



Mini review

Application of gellan gum in pharmacy and medicine



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ABSTRACT

Over the past few decades, microbial polysaccharides have been under intense investigation due to their advantageous physicochemical properties. A great structural diversity of these biomolecules has led to multiple applications in food industry, personal care products, pharmacy and medicine. Currently, one of the most widely studied and fully described member of this group is gellan. It is a linear polymer produced by *Sphingomonas elodea*. A polymer chain of gellan consists of a tetrasaccharide repeating unit of L-rhamnose, D-glucose and D-glucuronate. So far most of the studies have been focused on the application of gellan as a food ingredient. However, due to the unique structure and beneficial properties, gellan is currently described as a potent multifunctional additive for various pharmaceutical products. Specific gelling properties in different media led to the development of controlled release forms based on gellan. Various formulations have been studied including oral, ophthalmic, nasal and other. Recent reports suggest that gellan-based materials can also be used in regenerative medicine, stomatology or gene transfer technology.

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1. Introduction

The unique properties, biocompatibility, widespread availability and low production costs led to the application of natural gums in various areas of our life. This class of compounds consists of polysaccharides obtained from plant tissues (gum acacia, gum ghatti, gum tragacanth etc.), seeds (guar gum, konjac gum etc.), seaweeds (agar-agar gum, alginates, carrageenans etc.) or micro-organisms (gellan gum, xanthan gum, rhamsan gum, welan gum etc.). Primarily, gums were used mainly as additives for food products (Francois et al., 1986; Bayarri et al., 2001; Totosa and Pérez-Chabela, 2009; Imeson, 2010; Banerjee and Bhattacharya, 2011). Simultaneously, natural gums or their derivatives have been broadly investigated as excipients for pharmaceutical or biomedical purposes (Dumitriu, 2002; Rehm, 2010). Matrix tablets (Sujja et al., 1999; Toti et al., 2004; Vendruscolo et al., 2005; Mundargi et al., 2007b; Asghar et al., 2009; Rasul et al., 2010; Vijan et al., 2012), soft or cross-linked hydrogels (Shalviri et al., 2010), floating beads (Alhaique et al., 1996; Santucci et al., 1996; Verma and Pandit, 2011), pellets (Santos et al., 2004), microspheres (Sullad et al., 2011; Kajjari et al., 2012), *in situ* forming systems (Miyazaki et al., 1999) or transdermal films (Mundargi et al., 2007a) are the common examples.

One of the most extensively studied and described member of bacterial polysaccharides is gellan gum. It was discovered in 1978 (Kaneko and Kang, 1979; Morris et al., 2012) and is commercially provided by C.P. Kelco in USA and Japan. Gellan is produced by the bacteria *Sphingomonas* (formerly *Pseudomonas*) *elodea* (Kang et al., 1982; Nampoothiri et al., 2003; Bajaj et al., 2007). It is a linear, anionic exopolysaccharide, with the repeating unit consisting of α -L-rhamnose, β -D-glucose, and β -D-glucuronate, in the molar ratios 1:2:1 (Fig. 1) (Jansson and Lindberg, 1983; Milas et al., 1990). Native form of gellan contains two types of acyl substituents, namely L-glyceryl and acetyl (Chandrasekaran et al., 1992). Alkaline hydrolysis is used to remove both of the residues and gives deacetylated gellan, also called low-acetyl or low-acyl (Kang et al., 1982).

Both native and low-acyl gellan form hydrogels in the presence of mono-, di- (Shimazaki et al., 1995; Ohtsuka and Watanabe, 1996; Tang et al., 1996, 1997; Mao et al., 2000) and trivalent cations (Maiti et al., 2011). The process is temperature dependent. Initially, to obtain a clear water solution, heating to at least 70°C is needed. Subsequent cooling leads to conformation changes of the polymer chains which induce coil-to-helix transition. Native gellan gives soft, easily deformable gels, while the deacetylated one forms rigid and brittle gels. Various analytical techniques have been used to determine the properties of gellan solutions and gel formation mechanism. These include rheological measurements (Izumi et al., 1996; Miyoshi et al., 1996; Nakamura et al., 1996b; Jampen et al., 2000; García et al., 2011; Flores-Huicoche et al., 2013), texture analysis (Sworn et al., 1995; Mao et al., 1999a,b; Huang et al., 2003;

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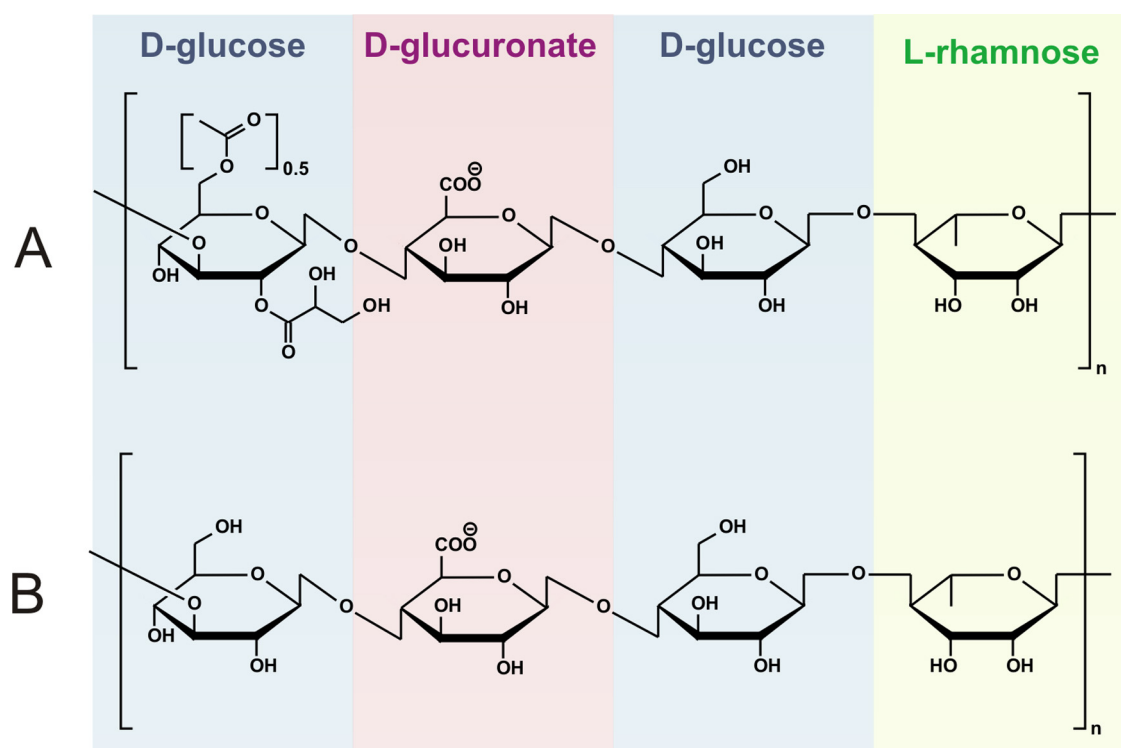


Fig. 1. The structure of native (A) and low-acyl (B) form of gellan gum.

Picone and Cunha, 2011), tensile testing (Teratsubo et al., 2002), circular dichroism (Miyoshi et al., 1995; Ogawa et al., 2002), differential scanning calorimetry (Mazen et al., 1999; Picone and Cunha, 2011), confocal laser scanning microscopy (Pérez-Campos et al., 2012), nuclear magnetic resonance (Matsukawa and Watanabe, 2007; Tako et al., 2009; Shimizu et al., 2012), polarization modulation spectroscopy (Horinaka et al., 2004), atomic force microscopy (Ikeda et al., 2004; Funami et al., 2009). It was stated that in case of native gellan, the acetyl and glyceryl groups located on the periphery of the helix hamper the polymer chain association and contribute to less effective packing (Morris et al., 1996; Mazen et al., 1999). After deacetylation the cations can easily form bridges between polymer chains. The process leads to generation of a branched network (Fig. 2) (Grasdalen and Smidsrød, 1987; Chandrasekaran et al., 1988; Quinn and Hatakeyama, 1993; Ikeda et al., 2004; Morris et al., 2012).

The gelling temperature, gel strength, texture, clarity and the rate of gel formation strongly depend on the pH value (Horinaka et al., 2004; Picone and Cunha, 2011), presence of sugars (Whittaker et al., 1997; Bayarri et al., 2002; Kasapis, 2006; Evageliou et al., 2010, 2011), type and concentration of cations (Dai et al., 2010). The specific gelling properties in different media led to the development of controlled release forms based on gellan. Various pharmaceutical solid, semi-solid and liquid formulations have been studied for oral (Miyazaki et al., 1999; Kubo et al., 2003), buccal (Remuñán-López et al., 1998), ophthalmic (Carlfors et al., 1998; Kesavan et al., 2010; Dickstein et al., 2001; Liu et al., 2010), nasal (Cao et al., 2009; Mahajan and Gattani, 2009) or rectal administration (El-Kamel and El-Khatib, 2006). Moreover, gellan-based materials are investigated in the field of tissue regeneration (Cencetti et al., 2011; Shin et al., 2012), dental care (Chang et al., 2012), bone repair (Chang et al., 2010), gene delivery (Goyal et al., 2011) or biosensor synthesis (Wen et al., 2008). The available

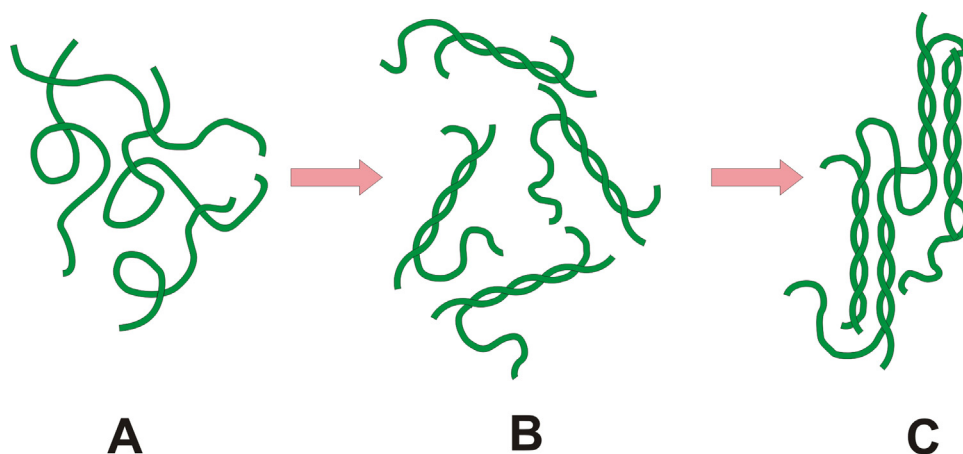


Fig. 2. Gradual transformation of gellan gum from aqueous solutions (modified from Miyoshi et al., 1996).

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