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Research paper

Hydroxypropylmethylcellulose (HPMC) as emulsifier for submicron emulsions: influence of molecular weight and substitution type on the droplet size after high-pressure homogenization

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Abstract

Hydroxypropylmethylcellulose (HPMC) is a known emulsifier as well as a common viscosity enhancer in eye drops. Therefore, HPMC stabilized emulsions appear as interesting drug carriers for ophthalmic use and as a suitable treatment of dry eye syndrome. Since submicron emulsions are known to have an improved drug delivery, attempts were made to reduce the emulsion's droplet size by high-pressure homogenization. Droplet size was dependent on the homogenization pressure and the polymer content. Differences were found between emulsions stabilized with higher and lower molecular weight HPMC. Smaller droplet sizes were obtained with the shorter chained HPMC. No considerable influence of the substitution type was observed.

Keywords: Hydroxypropylmethylcellulose; Cellulose ether; Surface tension; Molecular weight; Viscosity; Submicron emulsion; Droplet size; Laser diffractometry; Ophthalmic application

1. Introduction

Oil-in-water emulsions are interesting dosage forms for lipophilic drugs, which may be dissolved in the inner phase of the emulsion [1–4]. Compared with conventional emulsions, the reduction of the droplet size into the submicron range, i.e. a mean droplet size of less than 0.5 μm [5], improves drug delivery [6–9] and diminishes creaming. Especially for eye drops, these emulsions could be advantageous because they are supposed to diminish vision-blurring effects. The poor physiological tolerance of common emulsifiers [10] and the high sensitivity of the eye, however, prevent their use in eye drops. Some cellulose ethers, e.g. methylcellulose and hydroxypropylmethylcellulose (HPMC), on the other hand, are also surface active agents [11–13]. They are known to be physiologically tolerated from their abundant use as viscosity enhancer in aqueous eye drops [14].

Several recent investigations focused on the use of surface active cellulose ethers as the sole emulsifiers in emulsions, highlighting HPMC as an excellent emulsifier [15–17]: Emulsions containing 20% medium chain triglycerides (MCT) were exclusively stabilized with 2.5% HPMC100 [18]. These emulsions had a mean droplet size of 3 μm and they were stable on storage for years. In addition, HPMC has mucoadhesive properties, which might favor drug availability [19,20]. Emulsions exclusively stabilized with HPMC are thus interesting dosage forms for ophthalmic application.

The preparation of submicron emulsions requires a high energy input. Refined preparation techniques such as ultrasonic or high-pressure homogenization are vital, with high-pressure homogenization generally preferred due to better effectiveness and more homogeneous droplet size distributions [21]. It was also selected for the preparation of HPMC-stabilized submicron emulsions in the present study.

The present study investigated HPMC-stabilized emulsions containing 10% MCT. During preparation, several parameters including homogenization pressure, number of homogenization cycles and homogenization temperature, were varied to determine their influence on the droplet size of the emulsions. This study focused on the influence of the USP-substitution type and the molecular mass of the HPMC.

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2. Material and methods

2.1. Materials

Four different types of hydroxypropylmethylcellulose (HPMC) were used representing two USP-substitution types of two different molecular weights (Table 1). USP-substitution type 2208 and 2910 mainly differ in their degree of substitution with methoxyl groups. HPMC 2910 is more substituted than HPMC 2208, resulting in enhanced surface activity (Table 2) and lipophilic properties of type 2910.

The oil phase consisted of medium-chain triglycerides, MCT (Miglyol 812, Hüls, Troisdorf, Germany). MCT were selected as a model-oil phase since they are well tolerated when applied to the eye. Their low viscosity and their density close to water are additional advantageous properties for stable emulsions.

2.2. Methods

2.2.1. Molecular weight

The molecular weight of the polymer was determined as described by Crössmann et al. [22]. This method is based on viscosity measurements of highly diluted aqueous solutions using a capillary viscometer (Viskositätsmeßgerät AVS 350, Schott Geräte, Hofheim, Germany).

2.2.2. Droplet size measurement

For droplet size determination, a Mastersizer 1000 (Malvern Instruments, Worcester, UK), based on laser diffractometry, was used. To determine droplet sizes in the range of 100 nm to 80 μm a reverse Fourier optic with a focal length of 45 mm was applied. Particle sizes were calculated choosing the independent model and both the Fraunhofer and the Mie scattering matrices (Malvern software B.0). Although calculations using the Mie theory may seem more appropriate in the particle size range below a few micrometers, the difficulties in calculating the complex refractive index of oil droplets consisting of different components, HPMC and MCT, rendered this method less exact. Calculations with the Fraunhofer matrix may have caused some other systematic errors [23], but a comparison with microscopic droplet size determinations suggested this method to be more accurate.

Table 1
Types of applied HPMC

HPMC	Trade name and manufacturer	USP-substitution type	Molecular weight
100	Methocel K100LV, Dow Chemicals Ltd., Middlesex, UK	2208	52 300
50	Metolose 60 SH 50, Shin-Etsu Co. Ltd., Tokyo, Japan	2910	47 200
5	Methocel E5, Colorcon, Orpington, UK	2910	18 900
4	Pharmacoat 904, Shin-Etsu Co. Ltd., Tokyo, Japan	2208	10 100

Table 2
Influence of USP substitution type on the surface tension of aqueous HPMC solutions

HPMC	Polymer content (%)	Substitution type USP XXIII	Surface tension (mN/m)
100	2.5	2208	53.0
50	2.5	2910	46.6
5	6.0	2910	48.3
4	6.0	2208	51.7

The particle size of each emulsion was determined in triplicate 24 h after preparation. Droplet size distributions were characterized by at least two parameters, that were considered as approximations to a medium diameter D(50%) and a maximum diameter D(99%). Both parameters are diameters by volume, with either 50 or 99% of the volume of the internal phase distributed in droplets below that size.

For droplet size determination 1 to 5 ml of the emulsion was added to 1000 ml demineralized water. The stability of droplet sizes was determined by measuring a sample of the diluted emulsion continuously over 10 h. No significant change in droplet size was observed during that period (data not shown).

2.2.3. Emulsion preparation

All emulsions used were of the oil-in-water type. The aqueous phase was a solution of HPMC, while the oil phase consisted of MCT. Solutions were prepared one day before emulsion preparation to warrant fully soaked polymer molecules.

Pre-emulsions were produced by short manual shaking of the oil and water phase in a flask. These raw emulsions were passed through a high-pressure homogenizer (Micronlab 4, APV Homogenizer GmbH, Lübeck, Germany) several times to obtain homogeneous dispersions of small oil droplets. The applied homogenization pressure ranged from 10 to 160 MPa.

As in process control, the emulsion temperature was determined immediately after each homogenization step. Generally, the temperature was kept between 30 and 40°C. Since the processing temperature increased with increasing homogenization pressure, the pre-emulsions were thermostated to an appropriate temperature before homogenization, if necessary. Cooling in an ice bath between the homogenization cycles was required when the homogenization pressure exceeded 65 MPa. However, it was not possible to keep the processing temperature within the given limits when a homogenization pressure of 160 MPa was applied.

Further investigations were carried out to obtain information about the influence of the processing temperature on the droplet size distribution of the resulting emulsions. For this

purpose the temperature of the emulsion was adjusted to an appropriate range before each homogenization cycle to reach 40°C, 50°C or 60°C immediately after the homogenizing step.

These emulsions were prepared at a pressure of 90 MPa. Particle size was determined after each step 24 h after preparation.

2.2.4. Viscosity determination

The apparent shear viscosity of the emulsions was determined by Höppler's rolling sphere viscometer at 20°C. This simple but highly reproducible method was applied because measurements with a controlled stress rheometer (Bohlin CVO, Mühlacker, Germany) revealed only marginal shear thinning and no yield stress of the preparations. However, viscosity measurements using this rheometer resulted in fluctuating values due to the extremely low viscosity of some emulsions (Daniels et al., unpublished data).

2.2.5. Surface tension

Surface tension was determined at 20°C with a drop volume tensiometer (TVT 1, Lauda Dr R. Worbster, Lauda-Königshofen, Germany). Drop building velocities between 0.3 and 0.8 s/μl were applied.

3. Results and discussion

3.1. Emulsions with HPMC 100

The investigations started with emulsions consisting of 2.5% HPMC100 [15] and 10% MCT. Pre-emulsions passed the high-pressure homogenizer five times at either 50, 90 or 160 MPa. At 50 and 90 MPa, the droplet sizes decreased during each of the five homogenization cycles, while becoming increasingly reproducible (Fig. 1). These pressures yielded emulsions differing mainly in their medium droplet size (D(50%)), which was considerably lower at 90 MPa than at 50 MPa. An additional increase of the homogenization pressure could not, however, further decrease the droplet size: although 160 MPa were apparently more efficient during the first homogenization cycle, a strong increase of the D(99%) and broadened droplet size distributions occurred during the following three runs [24–26].

A similar effect was observed with increased processing temperature (50°C and 60°C) at 90 MPa which led to increasing D(99%) values [27], after the fourth homogenizing cycle (Fig. 2).

The results shown in Figs. 1 and 2 revealed optimum processing conditions for HPMC100 emulsions at a medium pressure of 90 MPa and a temperature of 40°C. A reduced pressure, 50 MPa, led to insufficient dispersion during five cycles, while overprocessing was observed at 160 or 90 MPa in combination with another type of additional energy input (e.g. temperature increase). Overprocessing caused increasing and strongly variable droplet size values. It probably occurs due to the development of a large interfacial area during homogenization, which causes a partial depletion of polymer in the water phase. At a certain threshold of depletion, newly formed droplets can no longer be sufficiently stabilized, thus triggering a coalescence process during the next homogenization run [28].

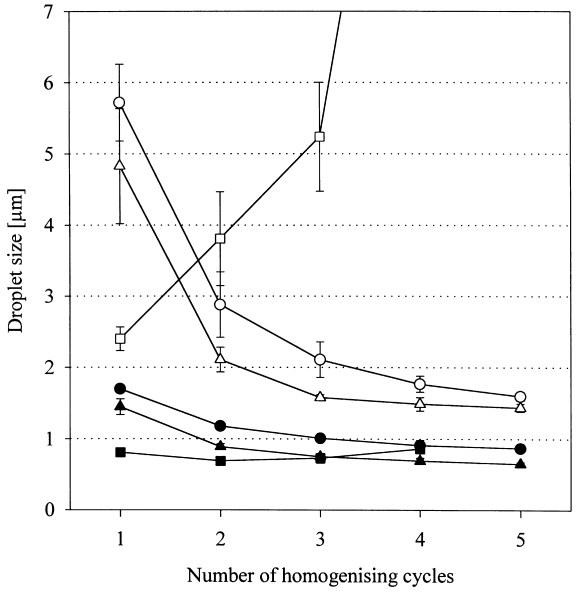

Fig. 1. Influence of the homogenization pressure and the number of homogenization cycles on the droplet size of emulsions with 2.5% HPMC 100 (40°C). D(50%) of emulsions processed at 50 MPa (●), 90 MPa (▲) and 160 MPa (■). D(90%) of emulsions processed at 50 MPa (○), 90 MPa (△) and 160 MPa (□).

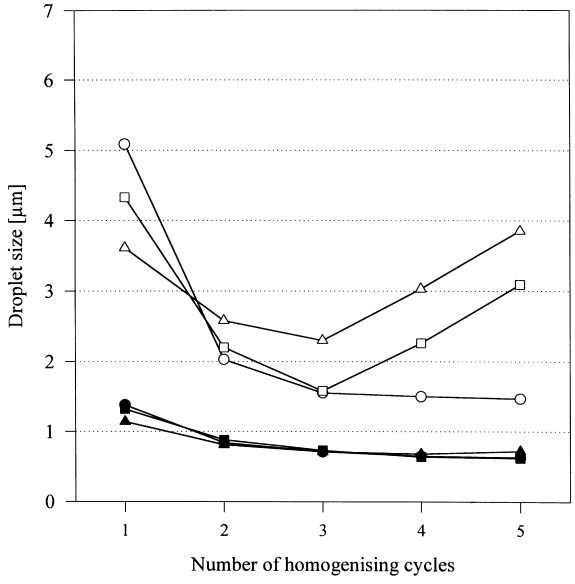

Fig. 2. Influence of the processing temperature on the droplet size of HPMC100 emulsions processed at 90 MPa (five cycles). D(50%) of emulsions processed at 40°C (●), 50 °C (■) and 60 °C (▲). D(99%) of emulsions processed at 40°C (○), 50 °C (□) and 60 °C (△).

Another effect might also influence overprocessing. The viscosity of HPMC100 emulsions decreases with increasing pressure, indicating polymer degradation due to the processing conditions (Table 3). The degraded polymer may no longer be sufficient for complete emulsion stabilization and could thus favor overprocessing.

As shown in Fig. 1, continuously decreasing particle sizes were highly reproducible, while overprocessing led to fluctuating values. To find the approximate threshold from maximum dispersion to undesirable overprocessing, process optimization was performed without considering standard deviations as long as clear trends in particle size development were detectable. Emulsion preparation was repeated several times under these optimized conditions. Based on these results, the polymer content was increased from 2.5 to 3% in order to improve and accelerate droplet stabilization [16,29]. Unexpectedly, increased polymer concentration did not reduce the droplet size. The viscosity of the preparations, on the other hand, increased to a level undesirable for ophthalmic application. The viscosity should not substantially exceed 50 mPas to prevent blockage of the endolacrimal channel [30].

Although the mechanisms of influencing droplet size and size distributions became evident during the investigations for HPMC100 stabilized emulsions, the medium droplet size of these emulsions could not be reduced below 0.65μm by varying processing conditions and polymer concentration.

3.2. Emulsions with HPMC5

For further reduction of the droplet size, another type of HPMC was introduced. HPMC100 was replaced by HPMC5, which has a lower molecular weight. Belonging to the USP-substitution type 2910, it is also more surface active (Table 2). The optimum conditions found for HPMC100 emulsions revealed relatively broad particle size distributions. Therefore, the scheme of a central composite design was applied to find both optimum polymer content and processing conditions. According to the results of preliminary investigations, the polymer content was varied between 2.4% and 6.6% while homogenization pressures in the range of 44–86 MPa were selected.

As a result, D(50%) values (Fig. 3) decreased with increasing polymer concentration. This trend continued until leveling off at 6% HPMC5. While the polymer content substantially influenced D(50%) values, the homogenization pressure had almost no effect.

D(99%) values, however, only decreased with increasing polymer content when low homogenization pressures were selected (Fig. 4), but escalating overprocessing developed with increasing HPMC5 content and pressures exceeding 50 MPa. Due to this overprocessing a statistical analysis of the central composite design did not appear appropriate.

HPMC5 emulsions are subjected to overprocessing problems similar to those seen in HPMC100 emulsions. While in emulsions with 6% HPMC5 overprocessing already occurred at 65 MPa homogenization pressure, emulsions with HPMC100 did not show increasing D(99%) values below pressures of 90 MPa. This might be due to a higher sensitivity of emulsions stabilized with the short chained HPMC5. On the other hand, the interfacial area of overprocessed HPMC5 emulsions was increased relative to HPMC100. The enlarged interfacial area of HPMC5 emulsions might be more sensitive to the mechanisms described above. This is also confirmed by the intensifying overprocessing effects observed with increasing HPMC5 content.

Although the short-chained HPMC5 was less effective at 2.5% than HPMC100, increased HPMC5 content could substantially reduce the droplet size to a D(50%) of 0.37 μm and a D(99%) of 1.5 μm (6% polymer, 50 MPa). Even with this increased polymer content, a viscosity resulted which was lower than that of 2.5% HPMC100. Thus, HPMC5 emulsions seem more appropriate for ophthalmic application (Table 3).

Table 3
Dynamic viscosities of HPMC-stabilized emulsions after five homogenization cycles

HPMC	Polymer content (%)	Homogenization pressure (MPa)	Viscosity (MPas)
100	2.5	50	107.8
		90	72.6
50	2.5	50	72.8
		90	52.2
5	6.0	50	53.8
		90	53.3
4	6.0	50	24.2
		90	24.3

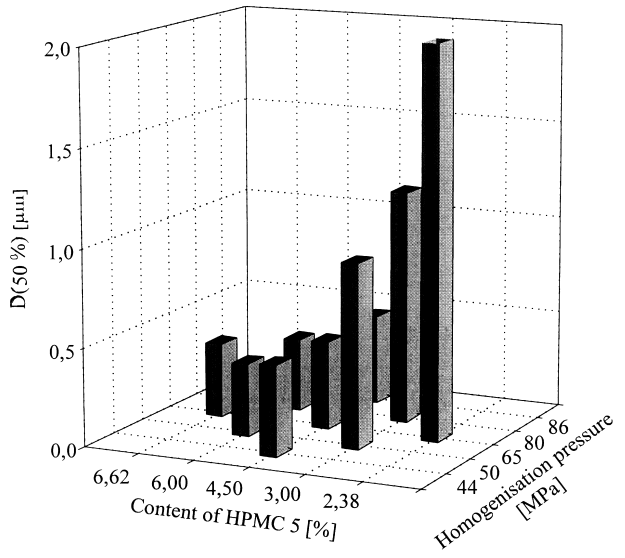

Fig. 3. Influence of the polymer content and the homogenization pressure on the D(50%) values of HPMC5 emulsions (five cycles, 40°C).

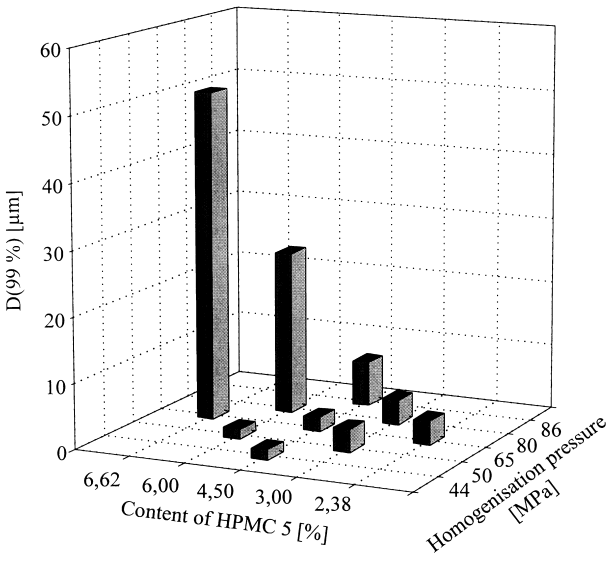

Fig. 4. Influence of the polymer content and the homogenization pressure on the D(99%) values of HPMC5 emulsions (five cycles, 40°C).

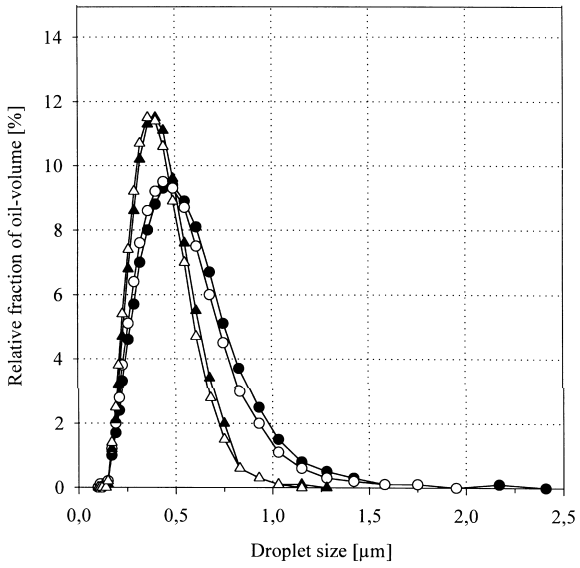

Fig. 5. Influence of the molecular weight and the substitution type of HPMC on the droplet size distribution of emulsions (five cycles, 40°C). (●) 2.5% HPMC100; (○) 2.5% HPMC50; (▲) 6% HPMC5; (△) 6% HPMC4.

3.3. Emulsions with HPMC4 and HPMC50

For discrimination between the influence of molecular weight and substitution type, two other HPMC were tested. While HPMC4 and HPMC5 share a rather low molecular weight, their substitution types differ. The applied HPMC4 is less surface active than HPMC5 (Table 2). Concerning the high molecular weight polymers, HPMC50 emulsions were prepared under the same conditions as HPMC100 emulsion. HPMC50 has a molecular weight comparable to HPMC100, but is more surface active.

Approximately equivalent particle size distributions resulted when emulsions were stabilized with HPMC4 or 5 when prepared under the same conditions. Emulsions stabilized with HPMC50 or HPMC100 also yielded similar but considerably broader droplet size distributions (Fig. 5) with larger D(50%) values than the short-chained HPMC emulsions. These results showed that particle size distributions, after processing, are strongly dependent on the molecular weight of HPMC, but largely independent of the substitution type.

The lower molecular weight HPMC seems to be less effective in stabilizing emulsions at low concentration, but in contrast to the long chained HPMC, a further increase in polymer content resulted in strongly decreasing droplet sizes. Since the droplet size of emulsions with HPMC100 leveled off at 2.5%, the interaction of polymer molecules, expressed as viscosity increase, may negatively affect the availability of stabilizing polymer. Thus, the availability of the polymer at its site of action, i.e. the oil–water interface, seems to be primarily responsible for the different droplet sizes observed in emulsions stabilized with low and high molecular weight HPMC.

3.4. Stability of the optimized emulsions

The stability of emulsions with HPMC100, -50, -5 and -4 was determined over a period of 2 months. While D(50%) values remained stable, the D(99%) of all emulsions increased during that time interval (Fig. 6). Except for emulsions with HPMC4, which showed considerably increasing droplet sizes even with an increased polymer content of 7%, only moderate changes were observed in the other emulsions. Further attempts to increase the stability of the emulsions will be the subject of subsequent investigations.

4. Conclusions

The results show that droplet size distributions of emul-

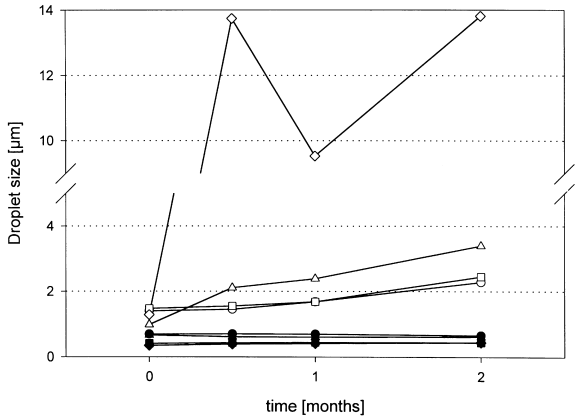

Fig. 6. Stability of the optimized emulsions. D(50%): (●) 2.5% HPMC100; (▲) 2.5% HPMC50; (■) 6% HPMC5; (◆) 7% HPMC4. D(99%): (○) 2.5% HPMC100; (△) 2.5% HPMC50; (□) 6% HPMC5; (◇) 7% HPMC4.

sions stabilized with HPMC are primarily controlled by the amount of polymer available at the oil–water interface during the homogenization step. This amount of polymer depends on the polymer concentration and viscosity as determined by the molecular weight. No influence of the substitution type of HPMC on the droplet size distribution was found within 24 h after processing.

It became obvious that overprocessing is mainly a problem of emulsions with high interfacial area and depends on the molecular weight of the stabilizing HPMC.

By selecting a low homogenization pressure and high polymer content, real submicron emulsions suitable for ophthalmic application can be stabilized exclusively with low molecular weight HPMC.

These results of a process development led to investigations on the emulsion's stability, which will be the scope of another paper.

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