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On formulating ophthalmic emulsions

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ABSTRACT

The formulation of dilute, transparent ophthalmic emulsions (eye drops) with long shelf lives is a challenge because of the tendency of the emulsion droplets to aggregate, particularly in the presence of the water-soluble polymers typically used in eye drops. While many functions of eye drops, such as lubricity and residence time in the eye, are promoted by high concentrations of high molecular weight water-soluble polymers, emulsified lipids and drugs aggregate in the eye drop bottle if the polymer concentration is above the critical flocculation concentration (CFC). The purpose is to develop a simple approach to predict the CFC for polymers based on information readily available in the literature. High molecular weight guar was hydrolyzed to give a series of guar samples spanning a wide range of average molecular weights. The CFC values and critical viscosity concentrations were measured as functions guar properties, using electrophoresis, dynamic light scattering and rheology measurements. The higher the guar molecular weight, the lower was the CFC, the maximum concentration that can be tolerated in the eye drop formulation. The guar CFC values were approximately equal to the overlap concentrations where guar molecules start to overlap in solution. We propose that the CFC can be estimated for any water-soluble polymer using the polymer molecular weight and the readily available Mark–Houwink parameters, thus providing a design rule for ophthalmic emulsions.

1. Introduction

Eye drops are important vehicles for delivering materials to the front of the eye. From a physical chemical perspective, there are two classes of eye drops–homogeneous solutions of water-soluble ingredients, and emulsions. Homogeneous solutions are attractive because they are clear, stable and have long shelf lives. However, water–insoluble materials do not form homogeneous solutions. Instead they must be formulated as emulsions where the water–insoluble materials are present as dispersed emulsion droplets [1]. Emulsions offer many challenges, particularly with respect to shelf life and product clarity. Herein we present some ophthalmic emulsion design guidelines based on results from model emulsions.

Emulsions can undergo creaming, aggregation, and coalescence—these are briefly described. Ophthalmic emulsions are oil-in-water emulsions, and buoyancy forces cause the lower density emulsion drops to rise (cream) toward the surface [2]. Creaming rates are lowered by continuous mixing, by decreasing the emulsion drop diameter, or by increasing the viscosity of the suspending aqueous phase by addition of water–soluble polymers. Small (diameter <50 nm) droplets offer the additional advantage of high transparency.

Like any colloidal or nanoparticle suspension, emulsion droplets have a natural tendency to aggregate. Surfactants and polymers present during the emulsification process concentrate at the oil/water interface and can prevent aggregation (colloidal instability) because of electrostatic and/or steric repulsive forces [3]. If emulsions do aggregate, they either remain as clumps of droplets, or the droplets coalesce into larger droplets, eventually producing an oil layer on top of the aqueous phase. Creaming, aggregation and coalescence are undesirable outcomes for ophthalmic products.

In this work we illustrate the challenges in formulating ophthalmic emulsions by using a model emulsion of hexadecane stabilized by phosphatidylcholine, a biological surfactant. The aqueous phase includes guar, a nonionic water–soluble polymer used in products to alleviate dry eye symptoms [4]. Depending upon molecular weight and concentration, guar can either improve or degrade emulsion properties. Rules are presented for optimizing the water–soluble polymer components of ophthalmic emulsions.

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2. Experimental

2.1. Materials

Native guar with a molecular weight of ~3 MDa was provided by Alcon Laboratories (Fort Worth, TX, USA). Hexadecane, NaN_3, (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) (HEPES) and NaCl were purchased from Sigma-Aldrich (Oakville, ON, Canada), and L-α-phosphatidylcholine was purchased from Avanti Polar Lipid (Alabaster, AL, USA). Aqueous solutions were made with 18.2 MΩ cm, Barnstead Nanopure Diamond system (Iowa, USA) water.

2.2. Guar hydrolysis

Guar samples with molecular weights varying between 130 kDa and 427 kDa were prepared by the acid hydrolysis of high molecular weight guar using Prud'homme's method [5]. A 0.1% (w/w) high molecular weight guar was prepared by dissolving guar powder in water with vigorous stirring using a mechanical stirrer for 24 h to maximize hydration. A volume of 200 mL guar solution was placed in a sealed 500 mL three-neck round bottom flask maintained at 50 °C in a water bath. The pH of the guar solution was maintained at 1 by 1 N HCl addition. Periodically, over a period of 24 h, 20 mL samples of partially hydrolyzed guar solutions were isolated and the pH adjusted to 6 by 1 N NaOH addition. The samples were then purified by dialysis for two weeks and then freeze dried (Millrock Tech., BT48A, NY, USA).

Guar molecular weight distributions were determined by gel permeation chromatography using a Waters 515 HPLC pump, three Waters Ultrastyragel Linear columns, and a Waters 2414 refractive index detector. The mobile phase was 300 mM $NaNO_3$ in 50 mM phosphate buffer at pH 7. MW calibration was based on poly(ethylene glycol) standards (Waters, MA, USA).

2.3. Viscosity measurements

Guar solutions were prepared at concentrations varying from 0.02% (w/w) to 0.6% (w/w) by dissolving dried samples of guar in water with 20 ppm of NaN_3 preservative. All samples were stirred for 24 h to ensure complete dissolution and followed by at least 2 h rest before viscosity measurements. The viscosity of samples was measured at 25 °C as a function of shear rate using an ATS controlled stress rheometer (Rheologica Stress Tech HR,) equipped with bob and cup geometry (CC25). Temperatures were controlled within ±0.2 °C using a water-bath.

2.4. Emulsion preparation

An amount of 10 mg L-α-phosphatidylcholine in chloroform solution (25 mg/mL) was evaporated in a round-bottom flask using a rotary evaporator at room temperature, followed by 10 min exposure to a nitrogen gas stream. To the flask were added 140 mg of hexadecane and 10 mL solution containing 5 ppm NaN_3, 10 mM HEPES buffer and 5 mM NaCl. The mixture was sonicated for 15 min using a Misonix Sonicator (S-4000 Ultrasonic Processors, USA, 20 kHz). The ultrasonic probe (90% amplitude and output power setting of 60) was immersed directly into the emulsion.

2.5. Electrophoresis

Electrophoretic mobility measurements were made with a Brookhaven Zeta PALS instrument at 25 °C in phase analysis light scattering mode (PALS software version 2.5). The reported mobility values were the average of 10 cycles, each comprised of 15 scans. The samples were all made in 5 mM NaCl.

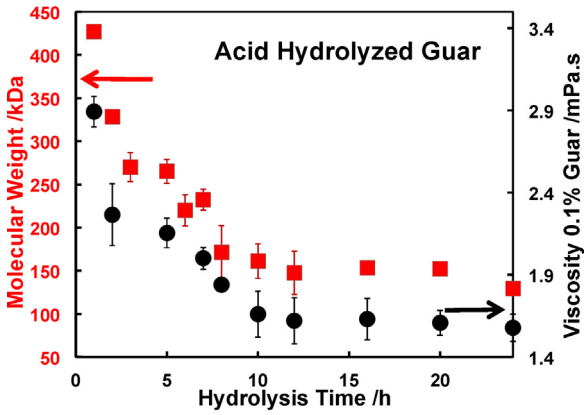

Fig. 1. The molecular weight (GPC) and viscosities of hydrolyzed guar samples as functions of the hydrolysis times. Viscosity measurements were made at 25 °C using a shear rate of 200 s^{-1}. Error bars are the standard deviation of triplicate measurements—in some cases the error bars are hidden within symbols.

2.6. Dynamic light scattering

Measurements were carried out at 25 °C using a BI-APD 8590 digital correlator (Brookhaven, NY, USA) apparatus at a fixed 90° scattering angle and a 35 mW 632.8 nm laser as the light source. Using the CONTIN program, the cumulative intensity distribution method was used to calculate the emulsion droplet diameter. Reported diameters are the average of 5 measurements.

Dynamic light scattering was used to determine the critical flocculation concentrations (CFC) of guar added to emulsions. CFC values corresponded to the first significant slope change in plots of average diameter versus guar concentration.

2.7. Creaming measurements

A volume of 0.2 mL emulsion were mixed with 2 mL of guar solution in a 5 mL vial and mixed for 120 s using a mini vortexer (VWR, VM-3000, USA). The emulsions were immediately transferred to glass test tubes (50 × 6 mm) and maintained at 23 °C. The thickness of the serum layer at the bottom of the tube was visually determined over a period of 500 h.

3. Results

A series of guar solutions of varying molecular weight was prepared by the controlled hydrolysis of very high molecular weight guar. The molecular weights of the purified products were measured by gel permeation chromatography. Fig. 1 shows the molecular weights and the viscosities of 0.1% solutions as functions of the hydrolysis times. This series of samples was used to assess the influence of water–soluble polymer molecular weight on ophthalmic emulsion stability.

Fig. 2 shows the viscosity versus concentration plots for three guar samples from the series of hydrolyzed samples—results for the remaining samples are shown in Fig. 2 of the supporting information file. As expected, the higher molecular guar gave the highest viscosity when compared at the same concentration. The inflection points in the log–log plots of viscosity versus guar concentration gave the minimum overlap concentration C^*. This is the lowest guar concentration where neighboring polymer coils in solution start to interact—the "dilute" to "semi-dilute" transition concentration [6].