Study of the Breakup Under Shear of a New Thermally Reversible Water-in-Oil-in-Water (W/O/W) Multiple Emulsion

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Purpose. Thickening of the external aqueous phase of W/O/W multiple emulsions is essential to increase the release under shear. However, it leads to globules bursting during fabrication. To reduce this problem, we have tested a novel thermally reversible hydrogel, EMP hydrogel. This way, the corresponding multiple emulsion (EMPME) would gel only at skin temperature, which may increase the active ingredient delivery when topically applied.

Methods. Samples were sheared at different shear rates and temperatures (20, 30, and 35°C) with a controlled rheometer. A granulometric analysis was then performed with a laser diffraction granulometer, to assess the break up as a function of the shear rate at the three temperatures. Conductometric measurements (CDM 230 conductometer) provided the corresponding release curves.

Results. As we expected, EMPME exhibited a thermally reversible behavior. Compared to a reference emulsion thickened by carbopol, this new thermo-sensitive multiple emulsion displayed higher break up and fraction released at 35°C.

Conclusion. The first thermally reversible multiple emulsion has been developed in the present work. This one presents interesting advantages: (1) an easy fabrication process with a higher entrapment yield and (2) a higher fraction released at 35°C compared with the reference emulsion.

KEY WORDS: water-in-oil-in-water multiple emulsion; breakup; thermally reversible; hydrogel; shear; release.

INTRODUCTION

The water-in-oil-in-water (W/O/W) multiple emulsions are vesicular systems composed of an aqueous volume fraction dispersed within oily globules, which are themselves dispersed in a continuous aqueous liquid (1). The applications of W/O/W emulsions range from pharmaceutical drug delivery, foods, and cosmetics to drilling fluids and hazardous material handling (2). The main benefits sought in the application of the W/O/W emulsions are their protection of the entrapped substances, their capacity to incorporate several actives in the different emulsion compartments, and their sustained release effect (3).

Two important release mechanisms are often cited in the literature: the diffusion through the oily barrier and the globules bursting that occurs either by dilution in a hypo-osmotic solution (with regards to the internal aqueous phase) (4,5) or by submission to a shear stress (6,7). Taylor (8,9) was the first to study the deformation under shear and the bursting of a simple, dilute emulsion. He considered that the breakup occurred when shear stress exceeds cohesion stress and defined in this way a capillary number $Ca = \eta_c Gr/\sigma$, where η_c is the continuous phase viscosity, G the shear rate, r the radius of the globule at rest, and σ the interfacial tension between oil and water. Bursting occurs when this capillary number exceeds a critical value Ca_{cr} close to unity. This relation points out that the thickening of the continuous phase is an important factor to encourage the globules bursting. This encouraged us to search some adequate thermoresponsive hydrogels to thicken the external aqueous phase of our multiple emulsions, which release would occur only at body temperature after a topical application.

Materials that exhibit a sol to gel transition in aqueous solution, between ambient and body temperature, are of great interest in the development of sustained release vehicles with *in situ* gelation properties. Most of these systems are based on poly *N*-isopropylacrylamide (polyNIPAm), which exhibits a lower critical solution temperature LCST at about 32°C, or related copolymers (10–12). *N,N*-diethylacrylamide (DEEAm), with its LCST in the range of 25–32°C, perhaps follows polyNIPAm on a list of widely studied temperature-sensitive gel constituents (13,14). The up-to-date thermoviscosifying materials approved by FDA and EPA are the block-copolymers of poly(ethylene oxide) and poly(propylene oxide) (PEO-PPO-PEO), which exhibit gelation at body temperature in concentrated solutions, at 16 wt% with Pluronic® F127 for instance (15). The newly developed poly(ethylene glycol-b-(DL-lactic acid-co-glycolic acid)-b-ethylene glycol) (PEG-PLGA-PEG) triblock copolymers have the advantage to be biodegradable (16), like the xyloglucan gels that exhibit a sol-to-gel transition at lower concentration (transition between 22 and 27°C over the concentration range of 1 to 2 wt%) but with a weak amplitude and a lag time (17). Hydrophobically modified polyacrylic acid (HMPAA) having poly(propylene oxide) (PPO) block as a hydrophobic moiety were recently introduced by Bromberg (18–21). These HMPAA are capable of stabilizing emulsions and form thermoreversible shear thinning hydrogels at body temperature (LCST of 25–30°C depending on the concentration). This occurs without phase separation, at low polymer concentrations (1–5 wt%), and with a rapid 10^3–10^4-fold increase in viscosity over a range of several degrees when neither parent Pluronic® show any sign of viscosification (22–24).

In the present work, we aimed at formulating a new shear-sensitive W/O/W multiple emulsion whereby the break up of the droplets (and thus the release of an active ingredient) occurs only upon application onto the skin and not during the fabrication process. The aforementioned useful properties of HMPAA prompted our own search of the temperature-sensitive HMP in order to thicken the external aqueous phase of the multiple emulsion. Herein, we applied HMPAA

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consisting of PAA blocks end-linked to Pluronic® segments (25). Because of the applications of these new polymers, we were able to resolve an important problem inherent to the fabrication of thickened multiple emulsion, which is the droplet break up during the fabrication process. This HMPAA-modified W/O/W emulsion, which is the first thermo-sensitive W/O/W multiple emulsion existing at the moment, would be thickened only upon its application on the skin, as described below.

MATERIALS AND METHODS

Raw Materials and Preparation of the Multiple Emulsions

The composition (wt%) of multiple emulsions is given in Table 1. The oil was an isohexadecane (Arlamol® HD, ICI, France). A polymeric lipophilic surfactant, a PEG-30 dipolyhydroxystearate with A-B-A structure (Arlacel® P135, ICI, France), was used to emulsify the W/O primary emulsion. Because the formulation of the W/O/W multiple emulsion required a hydrophilic surfactant, we have chosen an ethylene and propylene oxide copolymer (Arlatone® F127G, ICI, France) that is non-ionic. The surfactant concentrations were chosen so that the interfaces were saturated, based on respective CMC values of the two surfactants and the authors experience regarding W/O/W multiple emulsion formulation (5). The sodium chloride (NaCl) was purchased from Prolabo (France) and used to increase the stability of the system and to play the role of a breakdown indicator. Poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)-g-poly(acrylic acid) copolymer (EMP Hydrogel™) was obtained from MADASH, LLC. (Lexington, MA, USA). The EMP Hydrogel™ is a copolymer of Pluronic® F127 and poly(acrylic acid) (average molecular weight 3×10^6 Da) obtained via modification of the Pluronic® at both ends by acryloyl moieties following copolymerization (26). We used an EMP Hydrogel™ concentration that allowed a 10^3–10^4- fold increase in viscosity over a range of 20 to 40°C. Lightly crosslinked PAA (Carbopol® 974-P, B.F. Goodrich, France) was applied to prepare a reference emulsion. The concentration of this component was chosen in order to have an equivalent viscosity to the EMP multiple emulsion at room temperature. Practically, multiple emulsions named respectively EMPME (multiple emulsion thickened by EMP Hydrogel™) and CME (multiple emulsion thickened by Carbopol® 974-P) were prepared with a Rayneri mixer by, respectively, a two or three step process (27). The W/O primary emulsions were obtained by incorporation of the aqueous phase into the oily phase containing the lipophilic surfactant, after heating the two phases to 70–80°C, under high stirring (3000 rpm (g)) for 45 minutes. The resulting W/O primary emulsions were dispersed gradually into the aqueous phase containing the hydrophilic surfactant and the polymer (EMP hydrogel™ or carbopol® 974-P) under moderate stirring (500 rpm (g)) for 15 minutes at 15°C. The resulting pH of EMPME was around 6. The formation of the multiple emulsion gelled with the carboxyvinylic polymer required a third step, which was the carbomer neutralization by a 10% sodium hydroxide solution to obtain a pH around 6 (skin pH). A third W/O/W multiple emulsion was also prepared using another lipophilic surfactant, a cetyl dimethicone copolyol (Abil® EM90, Goldschmidt, France), to assess the role of the lipophilic surfactant in the release mechanisms.

Table I. Composition (wt%) of Multiple Emulsions

	EMPME	CME	CMEbis
W/O primary emulsion			
Demineralized water	66.7	66.7	66.7
NaCl	0.3	0.3	0.3
Arlamol® HD	29	29	29
Arlacel® P135	4	4	–
Abil® EM90	–	–	4
W/O/W multiple emulsion			
W/O primary emulsion	60	60	60
Demineralized water	36.8	37.2	37.2
Arlatone® F127G	1.6	1.6	1.6
EMP Hydrogel™	1.6	–	–
Carbopol® 974-P	–	0.4	0.4
10% NaOH solution	–	0.8	0.8

Methods

Firstly, thermogelling properties of 4 wt% EMP Hydrogel™ solution and corresponding multiple emulsion were studied with a controlled stress rheometer (CSL 100, Carrimed, France) using a cone and plate geometry that allows a homogeneous shear of the samples (plate, 40 mm; cone, 2°). Samples (volume 0.1 ml) were tested under constant stress of 10 Pa in the range of temperatures from 20 to 40°C.

Secondly, the multiple emulsions behavior under shear was studied by different methods including rheology, granulometry, conductometry, and microscopy. All measurements were performed 24 hours after preparation. To simulate a topical application, multiple emulsions were sheared for 3 minutes at different shear stresses with a controlled stress rheometer (RS 100, Carrimed, France) at 20, 30, and 35 ± 1°C using a cone-plate geometry (plate, 35 mm; cone, 0.5°; sample volume, 0.1 ml).

The granulometric analysis was performed with a laser diffraction granulometer (Coulter LS 230, Coultronics, France), equipped with a "microvolume" cell of 12 ml designed for liquid samples, to study the multiple globules fragmentation under shear. Each sample was diluted (dilution factor of 10^4–10^5) to obtain the convenient optical concentration, between 8 and 12%, to achieve the measure in optimal conditions. An iso-osmotic glucose solution with regard to the internal aqueous phase was used for the dilution to prevent globules from bursting; as the internal aqueous phase was a little hyper-osmotic with regard to water, a dilution in pure water (which is hypo-osmotic) would provoke an osmotic water flow from the external to the internal phase which would lead to the swelling and then the breakdown of the globules (4,5,28). The globule size distributions, characterized thanks to the Fraunhoffer model, were given as a function of the volume and the diameter of the globules. The defined diameter was the mean diameter "volume-moment" d_{32} (chosen as it took specially the big globules into account; these ones, including the major part of the internal aqueous phase, were of great interest in our study):

$$d_{32} = \frac{\Sigma n_i d_i^3}{\Sigma n_j d_j^2}$$

where n_i is the number of the particles having a d_{ii} diameter. Changes in the droplet size as a function of the shear rate in multiple emulsions were also monitored before and after shearing with an optical microscope (Olympus BX60, Olympus, France) connected to a video camera (Sony, France). To evaluate the release of NaCl under shear, conductivity of the multiple emulsion diluted (1/20) in the iso-osmotic glucose solution was measured before and after shear with a CDM 230 conductometer (Tacussel, Radiometer Copenhagen, France). Based on the estimate of the NaCl amount in the external aqueous phase, entrapment yields and fractions released can be calculated, using corresponding calibration curves. These ones were expressed in conductivity (μS/cm) as a function of NaCl concentration (mg/ml). The respective equations of the calibration curves for EMPME and CME were $y = 1.67 \times (R^2 = 0.99)$ and $y = 1.97 \times (R^2 = 1.00)$. Of note, as the shear rate values are better defined than the shear stress when skin application is concerned, the break up and release curves are given as a function of the shear rate which values are arbitrarily taken at the beginning of each 3 minutes stress ramp.

RESULTS

Thermal Viscosification Measurement for EMP Hydrogel™ and the Corresponding Multiple Emulsion EMPME

Thermoviscosifying behaviors of EMP Hydrogel™ in solution and EMPME are illustrated in Figure 1. As is seen, a 10^4-fold increase in hydrogel viscosity (equilibrium viscosity) occurred over a range of temperatures from 22°C to 37.5°C. The EMPME multiple emulsion also gelled with increasing temperatures, but to a lower extent, which was probably because of the dilution factor of the thermogelling copolymer solution in the multiple emulsion but also to the use of additional emulsion additives which could indeed interfere with the gelation process. Note that the sol-gel transition of both the EMP Hydrogel™ and the multiple emulsion was perfectly reversible.

Temperature-Dependent Behavior Under Shear of the New Thermo-Sensitive W/O/W Multiple Emulsion EMPME

Breakup Studies

The mean droplet diameter of the multiple emulsions as a function of shear rate is shown in Figure 2. The two emulsions tested were shear-sensitive, as indicated by the decrease of mean diameter with increasing shear. However, whereas no significant temperature effects were observed with CME, which was not so surprising since the carbopol viscosity does not vary with temperature, major temperature effects were noted with EMPME. The decrease of the mean diameter after shearing for 3 minutes at 100 s^{-1} was only 22% at 20°C instead of 55% at 35°C. Of course, this could be explained by the viscosity increase of the EMP Hydrogel™ at higher temperatures.

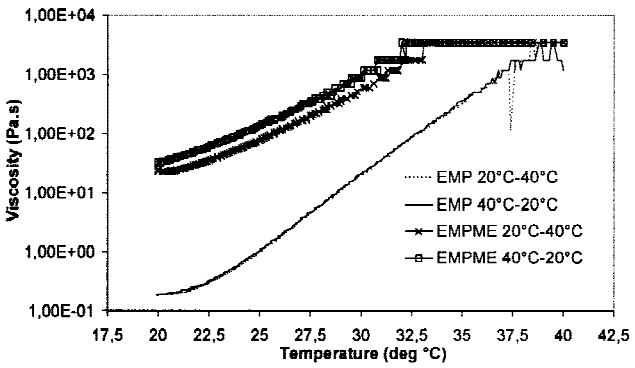

Fig. 1. Thermal viscosification measurement, in the range of 20 to 40°C, for EMP Hydrogel™ (4 wt%) and the corresponding multiple emulsion EMPME (10 Pa shear stress).

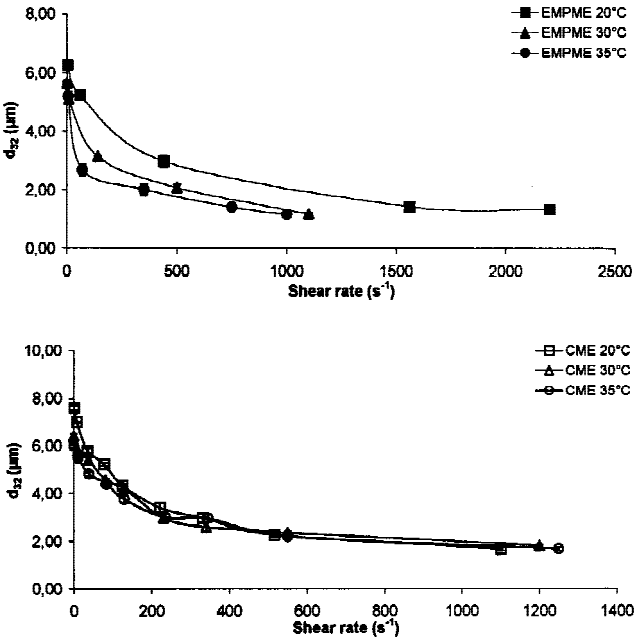

Fig. 2. Break up curves at different temperatures for EMPME (top) and CME (bottom) (mean ± SD μm, n = 3 analyses performed three times on the same emulsion; a different emulsion was used at each temperature).

Release Studies

The fractional release of NaCl as a function of the shear rate for the two multiple emulsions is presented in Figure 3. It is noteworthy that the higher release percentages were observed with EMPME at 35°C, even for the low shear rates. Contrary to the results obtained with CME, the fraction released from EMPME were temperature-dependent throughout the shear rate range studied. For example, shearing for 3 minutes at 1000 s^{-1} (which is a shear rate usually reached during topic applications) resulted in fractions released of 14% at 20°C, 30% at 30°C, and 53% at 35°C. Also, at 35°C, 25% NaCl is released after shearing of EMPME and CME at 250 s^{-1} and 850 s^{-1}, respectively. It is also of interest to note that the release was partial: only half of the total amount of NaCl encapsulated was released. However, as shown in Figure 4, a single shearing of 3 minutes at 1000 s^{-1} at 35°C led to at least one fragmentation of each globule.

The entrapment yields were respectively 99.9 ± 0.1% (n = 3) and 90 ± 4% (n = 3) for EMPME and CME.

Influence of the Lipophilic Surfactant on the Release Mechanisms

Figure 5 compares the break up and release curves of CME formulated with Arlacel® P135 and Abil® EM90. Both

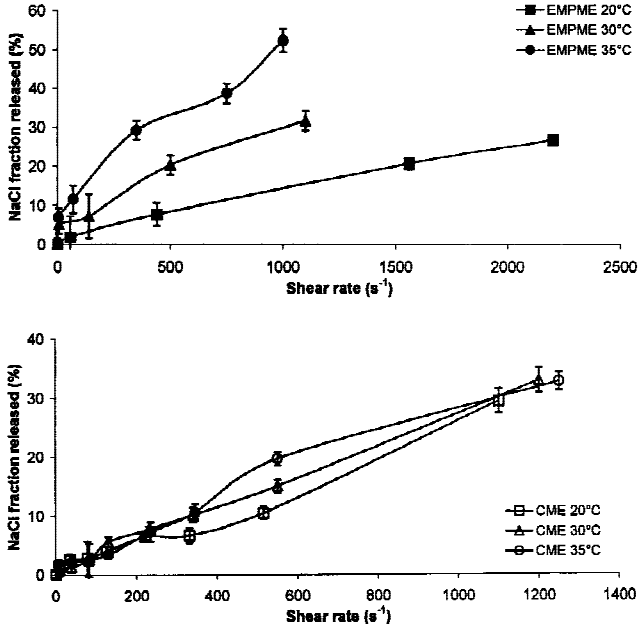

Fig. 3. Release curves at different temperatures for EMPME (top) and CME (bottom) (Mean ± SD %, n = 3 analyses performed three times on the same emulsion; a different emulsion was used at each temperature).

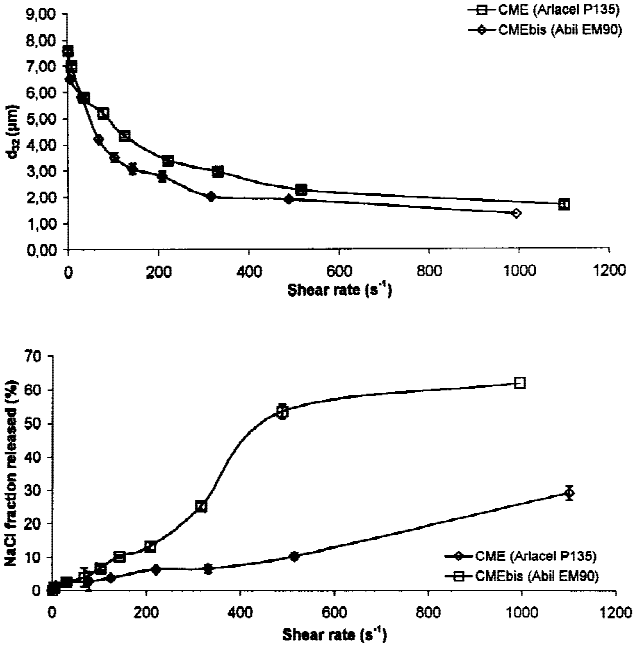

Fig. 5. Breakup and release curves obtained, at 20°C, with CME formulated with two different lipophilic surfactants, Arlacel™ P135 and Abil® EM90 (Mean ± SD µm or %, n = 3 analyses performed three times on the same emulsion; a different emulsion was used at each temperature).

the fragmentation and the fraction released were higher for the one formulated with Abil® EM90. For example, a 3 minutes shearing at 100 s^{-1} led to a mean diameter decrease of 54% (CMEbis) instead of 22% (CME). The fraction released was largely increased: a 3 minutes shearing at 1000 s^{-1} was 26% for CME formulated with Arlacel® P135 versus 62% for the one formulated with Abil® EM90.

DISCUSSION

Multiple emulsion that is insensitive to shear during the fabrication but releases its content upon application under conditions modelling these in cosmetic formulations (i.e. upon rubbing against the skin) has been successfully achieved by the design of a new heat sensitive thermogelling W/O/W emulsion. The specific HMP applied herein consists of poly-(acrylic acid) and Pluronic® and appears to be an effective thickener, both in aqueous solutions and in multiple emulsions.

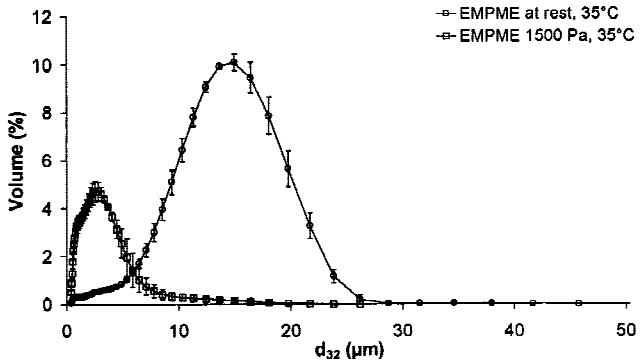

Fig. 4. Granulometric distributions obtained for EMPME at rest and submitted to a 1500 Pa shear stress (1000 s^{-1}), at 35°C (mean ± SD µm, n = 3 analyses performed three times on the same emulsion; a different emulsion was used at each temperature).

As shown by the break up and release data, the fraction released of NaCl increased with the temperature. In comparison with a more classical multiple emulsion thickened by the temperature-insensitive Carbopol® 974-P, the EMPME presented some interesting advantages. Firstly, this W/O/W multiple emulsion may be prepared by an easy two step process (instead of three steps for CME). Secondly, the reproducibility of the EMPME emulsion may be better: the third fabrication stage of CME, consisting in neutralization by NaOH, mixing with a flexible spatula, was a step not easily controllable. Thirdly, the mean encapsulation yield with EMPME was higher than with CME (99.9 ± 0.1% against 90 ± 4%), due to the low viscosity of EMP Hydrogel™ around 15°C (temperature of fabrication) making this emulsion practically insensitive to shear at this moment. Lastly, the release under a shear comparable to skin application of EMPME (around 33–35°C) would be higher than the CME one, although it was not as dramatic as the granulometric distribution showed in Figure 4 foresaw. If the coalescence phenomenon, which is generally not observed in the literature for multiple emulsions, may be excluded, two mechanisms could explain this partial release from the W/O/W emulsions. The first one could be a healing phenomenon, i.e. immediate reformation of two smaller droplets after breakup of the initial globule under shear. An excess of surfactant could induce it (6). The second one, already described by Srinivasan and Stroeve (29) could result from the fact that sheared microdroplets are covered by a thin film of oily phase, preventing in this way the electrolyte release. With regard to the first hypothesis, we have noted that the use of Abil® EM90 instead of Arlacel® P135 in W/O/W multiple emulsion led to a higher fraction

released (62% released instead of 26% after a 3-minute shearing at 100 s^{-1} at 20°C). As Abil® EM90 is of higher molecular weight (15000 instead of 5000 for Arlacel® P135), we think that this one was slower to move and thus diminished the healing phenomenon. The use of this lipophilic surfactant in further formulations would be very beneficial to reduce the partial release.

The ease of fabrication of the HMP-modified multiple emulsions and superior release characteristics of the modified emulsions (EMPME) suggest numerous applications in the controlled release of drugs. Besides, this study points out the fact that a total break up of the multiple emulsion is not necessarily correlated with the complete leakage of the encapsulated marker. A better comprehension of the interface problems could allow us to find the best surfactant composition needed to obtain an optimal balance between a higher release under shear and emulsion stability. Anyway, the use of a more concentrated hydrogel solution could be a good alternative to increase the electrolyte release under shear.

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