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Evaluation of gellan gum fluid gels as modified release oral liquids

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ABSTRACT

Oral liquids are often preferred for drug administration to patients for whom swallowing is difficult, however, formulating modified release versions can be challenging. A potential route to achieve modified release in oral liquids is by using fluid (sheared) gels formed by introducing a shear field during gelation in gel-forming biopolymers. These fluid gels can act as pourable viscoelastic fluids but retain true gel micro/nano structure. Here, we have demonstrated that fluid gels have potential as paediatric oral liquids preventing release of ibuprofen in simulated gastric fluid. Subsequent release at pH 7.4 was affected by the duration of exposure and magnitude of acid pH with a linear relationship between onset of release and the preceding acidic exposure duration. Delayed release was a result of increasing gel stiffness, a consequence of the acidity of the initial release media and exposure time. A much faster release rate was measured when exposure time in acid was 10 min compared with 60 min. This study highlights the potential to design fluid gels that are tuned to have a specified stiffness at a particular pH and exposure time. This could enable the preparation oral liquids with modified release behaviour.

1. Introduction

There is an ever increasing demand for the development of age appropriate dosage forms, especially for paediatric patients and older adults who have difficulties in swallowing. This is most apparent in modified release formulations where the functional excipients responsible for controlling drug release can become ineffective due to manipulation prior to administration to children. Even over the counter antipyretic formulations have an increased risk of side effects in children. Worryingly, there are very few oral modified-release drug delivery platforms suitable for administration to paediatrics. Generally, for children and patients who find swallowing is difficult, syrup-based oral liquids are the preferred dosage form, however, formulating these dosage forms to have modified release properties can be challenging. Recently researchers have looked to develop such dosage forms using enteric coated micro-particles (Dalmoro et al., 2010) and ion exchange resins (Cuña et al., 2000), however, these systems are often costly, suffer from poor mouth feel and are only suitable for use with specific drugs. There is, therefore, a real need for alternative formulations. A potential route to achieve modified release in oral liquids is by using polysaccharide solutions which undergo a sol–gel transition on exposure to stomach acid. Indeed several authors have evaluated the oral sustained delivery of drugs such as theophylline, ambroxol, paracetamol and cimetidine in various in situ gelling polysaccharides which have included xyloglucan (Miyazaki et al., 2003; Itoh et al., 2008, 2010), pectin (Itoh et al., 2008; Kubo et al., 2004; Miyazaki et al., 2005; Kubo et al., 2005), and sodium alginate (Itoh et al., 2010; Kubo et al., 2003). Although these systems have shown some promise as vehicles there are issues associated with their use such as leaching of water soluble drugs and lengthy gastric retention due to large bulk gel formation in situ (Kubo et al., 2003). These issues could potentially be overcome by using fluid gels.

Fluid gels (also referred to as sheared gels) can be defined as suspensions of gel particles prepared by introducing a shear field while gelation is occurring in biopolymer solutions. 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 formation of these gelled particles has been previously described by a nucleation and growth mechanism, with the applied shear field limiting the molecular ordering to within individual gel particles by physically ensuring that the original formed gel nucleation sites remain separate from one another (Norton et al., 1999). Along with the bulk viscosity, the size and strength of these micron-sized, gelled particles can also be controlled by varying the concentration of polymer and shearing rate used during production (Gabriele et al., 2009; Fernández Farrés and Norton, 2014). This creates an attractive opportunity to incorporate drugs into an acid-resistant fluid gel which could potentially delay release in the stomach.

Gellan gum is a biopolymer particularly suited for producing fluid gels for such applications. It is a microbial exopolysaccharide

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produced by *Sphingomonas elodea* (Doner, 1997; Dai et al., 2008) and consists of repeating tetrasaccharide units of glucose, glucuronic acid, glucose and rhamnose residues (Chandrasekaran et al., 1988). Gellan gum is an EU approved food additive (E418) that has been investigated by several groups for applications in pharmaceuticals (Deasy and Quigley, 1991; Carlfors et al., 1998) and as a biomaterial (Smith et al., 2007; Oliveira et al., 2010; Jahromi et al., 2011). At temperatures above 85 °C the gellan gum exists as a random coil, which forms helical structures upon cooling resulting in a "weak gel" formed by tenuous association of ridged ordered structures (Norton et al., 1984) rather than by stronger associations of junction zones present in normal polysaccharide gels (Rees et al., 1982). However, on addition of ions such as hydrogen, sodium, potassium and calcium true, self-supporting gels are formed. This occurs via a mechanism of aggregation of gellan double helices either by suppression of the negatively charged groups on the polymer with monovalent ions or by direct site binding of the helices with divalent cations (Grasdalen and Smidsrod, 1987; Sworn et al., 1995; Morris et al., 2012). The mechanical properties and gelation temperature can be controlled by salt concentration and species (Ogawa, 1996). The ability of gellan gum to form acid-insoluble gels renders it a particularly attractive candidate for developing oral bioresponsive drug delivery systems. Indeed, these have been investigated in the form of gastro-retentive controlled release (Babu et al., 2010), enteric release (Smith et al., 2010) and as floating in situ gelling systems (Rajinikanth and Mishra, 2008). Furthermore oral sustained delivery using gellan solutions (which formed acid gels in the stomach) has also been explored and bioavailability from the gels formed in situ was similar to that of a commercially available suspension (Kubo et al., 2003). Unlike tablet or capsule formulations, there is no standard technique for measuring the dissolution properties of oral liquids. Biopharmaceutical measurements of such formulations are usually performed using modified USP dissolution apparatus which can lead to high variability. This is a particularly important issue when designing medicines for children as extrapolating adult biopharmaceutical measurements is difficult due to the difference in gastrointestinal physiology in paediatric patients (Batchelor et al., 2013). Moreover, large variations in physiology within paediatric populations are also evident from birth through to adolescence (Bowles et al., 2010) which further complicates the design suitable biopharmaceutical methodologies.

In the present study gellan gum fluid gels loaded with ibuprofen, (a BCS Class II drug that is currently available as modified release tablets) were investigated as a modified release oral liquid. Fluid gel formulations were investigated over a range of pH and acid exposure times to evaluate how variations in gastric physiology may impact the mechanical properties of these physiologically responsive fluid gels and the consequential release behaviour.

2. Material and methods

2.1. Materials

Low acyl gellan gum (Kelcogel™) was kindly donated by CP Kelco (USA). Ibuprofen powder (Ibuprofen 38) was obtained from BASF. All other materials were obtained from Sigma–Aldrich, Poole, UK.

2.2. Preparation of fluid gels

Fluid gels were prepared by adding low acyl gellan gum at concentrations from 0.1 to 1% w/w to deionised water at 85 °C while stirring. Once fully dissolved, the solutions were allowed to cool to ~60 °C then a paediatric dose of ibuprofen (20 mg/ml) was added and the pH was adjusted to 7.4 using 1 M NaOH. Solutions were then cooled further at 2 °C min^{-1} whilst being sheared using Bohlin Gemini Nano HR rheometer at a shear rate of 500 s^{-1}. To evaluate the potential to vary the particle size during formulation, fluid gels were prepared with changes to the processing conditions. To investigate the effect of cooling rate, 0.75% w/w gellan gum fluid gels were prepared as described above at a fixed shear rate of 500 s^{-1} with cooling rates of 0.5 °C min^{-1}, 2 °C min^{-1} and 10 °C min^{-1}. Similarly, to investigate the effect of shear rate, 0.75% w/w gellan gum fluid gels were prepared at a fixed cooling rate of 2 °C min^{-1} using shear rates of 100 s^{-1}, 500 s^{-1} and 1000 s^{-1}.

2.3. Preparation of control formulations

2.3.1. Viscosity test controls

To ensure the fluid gel formulations had a suitable viscosity profile a marketed paediatric ibuprofen suspension was used as a standard comparison and referred to as C1.

2.3.2. Dissolution test controls

To ensure ibuprofen could be fully dissolved in the dissolution media (PBS pH 7.4) at the formulated dose following 20 min exposure to acid at pH 1.2 (and any delayed release was not an effect of the pK_a of the ibuprofen), control solutions were prepared by adding drug (20 mg/ml) to deionized water at ~60 °C which were cooled to room temperature and the pH was adjusted to 7.4 using 1 M NaOH (referred to as C2).

To ensure the same grade of ibuprofen was used in all dissolution experiments formulations based upon standard ibuprofen suspensions were prepared as a control by adding 0.3% w/w xanthan gum and 0.2% w/w sorbitol to deionized water/glycerol 50:50 at 85 °C while stirring (to prevent any interference with UV analysis no preservatives, colouring agents or flavours were added). Once fully dissolved, the solution was allowed to cool to ~60 °C then a paediatric dose of ibuprofen (20 mg/ml) was added. The suspension was then cooled to room temperature and referred to as C3.

2.4. Viscosity measurements

Viscosity of all samples was determined taken at 25 °C using the Bohlin Gemini Nano HR rheometer using the 55 mm parallel plate geometry across shear rates ranging from 1 s^{-1} to 1000 s^{-1}.

2.5. Microscopy

Fluid gel samples were imaged using an optical microscope (Keyence VHX digital microscope RZ x250-x2500 real zoom lens in high dynamic range). Samples were prepared for imaging by dispersing the fluid gel samples in 10 ml of 50 mM $CaCl_2$. The suspension was then centrifuged at 13,000 rpm and the pellet was then examined under the microscope. $CaCl_2$ was used as the diluent during the processing of the sample prevent aggregation of the gel particles during the centrifugation step.

2.6. Dissolution studies

A modified USP I apparatus (baskets at a stirring rate of 100 rpm) was used to study in vitro drug release. Each formulation (5 ml) was placed into dialysis tubing (12500 MWCO) then submerged (within the baskets) in small volume vessels containing 200 ml dissolution media at pH values of 1.2, 2, 3, 4, 5 and 7.4 for 20 min. The media were subsequently changed to pH 7.4 phosphate buffered saline (sodium chloride 137 mM,