CYCLODEXTRIN-GANTREZ NANOPARTICLES AS BIOADHESIVE CARRIERS FOR ORAL DRUG DELIVERY

M. Agüeros[1], M.A. Campanero[2], J.M. Irache[1*]
[1] Centro Galénico. University of Navarra. [2] Departamento de Farmacología Clínica. Clínica Universitaria. 31008 Pamplona (Spain).
E-mail: jmirache@unav.esT

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). On 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

Nanoparticles preparation and characterization

CDs were dispersed in Gantrez® AN 119 organic solution. Then, the nanoparticles were formed by solvent displacement method. For bioadhesión studies, nanoparticles were fluorescently labelled with Rhodamine B isothiocyanate (RBITC).

Size and zeta potential were determined by photon correlation spectroscopy (PSC) and electrophoretic laser Doppler anemometry, respectively. Also, RBITC content was determined by colorimetry. The amount of CDs associated to the nanoparticles was determined by HPLC coupled with Evaporative Light Scattering Detector (ELSD) (3).

In vivo bioadhesión studies

An aqueous suspension of 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 (Sto) intestine (I1, I2, I3 and I4) and caecum (Ce). RBITC was extracted and determined by spectrofluorimetry, to estimate the fraction of adhered particles to the mucosa. The kinetic parameters of bioadhesion (Qmax, AUCadh, Kadh and MRTadh) 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 140 nm. Interestingly, the association between CDs and Gantrez enabled us to obtain nanoparticles with a smaller size than conventional ones (180 nm). 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 µg/mg for β-CD and 70 µg/mg for OH-CD). The presence of CD was also confirmed by elemental analysis.

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 ßCD-NP and NP. On the other hand, ßCD-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.
Figure 2 shows microphotographs concerning the interaction between OH-CD-NP and the intestinal mucosa.

Table 1. 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 1 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 (Qmax). Similarly, the intensity of these interactions (AUCadh) 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 AUCadh was found to be 1.5-times higher than for CD. In any case, both CDs nanoparticles displayed 2-times lower elimination rates (Kadh) 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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References
[1] P. Arbós et al. J Control Release. 88(2) (2003) 345.
[2] F. Kihara et al. Bioconjugate Chem.14 (2003) 342.
[3] M. Agüeros et al. J Pharm and Biomed Anal. 39 (2005) 495.

Figures

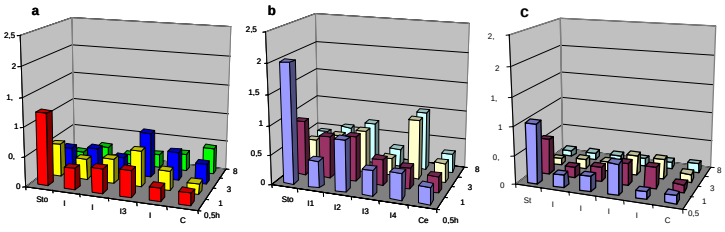

Figure 1. Distribution of nanoparticles in the GIT after the oral administration of 10 mg RBITC-nanoparticles at different time intervals. (a) βCD-NP, (b) OH-CD-NP, (c) NP. Plot: x-axis represents the adhered fraction (mg); y-axis represents the different gut segments (Sto:stomach; I1, I2, I3, I4: intestinal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

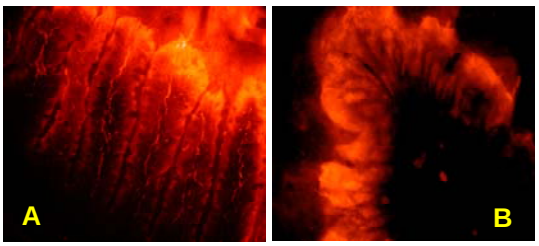

Figure 2. OH-CD-NP in the small intestine 2 h after administration to animals. (A) Magnification 20X (B) Magnification 100X.