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Interactions of biopolymers carrageenans with cationic drug doxazosin mesylate characterized by means of differential scanning calorimetry

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When ionic polymers (polyelectrolytes) are used as excipients in pharmaceutical formulations, the properties of oppositely charged drugs may be strongly affected by the charge-charge interactions or complex formation. Usually these effects are considered as a negative event resulting in a drug-excipient incompatibility. Sometimes ionic interactions are preferred to prolong drug release from dosage forms in a controllable manner. Ionic interactions of carrageenans with doxazosin mesylate were confirmed by differential scanning calorimetry (DSC). Evident peak shifts and shape changes of assumed desulfation peak of carrageenans in concordance with disappearance of melting peak of doxazosin mesylate (DM) in DSC curves were obtained. The range of thermal effects is depended on the ratio of doxazosin mesylate and carrageenans. The higher the ratio of DM compared to CARRs the more evident are the interactions.

Carrageenans (CARRs) are polymers of natural origin, very often used in food products as thickeners and stabilizers, however their use is also increasing in pharmaceutical applications (Bonferoni et al. 2000). They constitute a family of linear sulfated polysaccharides extracted from various species of the marine red algae *Rhodophyta* and differ mainly with the respect to the number of ester sulfate groups per disaccharide unit and the presence of anhydrogalactose. There are three main types: iota (ι), kappa (κ) and lambda (λ). The idealized amount of ester sulfate moieties per disaccharide unit is $3 (\lambda) > 2 (\iota) > 1 (\kappa)$ (Reilly 2003). Different charge densities are responsible for different polymer characteristics like viscosity in solution, gelling behaviour, susceptibility on different counterions in various media etc. (Bongaerts et al. 2000). Polyanionic nature of CARRs has a crucial influence on drug release behavior as well (Singh and Lelham 1998), especially on release of cationic drugs like doxazosin mesylate, which is used for the treatment of hypertension. Differential scanning calorimetry (DSC) was used for the characterization of various drug-excipient interactions. It represents a rapid analytical technique for evaluating these interactions through the appearance, shift, or disappearance of endo- or exothermal effects and/or variations in the relevant enthalpy values (Clas et al. 1999).

The aim of our work was to characterize the interactions of doxazosin mesylate with carrageenans, which were used to prolong

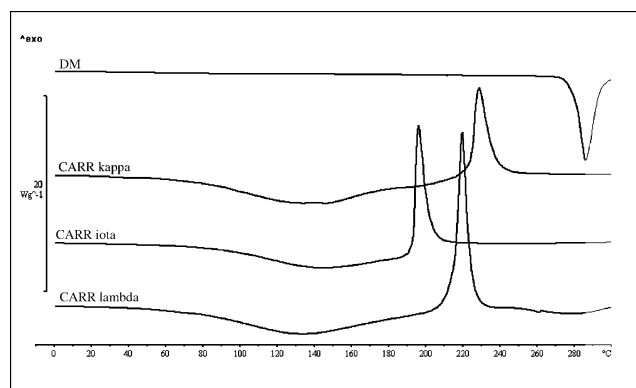


Fig. 1: DSC curves for DM (doxazosin mesylate), CARR (carrageenan) kappa, iota and lambda

the drug release from carrageenan matrix tablets. In order to simulate these interactions which take place in aqueous media, pastes of DM and CARRs were prepared and evaluated by DSC method.

Thermal properties of pure substances can be seen in Fig. 1. Doxazosin mesylate shows an endothermic peak at 280°C which represents melting of the pure drug crystals. In the case of CARRs strong exothermal effects between 190 and 220°C can be observed which are most probably representing the breakdown of the ester sulphate moieties on polysaccharide chains. The position of the assumed desulfation peak is different for each CARR and surprisingly does not correlate with the number of sulfate moieties ($\lambda > \iota > \kappa$). On CARRs DSC curves (Fig. 1) a broad endothermic peak can also be observed starting at around 40°C and finishing at the exothermic desulfation. This broad peak is the consequence of evaporation of residual water (moisture) of CARRs, also confirmed by Karl-Fischer method (data not shown).

DSC curves of pastes of DM with ι , κ and λ CARR (Fig. 2) are much different from those of pure substances (Fig. 1), what is an evidence of changed thermal properties. Since all DSC curves of pastes exhibited the same thermal pattern, only DM with ι CARR in different proportions is presented (Fig. 2). A shift of the desulfation peak of the CARR ι in pastes towards higher temperature in case of DM:CARR $\iota = 70:30$ and $50:50$ (w/w) is observed. At the same time the shape of these peaks has also changed. The desulfation peak of paste with the highest amount of CARR ι (DM:CARR $\iota = 30:70$) has practically remained on its position, however the shape of this peak has changed. Besides, a broad endothermic effect due to evaporation of residual water at lower temperatures in pastes was obtained, what was the same as in the case of pure CARRs.

Evident thermal difference compared to starting material can also be seen when comparing melting peaks of the DM from

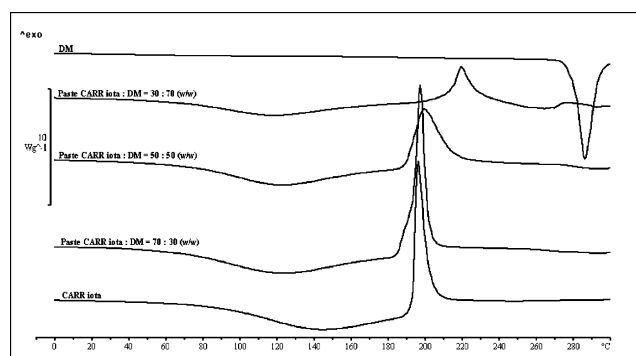


Fig. 2: DSC curves for DM (doxazosin mesylate), CARR (carrageenan) iota and pastes of CARR iota: DM in different ratios: 30:70 (w/w); 50:50 (w/w) and 70:30 (w/w)

pastes against pure drug – no peak can be observed in case of DM:CARR ι pastes.

The results presented indicate a presence of interactions between DM and CARRs. According to the chemical nature of both substances the presence of ionic interactions between the DM and carrageenans is most likely. DM molecule has 5 nitrogen atoms with varying proton affinities (from 880 kJ/mol to 1072 kJ/mol) (Kinsella et al. 2006) and nitrogen with the highest proton affinity is assumed to be involved in the interaction with the anionic ester sulfate moieties of the CARRs.

Furthermore, ester sulfate moieties of the carrageenans are abundant for possible interactions compared to DM in any ratio used since CARRs are large polymer molecules having 1–3 ester sulfate moieties per disaccharide unit. Subsequently the higher the amount of DM compared to CARR in paste, the higher the number of ionic interactions which consequently leads into more pronounced thermal effects observed in our DSC results. Ionic interactions between DM and CARRs are believed to inhibit desulfation of CARRs at temperatures observed for pure substances which can be seen as the desulfation peak shift towards higher temperatures. In accordance with this melting peak of the DM cannot be seen due to ionic interactions, which were confirmed also by dynamic vapour sorption and potentiometry, but are not described herein.

One possibility for the disappearance of the melting peak of DM would be the conversion of crystalline drug to an amorphous form during paste preparation. Tg of DM amorphous form is around 144.1 °C according to known data (Grčman et al. 2002) so it is clear that in our case this thermal event would be overlaid with the endothermic evaporation of water and could not be determined. Besides, if conversion to amorphous form would take place, cold crystallization should appear on DSC curve at higher temperatures. An exothermic event at around 275 °C is indeed the case with paste DM:CARR ι = 70:30. Nevertheless no melting is seen afterwards which indicates that this assumption is not valid.

With our study we were able to prove and characterize interactions between DM and CARRs. These interactions can be regarded as drug-excipient incompatibility, whereas in our case these interactions are beneficial since they allow us to additionally prolong the sustained drug release from carrageenan matrix tablets.

Experimental

1. Materials

Viscarin GP 209 (λ Carr), Gelcarin GP 379 (ι Carr) and Gelcarin GP 911 (κ Carr) (FMC Biopolymers, USA), active substance doxazosin mesylate (DM) (MM = 547,58 g/mol, supplied by Krka, d.d, Slovenia).

2. Preparation of samples

Physical mixtures of DM with each selected CARR were prepared in 30:70, 50:50 and 70:30 w/w ratio by simple blending of the components in a mortar for 10 min at room temperature.

To study drug-excipient interactions a paste from physical mixtures of different proportions of DM and CARR was made by adding small amounts of water to the physical mixture during mixing until paste properties were achieved. The paste was then dried in a drying chamber at 45 °C for 24 h (Bonferoni et al. 2000).

3. DSC Measurements

DSC experiments were carried out with a Mettler TA 1 Star software apparatus (MettlerToledo, Switzerland) equipped with a DSC 25 cell. Samples of about 5–10 mg were weighed (Mettler M3 microbalance) in pierced Al pans and scanned under nitrogen atmosphere over a temperature range of 0° to 300 °C at a heating rate of 40 °C/min.

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