Characteristics of an Emulsion Obtained Using Hydrophobic Hydroxypropyl Methylcellulose as an Emulsifier and a High-Pressure Homogenizer

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Hydrophobically modified hydroxypropyl methylcellulose (HM-HPMC), a polymer in which a small amount of HPMC is stearoxyl substituted, was used as an emulsifier of emulsion-type lotion. A high-pressure homogenizer (microfluidizer) was used. The viscosity of the 1% HM-HPMC aqueous gel decreased after passing through the microfluidizer from 5.5 to 2.7 Pa·s. When liquid paraffin (LP) was used as the oil phase, a stable emulsion was obtained with an LP ratio of 1–40%. The apparent viscosity decreased with LP ratios up to 20%, and then increased with increasing LP concentration. The emulsions with an LP ratio <20% presented a pseudo-viscous flow, similar to that of the diluted polymer solution. HM-HPMC likely adsorbed onto the oil with a stearoxyl group; thus, the interaction between the stearoxyl group, which explained the high viscosity of HM-HPMC, decreased, reducing the viscosity of the emulsion. The LP ratio was 40%, and the emulsion presented a plastic flow, which is typical of concentrated emulsions. The size of the droplet in the emulsion was approximately 1µm regardless of the LP ratio. When low-viscosity LPs or monoester-type oils such as isopropyl myristate were used, some of the emulsions presented creaming. An emulsion using HM-HPMC as an emulsifier and an appropriate oil homogenized with a microfluidizer is stable, has low viscosity, and can be easily spread on skin.

Key words microfluidizer; liquid paraffin; viscosity; droplet size; hydrophobically modified hydroxypropyl methylcellulose; ester oil

Introduction

Topical use of drugs for skin diseases is effective, with few systemic side effects. The choice of vehicle is based on the type of skin condition. Ointments, creams, and lotions are common dosage forms. Lotion is especially convenient for use on the scalp (or other site with hair), or to cover large areas because it has low viscosity and is easy to spread. The main component of lotion is water, and three types of lotion exist: solution, suspension, and emulsion. Drugs with low water solubility are hard to formulate in solution-type lotions without the use of solubilizing solvents/agents and procedures; therefore, emulsion-type lotion is especially attractive for oil-soluble drugs. Lotion is usually used on damaged skin. Thus, the ingredients of lotion, such as surfactants, should not cause irritation if, along with water, they are vaporized following application to the skin, and leave condensed on the skin surface.

In this study, we used hydrophobically modified hydroxypropyl methylcellulose (HM-HPMC), in which a small amount of the stearyl group was introduced to hydroxypropyl methylcellulose (HPMC). HM-HPMC forms a transparent gel and is used externally. The gel has higher viscosity than HPMC because of its hydrophobic interaction. HM-HPMC comprises both hydrophilic and hydrophobic parts; thus, it decreases the interfacial tension of oil and water. HPMC and HM-HPMC gels have been used for gel emulsions; however, a high concentration of oil is necessary, as emulsions begin to cream after a short time period. We investigated a new method of preparing stable emulsions with various concentrations of oil. We used liquid paraffin (LP), the most frequently used oil in the external dosage form, as the oil phase. Several oils with different characteristics from LP (Table 1) were also investigated.

Experimental

Materials

HM-HPMC (Sangelose 60L, methoxy group; 27.0–30.0%, hydroxypropoxy group; 7.0–11.0% and stearyl oxy-hydroxypropoxy group 0.3–0.6%, prepared from hypromellose 2910-10000) was a kind gift from Daido Chemical Co. (Osaka, Japan). LP was obtained from Wako Pure Chemical Corporation (Osaka, Japan). Other grades of LP, LP-17 (HICALL K-230), and LP-7 (HICALL K-160) included the food additive grade of Kaneda Co. (Tokyo, Japan). Isocetyl stearate was obtained from Kao Chemicals (Tokyo, Japan).

Table 1. Characteristics of Oils Used in This Study

| Name                  | Abbri. | Viscosity (mPa·s) | IOB value |
|-----------------------|--------|-------------------|-----------|
| Liquid paraffin        | LP     | 70                | 0         |
| LP-17                 | 17     | 0.09              |
| LP-7                  | 7      | 0.12              |
| Isocetyl stearate      | ICS    | 30                | 0.15      |
| 2-Ethylhexyl stearate  | EHS    | 17                | 0.18      |
| Isopropyl isostearate  | IPIS   | 10                |           |
| Isopropyl myristate    | IPM    | 3                 |           |
stearate (ICS, NIKKOL ICS-R), 2-ethylhexyl stearate (EHS, NIKKOL STO), isopropyl isostearate (IPIS, NIKKOL IPIS), and isopropyl myristate (IPM, NIKKOL IPM-EX) were gifts from Nikko Chemicals Co. (Tokyo, Japan).

**Preparation of Gels and Emulsions** Water was heated to approximately 80°C in a beaker, stirring with a magnetic stirrer at 300 rpm, and the required amount of HM-HPMC was added to the water. HM-HPMC dispersed in hot water was stirred for 30 min and then cooled in an ice water bath with stirring in order to obtain a transparent homogeneous gel. The oil phase was added to the gel and mixed with a spatula, and then mixed with a Quick Homomixer LR-1 (Mizuho, Osaka, Japan) at 3000 rpm for 2 min. The obtained emulsion was then introduced into a high-pressure homogenizer (Microfluidizer, M-110-EH, Powrex, Hyogo, Japan) and passed through the chamber 10 times at 70 MPa to yield emulsion.

**Rheological Measurement** An E-type viscometer (VISCOMETER TV-20, Tokimech, Tokyo, Japan) equipped with cone 3° × R12 was used for measurement of apparent viscosity. The viscometer was corrected with a standard liquid (JIS500). A sample of 0.5 mL was placed into the cup using a syringe. The temperature was maintained at 25°C by circulation of water around the sample cup. The apparent viscosity was measured at a shear rate of 20 s⁻¹.

Steady and dynamic rheological measurements were made using a stress-controlled rheometer (HAAKE RS600, Thermo Fisher Scientific Inc., MA, U.S.A.). Steady flow viscosity was measured using parallel-plate sensors (diameter: 35 and 60 mm; gap: 0.5 mm). Dynamic rheological measurements were performed using a low-inertia parallel-plate sensor (diameter: 60 mm; gap: 0.5 mm) or a parallel-plate sensor (diameter: 35 mm; gap 0.5 mm). A Peltier-based temperature control device was used to set the temperature at 25°C. A solvent trap was used to minimize evaporation. To measure steady-flow viscosity, the samples were subjected to the desired shear stress for a time sufficient to achieve a steady state. Dynamic frequency-sweep measurements were performed using the strain value from the linear viscoelastic region of the samples, as determined from dynamic stress-sweep measurements.

**Measurement of Oil Droplet Size** Emulsion was diluted 200–500 times with distilled water. A dynamic light-scattering photometer (DLS-8000HL, Otsuka Electron, Tokyo, Japan) was used to determine the particle size of the oil droplets in the emulsion.

The diameter of droplets in the LP 1% emulsion was calculated using Image J. Photographs of the microscopic observation of emulsions were opened with Image J and changed 8-bit binary image. Then, the measurement method was set as Feret’s diameter, and scale was set using photograph obtained with the same condition. About 500 particles of which circularity was over 0.8 were measured in each photograph. Three photographs were used.

**Observation of Creaming** Emulsions were stored at 25°C in glass sample containers with caps, and were observed with light.

**Results**

**Effect of Homogenizer and HM-HPMC Concentration on the Viscosity of the Gel and Emulsion** First, we attempted to emulsify HM-HPMC gel and LP using a Quick Homo-mixer; however, the obtained emulsion was not stable, and creaming was observed within 1 h. HM-HPMC is not a surfactant, and the ability is not sufficient for emulsifiers. Thus, a microfluidizer, which is a high-pressure homogenizer with high shear stress, was used to prepare the emulsion. A high-pressure homogenizer decreases the viscosity of a polymer solution because the long chain is cut by the high shear stress. The effect of pass number on the viscosity of the gel was studied. HM-HPMC 1% gel was introduced into a microfluidizer and the sample used to measure viscosity was corrected after each pass. Figure 1 shows the change in viscosity with the number of passes through the microfluidizer. The viscosity of the HM-HPMC 1% gel decreased by about half after three passes, after which the magnitude of the decrease reduced. The microfluidizer is a continuous type instrument, and it is difficult to strictly control the pass time; thus, the number of passes was fixed at 10, which was more than sufficient in further studies.

The viscosity of the gel, gel passed through a microfluidizer, and emulsions with 1% LP were studied at various concentrations of HM-HPMC (Fig. 2). The viscosity of the HM-HPMC

![Fig. 1. Preliminary Investigation of the Number of Passes through a High-Pressure Homogenizer (Microfluidizer)](image1)

The HM-HPMC concentration in the gel was fixed at 1%.

![Fig. 2. Effect of HM-HPMC Concentration and Oil on Viscosity](image2)

Apparent viscosity was measured with an E-type viscometer at a share rate of 20 s⁻¹. Each data point represents the average of two preparations.
gel increased with its concentration. Semilogarithmic relationship was observed between viscosity and concentration up to 0.3%. The viscosity of the gel passed through a microfluidizer was approximately one-tenth of that before passing through the microfluidizer when the HM-HPMC concentration was below 0.5%, and semilogarithmic relationship was observed under 1%. The viscosity was reduced by approximately half in the case of 1% HM-HPMC. The viscosity was reduced by approximately half in the case of 1% HM-HPMC. The influence of adding 1% LP on viscosity was small. Emulsion was obtained for all concentrations of HM-HPMC; however, creaming was observed within 1 week when the concentration of HM-HPMC was less than 0.3%, and within 2 months with 0.5% (Fig. 3(a)), although the size of the oil droplet did not change (Fig. 3(b)). The stability of the formulation is important; thus, the concentration of HM-HPMC was fixed at 1% in further studies.

Characteristics of Emulsions with 1% HM-HPMC and LP Emulsions with various LP ratios were prepared, in which the concentration of HM-HPMC in the emulsion was fixed at 1%, and the rheological characteristics and oil droplet size in the emulsion were studied. Figure 4 shows the effect of the LP ratio in the emulsion on viscosity. The apparent viscosity decreased with an increasing LP ratio, and was 0.14 Pa·s when the ratio of LP was 20%. The ratio of LP was higher than 20%, and the viscosity increased with the LP ratio. It was not possible to prepare an emulsion with LP > 40% because the viscosity of the pre-emulsified emulsion was too high for the microfluidizer. Similar phenomenon was observed in the emulsion with 0.5% HM-HPMC, the lowest viscosity was 0.019 Pa·s when the ratio of LP was 10%. As confirmed by the water dilution method, all emulsions were of the oil/water (O/W) type. In general, the viscosity of the O/W emulsion increases with a higher ratio of the oil phase, which was not observed in our study. Thus, we studied rheograms to clarify the rheological characteristics.

Figure 5(a) shows the rheogram, which is the relationship between the shear stress and shear rate of the HM-HPMC gel and emulsion with various ratios of LP. The flow curve of the HM-HPMC gel after passing through the microfluidizer presented a pseudo-viscous flow, which is typical of a diluted polymer solution. The emulsions containing 1–20% of LP also presented a pseudo-viscous flow, and the emulsion with 20% LP had an almost Newtonian flow. The slope of the curve increased in height with a higher LP ratio, indicating lower viscosity. When the ratio of LP was 40%, the flow curve demonstrated plastic flow, which is typical of a concentrated emulsion.

Dynamic frequency-sweep (variation in the storage modulus \[G'\] and loss modulus \[G''\] as a function of frequency \[\omega\]) was measured (Fig. 5(b)). \[G'\] and \[G''\] represent the elasticity and viscosity, respectively. After passing through the microfluidizer, HM-HPMC gel presents a viscoelastic response, with the curves for \[G'\] and \[G''\] intersecting at \[\omega = 6.31\] (rad/s), which is also typical of a dilute polymer solution. The emulsion with 1% LP also showed a viscoelastic response, intersecting at a higher frequency and lower modulus. The ratio of LP in the emulsion was increased to 10%, and a viscous response was observed, with \[G''\] exceeding \[G'\] over the entire \[\omega\] range. This suggests that the network between the polymer chains decreased with the addition of LP. In contrast, emulsions with 40% LP exhibited an elastic response, with \[G'\] exceeding \[G''\] over the entire \[\omega\] range. This is typical in emulsions with a high internal phase ratio.

The size of the oil droplets in the emulsion measured...
by the DLS method was approximately 1 µm, regardless of the LP concentration (Fig. 6(a)). Microscopic images of the emulsions are shown in Fig. 6(b). The number of droplets increased with the ratio of LP, and the droplets were similar in size. The Feret’s diameter of droplets in 1% LP emulsion was 1.04 ± 0.55 µm. With a higher LP ratio, the droplets overlapped so that the Feret’s diameter could not be determined from the images. Both methods showed that the size of the oil droplet was independent of the LP ratio in the emulsion.

The stability of the emulsion was studied by observing the creaming and oil droplet size. Creaming was not observed over 3 months regardless of the LP ratio. In addition, the oil droplets were approximately 1.0 ± 0.55 µm in size, regardless of the formulation (Fig. 7). Thus, the emulsion with HM-HPLC 1% is stable.

**Effect of Oil on the Emulsion Characteristics**

LP is one of the most popular oils used in external formulations. To alter the skin permeation or solubility of a drug, or the texture of a formulation, various kinds of oils are used. Table 1 shows the characteristics of the oils used in this study. LP has a different viscosity grade; therefore, we used some low-viscosity oils. Fatty acid esters are also common oil phases of cream, and different chain lengths were used in this study. Inorganic and organic balance (IOB) values, which are commonly used to describe the hydrophilic and hydrophobic balance of oils, are 0 for hydrocarbon oils (LP). Fatty acid esters show some hydrophilicity, which is due to the ester bond.

The viscosities of the emulsions are shown in Fig. 8(a). The emulsions with 1% oil showed similar viscosity to the LP emulsion. However, the viscosities of emulsions with 10% oil seemed to depend on the viscosity of the oil used. The lowest viscosity was observed for the IPM emulsion; this was consistent with the value for 20% LP emulsion. Figure 8(b) shows the oil droplet size in the emulsions. In all cases, the size of the droplet was smaller than that of the LP emulsion. Emulsions with 1% oil presented no creaming within 1 month;
however, some emulsions with 10% oil presented creaming (Table 2). The stability of emulsions differed between the oils. An increase in droplet size was observed for the IPM emulsion (Fig. 7). Other emulsions showed no change in droplet size.

Discussion
HM-HPMC was modified with a long-chain alkyl group, which showed higher viscosity than HPMC because of the interlocking of the main chains and the interaction between the stearoyl substituent. The viscosity of the HM-HPMC gel is independent of pH. Thus, HM-HPMC has highly favorable properties as an aqueous gel base for external use. We used a low stearoyl substituent type because it is soluble without alcohol.

There have been some reports on emulsions using polymers as emulsifiers. A relatively high concentration of oil was enclosed in the polymer chains and stabilized. Oil droplets are 20–40 µm in size and are therefore termed macroemulsion. Various polymers were used, including HPMC. HPMC gel emulsion with LP or silicon oil has been reported to present creaming within a short period. Futamura and Kawaguchi found that HM-HPMC stabilized the emulsion; however, it also showed creaming. HPMC and HM-HPMC have both hydrophilic and hydrophobic parts; thus, they exist on the surface of oil droplets in water and decrease the interfacial tension of oil and water. HM-HPMC was better able to stabilize the gel emulsion than HPMC; however, it presented creaming within a short period.

In our study, the emulsion obtained using a Quick Homomixer started to cream after a short time period, which was consistent with previous reports. The stability of an emulsion differs from that of instruments used in the emulsification process. A microfluidizer, which is a type of high-pressure homogenizer, has high energy and is suitable for obtaining small oil droplets. However, its high shear stress causes the polymer to degrade, and the degree of degradation differs among polymers. We confirmed the effect of the microfluidizer on the viscosity of the HM-HPMC solution. The decrease in viscosity was similar to that of other polymers (Fig. 1). Semilogarithmic relationships was observed between viscosity and concentration, which often observed in polymer solution (Fig. 2). It indicates the molecular weight of HM-HPMC became smaller than that before passed through a microfluidizer and its extent was almost the same regardless the concentration of HM-HPMC. The size of oil droplets became larger with increasing HM-HPMC concentration. The efficacy of mechanical emulsifying might decrease the viscosity of emulsion. Creaming was observed with low HM-HPMC concentration, although the sizes of oil droplets were not changed (Fig. 3). The viscosity of 1% HM-HPMC emulsion was 30, 100 and 1000-times larger than those of 0.5, 0.3 and 0.1% HM-HPMC emulsion, respectively. The viscosity of emulsion is important factor to prevent creaming. The size of oil droplets in the emulsion was larger with increasing HM-HPMC concentration (Fig. 3) and was approxi-

| Oil | 1 week | 1 month | 2 months |
|-----|--------|---------|----------|
| LP  | −      | −       | −        |
| LP-17| −     | −       | +        |
| LP-7 | −     | −       | +        |
| ICS | −      | −       | −        |
| EHS | −      | −       | +        |
| IPIS | −    | −       | +        |
| IPM | +      | +       | +        |

Each emulsion contains 10% oil and 1% HM-HPMC.
mately 1 µm, regardless of the LP ratio when the concentration of HM-HPMC was 1% (Fig. 6). The microscopic image also showed that different LP concentrations only affect the droplet number. The small size of the oil droplet was effective in preventing demulsification by creaming (Fig. 7). The high energy of the microfluidizer was effective at reducing the size. It is known the energy input during emulsification is the same, droplet size become larger with higher viscosity of continuous phase or dispersed phase. Thus, the size of oil droplets in lower concentration of HM-HPLC is smaller. The droplets size also depend on re-coalescence. Adsorption of HM-HPMC on the surface of oil droplet might be fast and strong, so droplets re-coalescence is prevented, and the oil droplets size was not change even if creaming was observed (Fig. 3).

The apparent viscosity of an O/W type emulsion increases with the ratio of the oil phase. However, the viscosity of the HM-HPMC emulsion decreased with an LP ratio less than 20%, even though the emulsion was O/W type (Fig. 4). When 0.5% HM-HPMC gel was used, and minimum viscosity was observed with LP 10%. This suggests there is a relationship between the ratio of HM-HPMC and LP. The stearyl group of HM-HPMC adsorbed on the interface, preventing their interaction. The process of emulsification might affect the interaction between HM-HPMC and LP. The low viscosity of emulsion with 20% oil phase is useful for external use, emulsion-type lotion, and is easy to spread, and has a favorable texture. When the ratio of LP exceeded 20%, the viscosity increased as the LP ratio increased. They presented a rheogram similar to that of the diluted polymer solution. Conventional gel emulsion is prepared with a low-energy emulsification process to avoid destroying the gel structure.

In our method, a high-energy process was adapted so that the structure of the gel maintained by hydrophobic interactions could be cleaved. Moreover, the area of the oil and water interface increased because of the small droplet size of the oil. Thus, the stearyl group was adsorbed on the interface, preventing their interaction. The process of emulsification might affect the interaction between HM-HPMC and LP. The low viscosity of emulsion with 20% oil phase is useful for external use, emulsion-type lotion, and is easy to spread, and has a favorable texture. When the ratio of LP exceeded 20%, the viscosity increased as the LP ratio increased. They presented a rheogram similar to that of the diluted polymer solution. Conventional gel emulsion is prepared with a low-energy emulsification process to avoid destroying the gel structure.

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