of bubbles (Figure 1E).

Cross-sections (Figures 1C, F and I) evidence the matrix structure of microcapsules and the boundary region between the microcapsule core and the coating.

Table 1. Mucoadhesive properties of samples.

<table>
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<tr>
<th>Sample</th>
<th>F_md (N)</th>
<th>W_a (N.s)</th>
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<tbody>
<tr>
<td>15</td>
<td>1.6503 ± 0.2451</td>
<td>0.9450 ± 0.0538</td>
</tr>
<tr>
<td>20</td>
<td>1.0897 ± 0.1327</td>
<td>0.5263 ± 0.1214</td>
</tr>
<tr>
<td>25</td>
<td>2.7403 ± 0.2403</td>
<td>2.5290 ± 0.2727</td>
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The higher F_md (p<0.05) of 25 sample (Table 1) should be related to this increased polymer concentration enables a great number of polar functional groups to interact with mucin

The results of W_a are in agreement with F_md, since the higher work of adhesion value spent in detachment was presented by 25 sample. There was no statistically significant difference between the 15 and 20 microcapsule (p>0.05).

CONCLUSION

Microcapsules of gellan gum containing insulin were successfully prepared by ionotropic gelation and coated by immersion with retrograded starch films. The morphology analyzes revealed the matrix structure of the microcapsules as well the presence of a continuous coating. The microcapsules presented also important mucoadhesive properties. The evaluated properties can be modulated by change of polymer concentration.

REFERENCES


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