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Research Article

Effect of Formulation Conditions on Hypromellose Performance Properties in Films Used for Capsules and Tablet Coatings

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Abstract. This study investigated the effects of polymer dispersion and hydration conditions on hypromellose (HPMC) film properties, such as strength, oxygen permeability, water vapor transmission, clarity, and haze. The focus of the study was to build a better understanding of the impact that changes to HPMC dispersion and hydration conditions have on performance properties of the resulting films. This understanding could potentially lead to more flexible formulation guidelines for formulators. Films of HPMC 2906 (USP) were produced from aqueous solutions prepared using various formulation conditions. Results showed that tensile properties and oxygen permeability were not significantly affected by the variables used. The differences observed in water vapor transmission are unlikely to affect practical application of the material. However, the differences observed in clarity and haze at 50°C hydration temperature could affect the appearance of a capsule or coated tablet. Several methods were used to determine whether loss of optical properties was due to surface phenomena or bulk defects within a film. Results indicated that the cloudy appearance was primarily due to surface roughness. Based on this information, there is some flexibility in formulation conditions; however, hydration temperatures greater than 25°C are not recommended.

KEY WORDS: film properties; formulation conditions; HPMC; hypromellose; polymer hydration.

INTRODUCTION

Hypromellose (HPMC) is a common excipient used in pharmaceutical films, such as tablet coatings and hard capsule shells. The process of preparing formulations of HPMC to produce films that meet high-quality requirements can be an exacting process. Standard preparation protocols call for the polymer to be first dispersed in hot water (>80°C) and then hydrated at lower temperatures (<10°C) (1). If the powder is added directly to cold water, lumps may form in which the outer layer of polymer begins to hydrate, forming a shell around the dry powder, which can result in extended polymer hydration times.

Such exacting formulation conditions can be difficult to maintain, prompting a desire from formulators for more flexibility in the formulation process. The focus of this study was to build a better understanding of HPMC dispersion and hydration, and the impact that changes to these processes have on the performance properties of the resulting films. A secondary emphasis was to determine if the recommended formulation conditions for HPMC could be broadened to make the formulation process more flexible.

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BACKGROUND

Several film properties are assessed when considering formulations for film-forming polymers, including mechanical strength, permeation, and optical properties (2–5). Strength is a particularly important property for films used to form capsule shells or tablet coatings. The film must be able to protect the contents during filling, packaging, shipping, and storage processes.

In addition to mechanical strength, low oxygen permeability and water vapor transmission are desired properties for capsule shells, since certain active pharmaceutical ingredients react with either water or oxygen. Gasses travel through the films by two methods, capillary flow and diffusion. Capillary flow occurs when a gas passes through pores within a film. Transmission of water vapor occurs when the substance dissolves on the surface, diffuses through the film, and evaporates on the other side (6). Both processes are affected by the structure of the polymer composing the film and the affinity of the gas to the material. For example, water vapor would have high transmission through a hydrophilic material such as HPMC. Capillary flow would be increased by defects within the film that allow the gas to easily pass through. The presence of additives or moisture in the film can also affect the

interaction of the gas with the material and therefore the permeation/transmission rates. For example, the rate of oxygen permeation through an HPMC film is sensitive to the humidity of the testing conditions (7).

Although strength and gas permeation/transmission properties are critical to protecting the contents of a capsule or tablet, the initial perception of the customer will be based on the appearance of the film. In cases where a clear film is desired, a lack of clarity or the presence of haze would be a negative feature. Typically, as clarity decreases, haze increases. Clarity is determined by small-angle light scattering; haze is determined by large-angle light scattering.

Poor optical quality can be due to defects that exist either on the surface or within the bulk of the film (8). Inconsistent structure within the bulk of the film can lead to a non-uniform refractive index, resulting in poor optical quality. Crystallization within the film can also create defects that will alter the optical properties of the material (9–11).

Several methods exist for investigating the source of poor optical quality. Optical properties can be compared to film thickness. If the defects lie on the surface of the film, these properties would remain constant as film thickness is varied. If the reason for poor optical quality is within the bulk of the film, optical properties would probably correlate with film thickness. An alternative method is to coat the surface of the film with oil that has a refractive index similar to the film material. The oil will fill any surface defects but not affect those within the bulk of the film. If the optical quality of the oil-coated film improves, this would indicate the defects are on the surface. Analysis of surface morphology may be conducted through either contact (profilometry) or noncontact (interferometry) methods, both of which provide information on surface roughness. Increased surface roughness can affect both the optical properties of the film and also the visual appearance of the film texture (12).

MATERIALS AND METHODS

Materials

The films in this study were made from low-viscosity (low molecular weight) HPMC 2906 (METHOCEL[1] F5 Premium cellulose ether, The Dow Chemical Company, Midland, MI, USA).

Hypromellose Solution Preparation

All formulations were prepared using the conventional "hot–cold" method in which the HPMC powder is dispersed in water at an elevated temperature and then cooled for hydration of the polymer (1). Temperature during dispersion and hydration was maintained with a water bath monitored with a thermocouple to within a degree of the target. The solutions (20% HPMC in water) were prepared by quickly adding the powder to a 500-mL jar containing water at the dispersion temperature (60 or 80°C) and equipped with a three-blade stirring shaft. During the powder addition, the stirring rate was set to 600 rpm to efficiently draw the powder into the water by creating a vortex. After powder addition, the rate was reduced to 400 rpm to reduce the number of bubbles incorporated into the solution. Stirring during the dispersion phase was continued for 1 h. Following dispersion, the water bath was adjusted to the hydration temperature (4°C, 25°C, or 50°C). Timing of the hydration phase began once the solution had reached the appropriate temperature, typically 5–15 min, depending on the magnitude of the temperature drop. Once the hydration temperature was achieved, stirring was stopped. Samples were removed at 1, 3, and 5 h. Before films were prepared, dissolved gas was removed from the solution by placing the sample under vacuum for 2 min followed by centrifugation at 2,800 rpm for 5 min to remove bubbles.

Preparation of Films

Films were hand-drawn on glass plates using the 40-mil gap option of a multiple clearance application square (BYK, Columbia, MD, USA). The HPMC solution (at hydration temperature) was poured into the square near the edge of the glass plate, and the square was pulled steadily down the glass to minimize formation of defects. Films were dried overnight under ambient conditions, typically about 21°C with relative humidity ranging from 20% to 40%. Thermogravimetric analysis (TGA 2950, DuPont Instruments, Cincinnati, OH, USA) was used to confirm that the water content of the films was consistent with dry films, about 6% moisture content. After removal from the glass, the films were stored in a laboratory with constant temperature and humidity (22°C, 50% relative humidity) for at least 18 h prior to analysis to equilibrate the water content. For all film testing, samples were taken from areas of the film that did not contain any obvious defects or bubbles. Film thickness is reported in the unit mil or 0.001 in.

Tensile Strength Measurements

Tensile strength was measured using an Instron universal testing machine (Model 4201/5501R, Instron, Norwood, MA, USA) following ASTM method D-638 with an extension rate of 0.2 in./min. Samples were cut from the film using a type IV die. Thickness of each sample was measured prior to testing and was generally between 4 and 5 mil.

Oxygen Permeability and Water Vapor Transmission Rate Measurements

Oxygen permeability was measured on an Ox-Tran 2/21 system (Mocon, Minneapolis, MN, USA). Test conditions were 10% oxygen, 23°C, and 50% relative humidity. Films were masked to a 1-in. diameter testing area, which was normalized to a 5 cm^2 testing area in final calculations. The permeability was normalized for the film thickness to yield a value with units of cc·mil/[100 in^2·day·atm]. Four samples were tested for each condition at an HPMC hydration time of 5 h.

Water vapor transmission rates were measured using a dry cup method. Two grams of calcium chloride was weighed

[1] ™Trademark of The Dow Chemical Company ("Dow") or an affiliated company of Dow

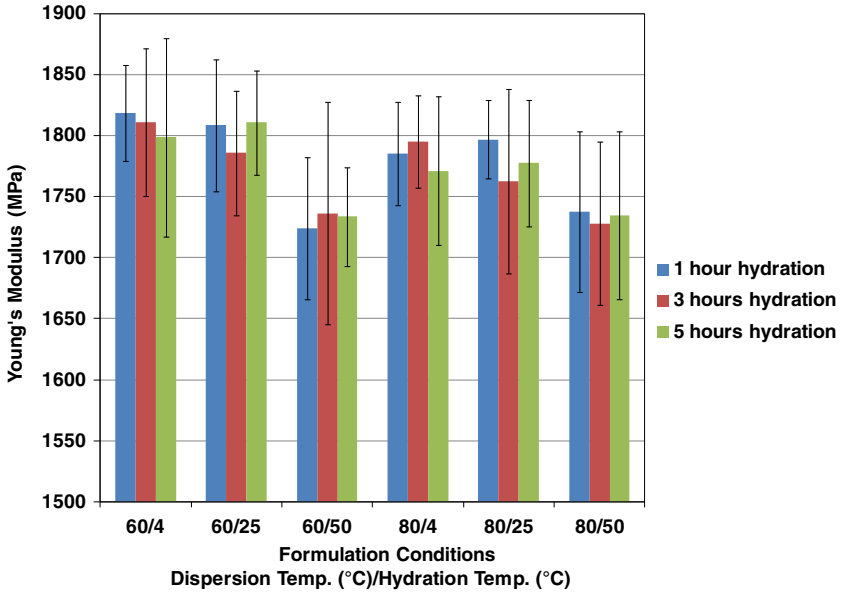

Fig. 1. Effect of formulation conditions on Young's modulus

into a 4-oz jar and allowed to equilibrate at 50% relative humidity and 73°F with a closed cap for 1 h. Next, a small amount of vacuum grease was placed around the edge of the jar's mouth. Films were cut into 1.3-in. diameter circles using a metal punch. The film samples were placed over the mouth of the jar, and a 1-in. diameter, open-hole lid was placed on top. The lid was tightened enough to form a seal, but not enough to damage the film. The jars were then placed in a temperature/humidity chamber equipped with an Environ-Cab controller (Lab-Line Instrument, Inc., Melrose Park, IL, USA) set at 75% relative humidity and 25°C. The total weight of the jar, lid, film, and calcium chloride was recorded and measured again approximately every 24 h for 5 days. The rate was normalized for film thickness and to a 5 cm^2 testing area to yield a value with units of grams per meter per square centimeter per minute. Four samples were tested for each condition at an HPMC hydration time of 5 h.

Clarity and Haze Measurements

Clarity was measured on a clarity meter (Model CL-100, Zebedee Corporation, Moore, SC, USA). Haze was measured at four places on each film using a Haze-guard unit (BYK Gardner, Columbia, MD, USA) equipped with a CIE-C light source. The thickness of each film was measured prior to analysis.

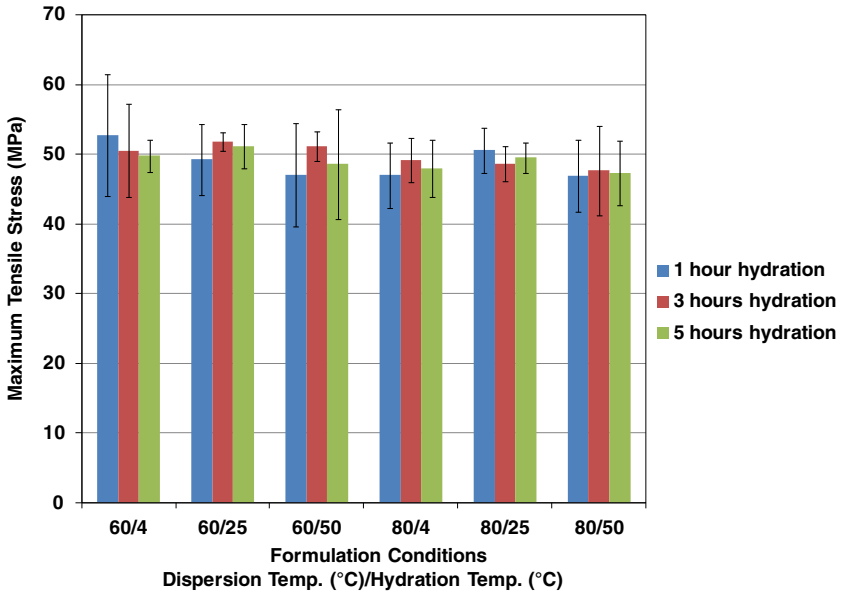

Fig. 2. Effect of formulation conditions on maximum tensile stress

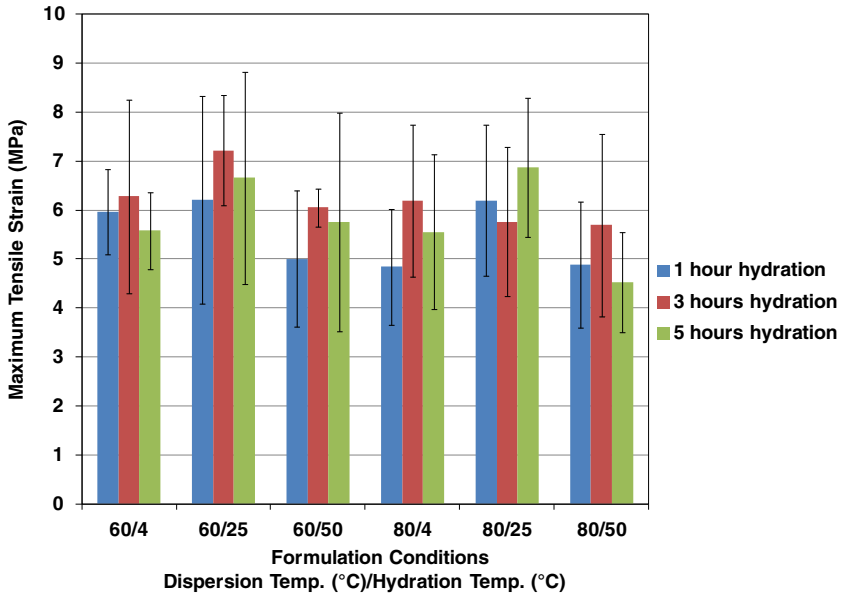

Fig. 3. Effect of formulation conditions on maximum tensile strain

Film Surface Property Measurements

To check for surface vs bulk defects, a drop of silicone oil was placed on the surface of both the clear and cloudy films. Silicone oil has a refractive index near that of HPMC film ($n \sim 1.52$). Microscopy was used to collect images of each film type (clear or cloudy) at five or 10 times magnification. Comparison of the areas coated with oil to those without can indicate if the defects are on the surface or within the bulk of the film.

For surface roughness determinations, each film was mounted to a glass slide and imaged using a Tencor P-15 stylus profilometer (KLA-Tencor Corporation, Milpitas, CA, USA). A 1,000×1,000 μm area was imaged with a 1.0-mg load, 200-μm/s scan speed, 50-Hz sampling rate, 4-μm *y*-spacing, and 131 μm/0.0781 Å range/resolution. Data were processed and analyzed using SPIP v.5.1.5 software (Image Metrology, Hørsholm, Denmark). Images were plane-fit and filtered for noise before roughness analysis.

A white light interferometer (Model NT9100, Wyko Corporation, Tucson, AZ, USA) was also used to analyze the surface characteristics of the films. To ensure that analysis was representative of the whole film, several locations on each film were tested, avoiding any areas of visible defects, such as bubbles. Each scan analyzes an area of approximately 0.1 x 0.1 mm. The images presented are of representative locations

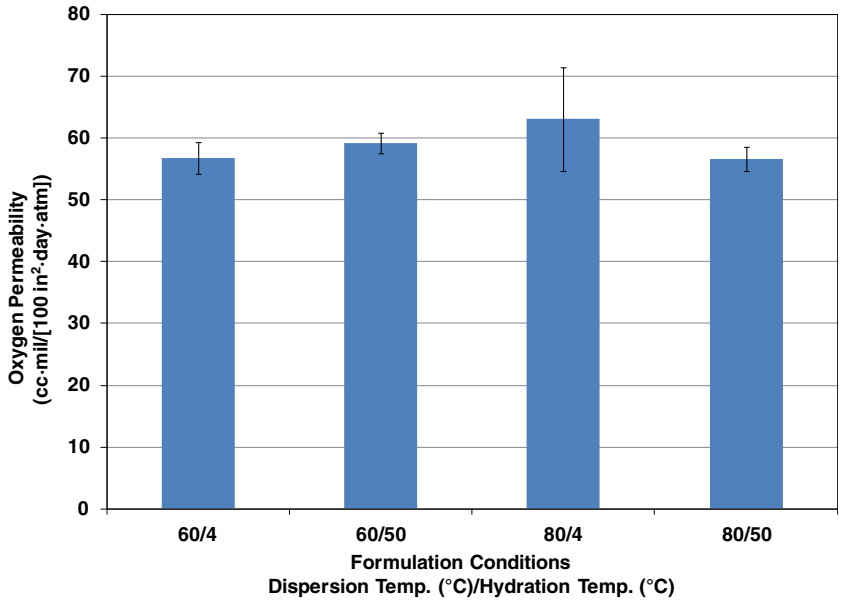

Fig. 4. Effect of formulation conditions on oxygen permeability at 5 h hydration time, 50% RH, 23°C

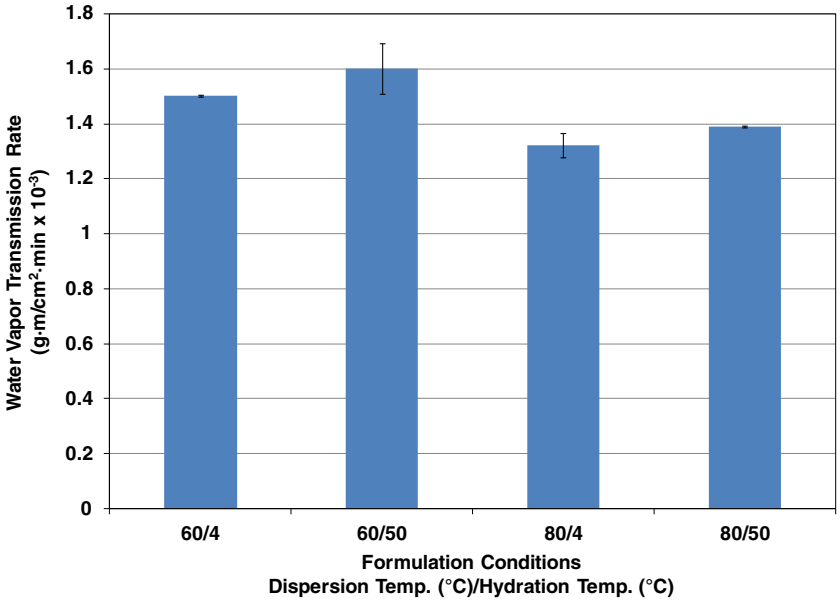

Fig. 5. Effect of formulation conditions on water vapor transmission at 5 h hydration time, 75% RH, 25°C

and numerical results show an average of at least three locations.

RESULTS AND DISCUSSION

Film Mechanical Properties

Mechanical strength is a key property for excipient films used in capsules and tablet coatings. The capsules must be able to withstand the filling process and both capsules and tablet coatings must provide protection of the contents during shipping and storage. In this study, tensile properties were used as a measure of strength. Figure 1 shows average Young's modulus for each formulation condition. There were no clear trends when the dispersion or hydration temperature was varied, and extending the hydration time from 1 to 3 or 5 h had no significant effect on the modulus. This data set was analyzed using the Tukey–Kramer test for statistically relevant similarity, and results showed no difference between the data from any formulation condition to a 95% confidence level. Maximum tensile stress and strain were also measured, with the data compared in Figs. 2 and 3. These properties exhibited a relatively large standard deviation compared to Young's modulus, an inherent difficulty when measuring tensile properties of films, but there were no clear trends across the range of conditions tested.

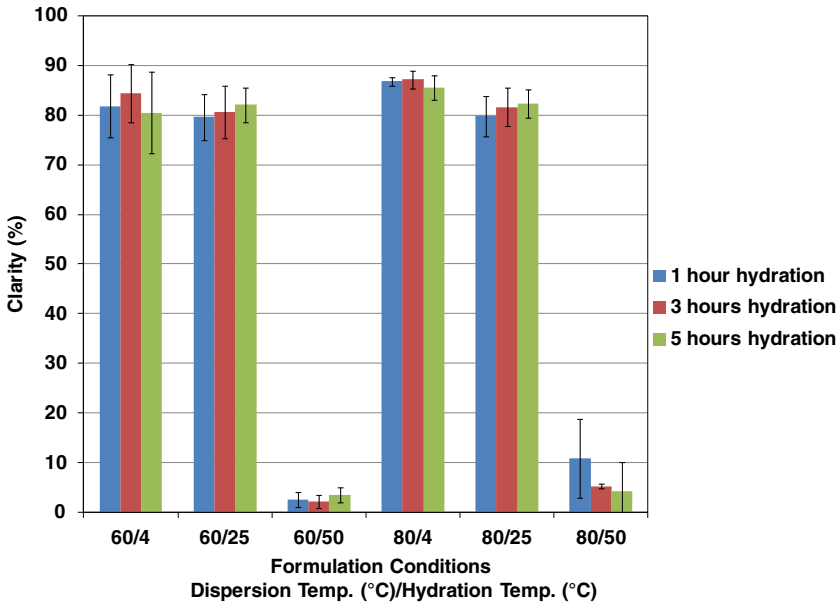

Fig. 6. Effect of formulation conditions on film clarity

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