Cyclodextrin-bioadhesive nanoparticles for oral delivery of paclitaxel

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INTRODUCTION

Oral delivery is the most convenient and desired way for drug delivery. The major factor determinant for bioavailability of orally administered drug is the membrane permeability and drug solubility in the intestinal lumen. Many drugs show bioavailability problems due to their low water solubility, slow dissolution rate and instability in the gastrointestinal tract.
One possibility to enhance drug absorption may be the use of biodegradable nanoparticulate systems with bioadhesive properties.
Recently, Gantrez® AN (PVM/MA) has been proposed as a new polymer to prepare bioadhesive nanoparticles for oral drug delivery (1). In the other hand, cyclodextrins (CDs) can improve drug solubility, and also increase the loading capacity of nanoparticles (2). Thus, the association between CDs and Gantrez nanoparticles would be a good strategy to increase the loading capacity of lipophilic drugs and modulate their release from these pharmaceutical forms.
The objective of this study was to evaluate the feasibility of CD-Gantrez nanoparticles and their behaviour within the gut.

EXPERIMENTAL METHODS

Materials

Gantrez® AN 119 [poly (methyl vinyl ether-co-maleic anhydride)] was gifted by ISP (Spain). β-cyclodextrin (β-CD) was provided by Sigma-Aldrich (Steinheim, Germany) and 2-hydroxypropyl-β-cyclodextrin (OH-CD) by RBI (Massachusetts, USA). Rhodamine B isothiocyanate (RBITC) was purchased from Sigma (Spain).

Nanoparticles preparation

Nanoparticles were prepared as previously described (1). Briefly, β-CD or 2-HP-β-CD were sonicated in 2 ml of acetone containing 100 mg Gantrez. Then, the nanoparticles were formed by the addition of an ethanol/water mixture (1:1) and the organic solvents were eliminated by evaporation under reduced pressure. For bioadhesión studies, nanoparticles were fluorescently labelled by incubation with 1.25 mg of Rhodamine B isothiocyanate (RBITC). Finally the different CDs – Gantrez nanoparticle formulations were purified by centrifugation and lyophilized using sucrose (5%) as cryoprotector.

Characterization of nanoparticles

Size and zeta potential were determined by photon correlation spectroscopy (PSC) and electrophoretic laser Doppler anemometry, respectively, using a Zetamaster analyser system.
The amount of CDs associated to the nanoparticles was determined by HPLC coupled with Evaporative Light Scattering Detector (ELSD) (3). These results were confirmed by elemental analysis.
The quantity of loaded RBITC was estimated after total hydrolysis of certain a amount of nanoparticles in 0.1 N NaOH medium (24 h, 37 °C). RBITC was determined by colorimetry at wavelength 540 nm.

In vivo bioadhesión studies

The bioadhesion study was carried out using a protocol previously described (4). An aqueous suspension containing 10 mg nanoparticles-RBITC was administered perorally to male Wistar rats fasted overnight. At 0.5, 1, 3 and 8 hours post administration, animals were sacrificed, the entire gastrointestinal tract removed and cut in six anatomical regions: stomach, intestine (I1, I2, I3 and I4) and caecum. RBITC was extracted with methanol and determined by spectrofluorimetry, to estimate the fraction of adhered particles to the mucosa. The kinetic parameters of bioadhesion (Q_{max}, AUC_{adh}, K_{adh} and MRT_{adh}) were estimated using the WinNonline 1.5 software.

RESULTS AND DISCUSSION

Nanoparticles characterization

CD-Gantrez nanoparticles displayed a spherical- shape and a typical size of about 150 nm (Table 1). Interestingly, the association between CDs and Gantrez enabled us to obtain nanoparticles with a smaller size than conventional ones. In addition, this decrease in the size was associated with a high yield of the process (about 90% by HPLC). The amount of CDs associated to nanoparticles was found to be dependent on the type of the oligosaccharide used (about 90 g/mg for beta-CD and 70 g/mg for OH-CD). The presence of CD was also confirmed by elemental analysis.

Table 1. Physico – chemical characteristics of PMV/MA nanoparticles (mean±SD, n=10).

	Size (nm)	Zeta pot. (mV)	CD loading (μg/ mg NP)	RBITC content (μg/ mg NP)
NP	179±2	-48.1±0.8	-	10.9±0.3
βCD-NP	144±6	-51.1±8.8	88.4 ±9.9	13.3±2.1
OH-CD-NP	140±7	-52.1±3.7	68.4±4.3	12.4±1.1

Bioadhesive profile of NP in the GI tract

Figure 1 shows the bioadhesive profiles of the formulations tested by representing the amount of NP adhered to the different GIT segments (stomach, small intestine and caecum) at different times post-administration.

OH-CD-NP displayed a significantly higher ability to develop adhesive interactions within the gut that CD-NP and NP. On the other hand, CD-NP displayed a quite homogeneous distribution within the whole gut, whereas OH-CD-NP displayed a significant tropism for the upper regions of the gut. Formulations displayed a homogeneous distribution along the gastrointestinal tract.

Table 2. Bioadhesion parameters for the different formulations tested.

	Q_{max} (mg)	**AUC_{adh} (mg h)**	**K_{adh} (h^{-1})**	**MRT (h)**
NP	2.3±0.3	9.90	0.19±0.03	3.19
βCD-NP	2.3±0.3	13.86	0.07±0.01	3.53
OH-CD-NP	3.5±0.5	18.16	0.09±0.08	3.41

Table 2 summarises the parameters used to quantify the in vivo bioadhesive characteristics of the different formulations tested. OH-CD-NP showed the highest initial capability to develop adhesive interactions within the gut (Q_{max}). Similarly, the intensity of these interactions (AUC_{adh}) was found 2-times higher than for NP. On the other hand, CD-NP did not show a special ability to interact with the gut mucosa; although the AUC_{adh} was found to be 1.5-times higher than for CD. In any case, both CDs nanoparticles displayed 2-times lower elimination rates (K_{adh}) than conventional nanoparticles.

These results enable us to hypothesise that the presence of CDs (mainly OH-CD) may facilitate the interaction with the mucosa and the development of stronger adhesive interactions with components of the mucosa than NP.

In summary, the combination between CDs and Gantrez nanoparticles may be of interest for the oral delivery of lipophilic drugs. The rationale selection of the cyclodextrin can, not only modify the drug loading and modulate its release, improve the residence of the drug delivery system in intimate contact with the gut mucosa.

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Figures:

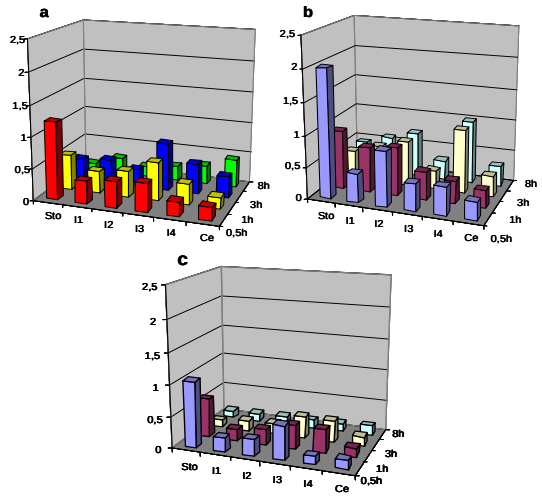

Fig. 1. Distribution of nanoparticles in the GIT after the oral administration of 10 mg nanoparticles. Each value represents the mean of the results of four experiments. (a) βCD-NP, (b) OH-CD-NP, (c) NP. Plot: x-axis represents the adhered fraction (mg); y-axis represents the different gut segments (Sto: stomach; I1, I2, I3, I4: intestinal portions; Ce: caecum); z-axis represent the time post-administration (in hours).