International Journal of Pharmaceutics 488 (2015) 12–19

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Development of mucoadhesive sprayable gellan gum fluid gels

Mohammed H. Mahdi, Barbara R. Conway, Alan M. Smith *

Department of Pharmacy, School of Applied Sciences, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK

ARTICLE INFO

Article history:
Received 2 February 2015
Received in revised form 3 April 2015
Accepted 6 April 2015
Available online 8 April 2015

Keywords:
Gellan gum
Mucoadhesion
Fluid gel
Nasal spray
Caffeine
Modified release

ABSTRACT

The nasal mucosa provides a potentially good route for local and systemic drug delivery. However, the protective feature of the nasal cavity make intranasal delivery challenging. The application of mucoadhesive polymers in nasal drug delivery systems enhances the retention of the dosage form in the nasal cavity. Several groups have investigated using low acyl gellan as a drug delivery vehicle but only limited research however, has been performed on high acyl gellan for this purpose, despite its properties being more conducive to mucoadhesion. High acyl gellan produces highly elastic gels below 60 °C which make it difficult to spray using a mechanical spray device. Therefore, in this study we have tried to address this problem by making fluid gels by introducing a shear force during gelation of the gellan polymer. These fluid gel systems contain gelled micro-particles suspended in a solution of un-gelled polymer. These systems can therefore behave as pourable viscoelastic fluids. In this study we have investigated the rheological behavior and mucoadhesion of fluid gels of two different types of gellan (high and low acyl) and fluid gels prepared from blends of high and low acyl gellan at a 50:50 ratio. The results demonstrated that by preparing fluid gels of high acyl gellan, the rheological properties were sufficient to spray through a standard nasal spray device. Moreover fluid gels also significantly enhance both high acyl and low acyl gellan mucoadhesion properties.

1. Introduction

Liquid nasal sprays are useful dosage forms for local and systemic delivery, but often suffer from poor retention, dripping out of the nose or down the back of the throat, which leads to reduced bioavailability (Jansson et al., 2005). Many ways have been introduced to address this problem; one such way is by formulating nasal sprays that contain polymers which are mucoadhesive. These polymers possess suitable rheological properties that enable them to flow during administration and then to adhere to mucosal tissue, consequently increasing the residence time and improving bioavailability. A complete understanding of the mucoadhesion mechanism is not fully understood. It is generally accepted however, that inter-diffusion and interpenetration take place between the chains of the mucoadhesive polymer and mucus gel network, which creates sufficient contact for entanglement. Secondary chemical bonds are then formed between the polymer chains and mucin molecules (Hägerström, 2003). Several polysaccharides have been widely investigated as mucoadhesive polymers due to their intrinsic physicochemical properties that facilitate mucoadhesion such as hydrophilicity, numerous hydrogen bonding functional groups and viscoelastic properties when hydrated. Gellan gum is a bacterial exo-polysaccharide produced by the bacteria *Sphingomonas elodea* (Sworn et al., 1995; Gibson and Sanderson, 1997) and is a linear tetrasaccharide repeat unit consisting of (1→4)-l-rhamnopyranosyl-(α-1→3)-D-glucopyranosyl-(β-1→4)-D-glucuronopyranosyl-(β-1→4)-D-glucopyranosyl-(β-1→(Morris et al., 2012). Gellan gum is a promising polymer for use in nasal formulations because of its ability to form a gel in situ on exposure to physiological concentrations of cations (Mahdi et al., 2014). Typically, ion concentrations required to gel gellan are in the region of 100 mM for monovalent cations and 5 mM for divalent cation however the strength of the gels produced depend on the concentration of gellan (Morris et al., 2012). The native polymer is high acyl gellan (HA) which contains O-5-acetyl and O-2-glyceryl groups on the (1→3)-linked glucose residue (Fig. 1A). When exposed to alkaline media at high temperatures, both acyl groups are hydrolyzed and the deacylated form, low acyl gellan (LA), is obtained (Fig. 1B) (Mao et al., 2000). The resulting texture of HA and LA gellan gum gels are very different, and can be considered to be at the opposite ends of the textural spectrum for hydrogels, with LA gellan forming hard but brittle gels and HA gellan forming soft, elastic gels. By varying the ratio of HA:LA gellan gum, a diverse

* Corresponding author. Tel.: +44 1484 472 350; fax: +44 1484 472 350.
E-mail address: a.m.smith@hud.ac.uk (A.M. Smith).

http://dx.doi.org/10.1016/j.ijpharm.2015.04.011
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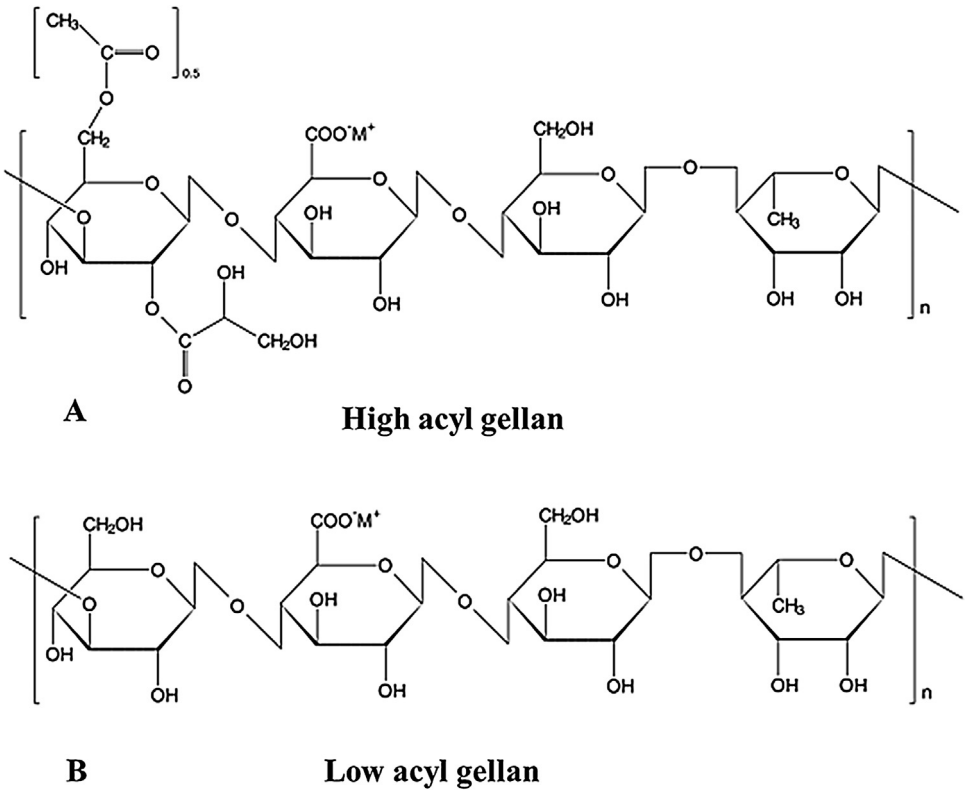

Fig. 1. Chemical structure of gellan gum (A) high acyl gellan gum (B) low acyl gellan.

range of textures can be obtained. The properties of blends of HA and LA gellan are intermediate between that of high and low acyl gellan and it is possible to obtain textures close to those of other hydrocolloids such as xanthan gum, locust bean gum and alginate (Sworn, 2009).

Bacon et al. (2000), investigated using LA gellan gum for an in situ intranasal formulation to deliver influenza vaccine. Jansson et al. (2005) reported that LA gellan can enhance epithelial uptake of high molecular weight fluorescein dextran. In addition, *in vivo* studies confirmed gellan gum to be nonirritant and not toxic to the epithelial tissue even for a prolonged period of time (Cao et al., 2009; Mahajan and Gattani, 2009) and these gellan formulations retained stable over 6 months (Cao et al., 2009; Belgamwar et al., 2009). Recently researchers have looked to develop such dosage forms using micro-particle and liquid nasal formulations (Cao et al., 2009; Mahajan and Gattani, 2009). Although these systems have shown some promise as vehicles for nasal delivery, there are issues such as erosion and rapid clearance by microvilli. These issues could potentially overcome by using fluid gels.

Fluid gels can be formed by applying shear force to a biopolymer during a sol–gel transition, the end product is gelled particles suspended in un-gelled polymer solution. These fluid gels can be formulated so the bulk material acts as a pourable viscoelastic fluid whilst retaining a cross-linked gel microstructure within the particles. The physical properties of fluid gels can be tuned by simply changing the concentration of the polymer or by the rate of cooling and/or shear rate during fluid gel formation (Gabriele et al., 2009; Fernández Farrés and Norton, 2015; Mahdi et al., 2014).

In this study we have investigated the rheological behavior and mucoadhesion of fluid gels of two different types of both LA gellan and HA gellan and fluid gels prepared from blends of LA gellan and HA gellan at a 50:50 ratio. Gellan gum fluid gels of HA, LA and HA/LA blends loaded with a model drug (caffeine) were investigated as a mucoadhesive nasal spray formulation and compared with in situ gelling gellan solutions. The rheological properties and *in vitro* measurements of retention time on mucosal tissue were investigated.

2. Materials and methods

2.1. Materials

High acyl gellan gum (KELCOGEL^{TM}) was kindly donated by CP Kelco (USA). Low acyl gellan and caffeine were purchased from Sigma Scientific (UK). Phosphate buffer saline (PBS) was purchased from Fisher Scientific (UK). Fresh porcine mucosal tissue was donated from a local abattoir.

2.2. Preparation of fluid gel formulation

Gellan solutions were prepared by adding precise amounts of high and low acyl gellan gum to produce a 0.25% w/w final polymer concentration to deionised water at 85 °C containing 2 mg/mL caffeine. This was allowed to quiescently cool to room temperature prior to use.

To prepare the fluid gels, sodium chloride (0.1%, 0.5%, and 1% w/w) was added to the hot caffeine-loaded gellan solutions, as crosslinking cations (as described above) then loaded on to a Bohlin Gemini HR Nano Rheometer and allowed to cool at 2 °C min^{-1} to 20 °C whilst being sheared at a shear rate of 500 s^{-1} using a 55 mm cone and plate geometry. Once cooled, the fluid gels were recovered and stored at room temperature prior to use.

2.3. Rheological measurements

All rheological measurements were performed using a Bohlin Gemini Nano HR rheometer (Malvern Instruments, Worcestershire, UK) fitted with a 55 mm cone and plate geometry.