Gellan Gum Fluid Gels as Modified Release Oral Liquids

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ABSTRACT SUMMARY
The objective of our investigation was to design a new oral liquid modified release platform for pediatrics. To achieve this, fluid gels prepared from gellan gum were used. Fluid gels are formed by applying shear as a material undergoes a sol-gel transition. The resulting material consists of gelled microparticles which can be formulated to act as pourable viscoelastic fluids but retain the gel characteristics at the micro/nano level. In this study we have demonstrated that gellan gum fluid gel has the potential to be formulated with a similar viscosity profile as other marketed oral pediatric liquids. Furthermore, we have demonstrated that it is possible to encapsulate and prevent release of ibuprofen in simulated gastric fluid and that subsequent ibuprofen release in simulated intestinal fluid was affected by both the pH and exposure time, at acidic pH.

INTRODUCTION
Drug delivery through oral cavity is the most popular route of drug administration. However, solid dosage forms are often problematic for patient groups such as pediatrics and geriatrics who may have difficulty swallowing conventional solid dosage forms. These patient groups usually prefer oral liquids however, this creates problems when modified release formulations are required. A potential route to achieve modified release in oral liquids is by using fluid gels (also referred to as sheared gels). A Fluid gel can be defined as a suspension 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 cross-linked gel microstructure within the particles. Along with the bulk viscosity, the size and strength of these micron scale gelled particles can also be controlled depending on the concentration of polymer and shearing rate used during production [1]. This creates an attractive opportunity to incorporate drugs into an acid resistant fluid gel which could potentially delay release in the stomach.

It is recognized that gastric pH is neutral at birth, and it may not reach comparable adult values until 3 years. This acidic variation requires careful consideration when designing modified release formulations [2]. Moreover, gastric emptying in children is also varied being much slower in infants less than 6 months, than in older children and adults [3].

In the present study gellan gum fluid gels loaded with ibuprofen were formulated as an oral liquid and the release profile was investigated using a range of different pH dissolution media. The effect of exposure to gastric pH on subsequent drug release at simulated intestinal pH was also investigated.

EXPERIMENTAL METHODS
Fluid gels were prepared by adding the low acyl gellan gum at 0.75 % w/v to deionized water heated to 85 °C while stirring. Once fully dissolved the solution was cooled to ~60 °C and a pediatric dose of ibuprofen (20 mg/ml) was added. The pH was adjusted to 7.4 using 0.1M NaOH to allow complete dissolution of the ibuprofen. The solution was then allowed to cool to room temperature whilst stirring at a shear rate of 500 s⁻¹. USP I apparatus was used to study in vitro drug release. 5 ml of the formulation was placed into a dialysis tube (14000 MWCO) then submerged in 200 ml dissolution media at a pH ranging from pH 1.2-7.4 for 20 min following which, the media was changed to pH 7.4. To understand how release in simulated intestinal conditions was affected by residence time in acidic media, samples were also exposed to pH 1.2 for time periods
increasing from 5 min to 120 min before changing the media to pH 7.4 and recording the subsequent onset of release. The concentration of ibuprofen released from the sample was determined spectrophotometrically at a wavelength of 254 nm. All experiments were carried out in triplicate.

RESULTS AND DISCUSSION
To understand the effect of the wide variation in stomach pH found in pediatric patients, release characteristics were determined in vitro at different pH values (1.2, 2, 3, 4, 5 and 7.4) then the release medium was changed after 20 minute to phosphate buffer saline pH 7.4.

Fig. 1 Cumulative % release of ibuprofen at different acidic pH values for a period of 20 minutes. Dotted line indicates the point the media was changed to PBS at pH 7.4

Fig.1 highlights that the release of ibuprofen from the gellan gum fluid gel is strongly affected by pH value of the dissolution media. There was no significant difference in release between samples in pH 7.4 and pH 4. However as the pH decreased below the pKa of the carboxyl group (~3.4) of the gellan gum an acid gel was formed preventing the dissolution of the gel and therefore ibuprofen release. This retardation of release becomes progressively more pronounced as the pH is dropped further and the acid gel becomes stronger. The exposure to pH 1.2 for just 20 min prevented the onset of release for a further 60 min when transferred to pH 7.4.

Fig. 2 shows a linear relationship between onset of release in simulated intestinal fluid and the preceding exposure time at pH 1.2 for up to 120 min. This correlates with the stiffness of the gel which was also shown to increases on exposure to pH 1.2 as a function of exposure time (results not shown). These results indicate that drug release may be substantially delayed with prolonged gastric emptying time.

CONCLUSION
In this study we have demonstrated that the release of ibuprofen from gellan gum fluid gels is dependent on the pH of simulated gastric fluid and that subsequent release at simulated intestinal pH can be delayed depending on the gastric pH exposure time. This highlights the potential application of gellan gum fluid gels as modified release oral liquids. Furthermore this work illustrates the importance of understanding that subtle differences in patient physiology could impact on the release from such formulations, and a realization of this is very important especially when designing medicines for pediatrics.

REFERENCES