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Short communication

Ionotropic gelation and chemical crosslinking as tools to obtain matrix capsules with mesalazine

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Introduction

Many drugs applied orally are either sensitive to the acidic environment of the stomach or cause moderate to severe side effects in the proximal regions of gastrointestinal tract (GIT) (Liechty et al., 2010). Such disadvantages may contribute to lower therapeutic efficiency or lead to reluctant use by the patients. In order to avoid it, the drug release often needs to be modified and shifted to the distal parts of the GIT, which is usually achieved by coating with pH-sensitive polymers or incorporation into polymeric matrices (Zia et al., 2018).

In the case of some intestinal malfunctions, it is necessary not only to deliver the drug to the site of action but also to extend the release as much as possible to provide proper API concentration in time. Such diseases like ulcerative colitis (UC), Crohn's Disease (CD) or bowel inflammations are the most known examples. They are usually treated with anti-inflammatory drugs, steroids and immunosuppressants. Among the first mentioned, mesalazine (5-ASA) is the most commonly used. Unfortunately, to the best of our knowledge, none of the marketed 5-ASA formulations provide sufficient prolonged release after reaching the colonic environment. Therefore, taking into account the improvement of the therapy, it is fully justified and desired to search for novel pH-sensitive carriers for 5-ASA. One of the possibilities, which currently gains much interest is incorporation of drugs into spherical polysaccharide matrices by means of ionotropic gelation. Lately, the most extensively studied and described polymer in this case is gellan gum (Maiti et al., 2015). Unfortunately, according to the literature, gellan-based matrices (beads) stabilized only by cations may not be resistant enough to higher pH values (Patil et. al., 2006). The solution to this disadvantage may be the use of chemical reactions to covalently link the polymer chains and reduce their mobility in the three-dimensional network, followed by improvement of its stability.

Taking into account the facts presented above, the aim of the project was to design, obtain and characterize gellan gum-based beads for colon-specific, prolonged release of mesalazine. The main goal was to verify the hypothesis whether and to what extent the glutaraldehyde crosslinking affects the properties of the beads in comparison to the traditional ones, stabilized only by calcium cations. Moreover, gellan was not only crosslinked solely but also its blends with other natural polymers were prepared.

Materials and methods

Capsules prepared by ionotropic gelation method or both ionotropic gelation and chemical crosslinking based on gellan gum, hydroxyethylcellulose and κ carrageenan were analyzed, both immediately after receiving and after traditional drying (48 h, 40 °C) or lyophilization (Epsilon 2–4(LSCplus) (Martin Christ GmbH, Osterode am Harz, Germany). In the first case, shape and surface assessment using a stereoscopic microscope were applied, as well as mechanical tests, using a texture analyzer (Shimadzu Autograph AGS-X Texture Analyzer) and rheometer (HAAKE^{TM} RheoStress1, Thermo Electron Corp., Waltham, MA, USA) working in oscillatory mode. The samples were tested with the serrated titanium plate-plate geometry with a diameter of 35 mm to avoid slippering. The samples (1.0 mL) were placed on the lower plate with a syringe. The measuring gap was set at 1.0 mm. After lowering the upper plate, the excess of the sample was gently removed with special care to avoid any unwanted shearing. To equilibrate the sample, the time between loading and measurement was set at 300 s. The temperature

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during the measurements was set at 25.0 ± 1.0°C. Capsules after dehydration were characterized by the following techniques: Raman analysis, differential scanning calorimetry, scanning electron microscope (JEOL JSM-6380LA equipped with EDS (energy dispersive spectroscopy) detector). To obtain the electrical conductivity, the samples were coated with gold under a vacuum in a sputter coater for 75 s and at 15 kV. The samples were examined under the magnification of ×1000 by a scanning electron microscope. The crosslinked gellan were analyzed in terms of cell toxicity. In addition, parameters such as swelling at different pHs (2; 4,5; 7,4), drug content and degree of encapsulation and dissolution studies using USP 1 apparatus in various pH (2 and 7,4). The cross-linked polymer was also evaluated for cellular toxicity (MTT assay). Studies also included assessing the behavior of the capsules in the gastrointestinal tract of rats (Male Wistar rats).

Results and discussion

The rheological analysis included oscillatory stress and frequency sweeping. The texture profile analysis was performed to calculate texture parameters. Placebo gels without the addition of gelling agents had the weakest structure. The drug had the strongest ability to increase the stiffness of the polymer network. The weakest structure revealed the placebo samples without the addition of gelling agents. Texture analysis revealed no significant influence of the drug on the strength of the gels, while rheological measurements indicated clear differences. It can be concluded that in the case of some parameters methods correlate, that is, the effect related to gelling ions. However, the rheological analysis seems to be more precise and sensitive to some changes in the mechanical properties of the gels. According to the scanning electron microscopy (SEM) images presented in Figures 1 and 2 no significant differences regarding the polymer composition of the samples are visible.

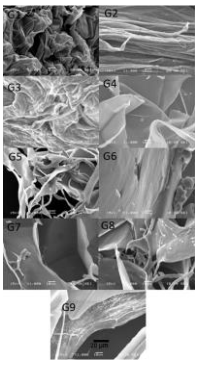

Fig. 1. SEM photographs of placebo (G1-G9) formulations presenting internal structure of lyophilized gels

However, taking into consideration the differences between the images of placebo (Figure 1) and the corresponding drug loaded samples (Figure 2), the drug crystals may be noticed in the latter ones. Furthermore, significant differences were observed in case of drug release profiles between formulations crosslinked only with calcium ions and additionally crosslinked with glutaraldehyde (GA). GA assured more prolonged release. Such observations were confirmed in *in vivo* study using Wistar rats.

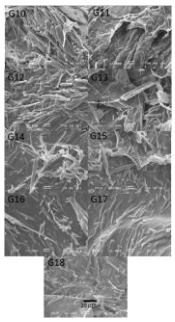

Fig. 2. SEM photographs of MSN-loaded (G10-G18) formulations of lyophilized gels presenting visible crystals of MSN incorporated into gel matrices

Conclusion

Ionotropic gelation and crosslinking with glutaraldehyde of gellan gum based beads seems to be very promising tools to obtain colon-specific and prolonged release beads to deliver mesalazine to the distal parts of gastrointestinal tract.

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