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Research paper

Ethylcellulose: a new type of emulsion stabilizer

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Dedicated to Prof. Dr. Dr.h.c. Bernd W. Müller on the occasion of his 60th birthday.

Abstract

Cellulose ethers, in particular hypromellose, represent an interesting alternative when emulsions have to be stabilized avoiding conventional low molecular weight surfactants. So far this option has been only described for the formulation of oil-in-water (o/w) emulsions. Since surfactant-free water-in-oil (w/o) emulsions seem to be also attractive as drug carriers, ethyl cellulose, an oil-soluble cellulose derivative, was studied for its ability to stabilize w/o emulsions. Measurements of the interfacial tension confirmed that ethylcellulose was positively adsorbed at the water/oil interface with diverse lipids. Appearance of model emulsions was dependent on the processing temperature. At low temperatures (15 °C) cream-like o/w emulsions were obtained. Processing at 30 °C yielded fluid w/o-lotions. Investigation of the microstructure showed that the surface of the emulsion droplets was covered with particles which formed a mechanical barrier. These colloidal particles were shown to be a precipitate of ethylcellulose which forms when the polymer which was dissolved in the lipid phase comes into contact with water. Thus, ethylcellulose was demonstrated to represent a new type of particulate polymeric emulsifier.

Keywords: Ethylcellulose; Interfacial tension; Water-in-oil emulsion; High-internal-phase-ratio emulsion; Transmission electron microscopy; Light microscopy; Pickering emulsion; Solid-stabilized emulsion

1. Introduction

Emulsions are interesting carrier systems for drugs, which can be dissolved in the inner phase of the emulsion [1,2]. Oil-in-water (o/w) emulsions can be used as carriers for lipophilic drugs and water-in-oil (w/o) emulsions may allow the sustained release of hydrophilic drug molecules. Since emulsions represent a mixture of at least two materials that are not miscible in each other, they are, according to the second law of thermodynamics, inherently unstable. They require the addition of suitable stabilizers to guarantee an appropriate shelf life. Traditionally, ionic or non-ionic surfactants are used as emulsifiers. However, the poor physiological tolerance of such classical emulsifiers [3] often prevents their widespread use. In contrast to the traditional formulation concept, emulsions also can be stabilized by appropriate macromolecules without using any low molecular weight surfactant.

Several recent investigations focused on the use of surface active cellulose ethers as the sole emulsifiers in o/w emulsions, highlighting hypromellose as an excellent emulsifier [4–8]. This substance is known to be physiologically well tolerated, e.g. from its abundant use as a viscosity enhancer in aqueous eye drops [9].

So far there is no evidence that the stabilization of w/o emulsions can also be achieved by using polymers which are as well tolerated as hypromellose and which are also unrestrictedly accepted for topical as well as peroral use by health authorities. Promising polymer candidates which can act as w/o emulsifiers must show sufficient interfacial activity and should be soluble in the external lipid phase.

The present study investigated ethylcellulose as a potential polymeric w/o emulsifier. The main focus was on the interfacial activity of ethylcellulose and on the influence of processing temperature on the resulting emulsions. The spatial arrangement of structural elements was studied by visual observation techniques, i.e. light and electron microscopy.

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2. Material and methods

2.1. Materials

Ethylcellulose (Ethocel 10) was obtained from Dow Chemicals (Schwalbach, Germany). 2-Octyldodecanol (Eutanol G) and hexyldecanol (Eutanol G16) were a gift from Cospha Henkel KgaA, Düsseldorf, Germany. Medium-chain trigylcerides (Miglyol 812) were kindly provided by Hüls, Witten, Germany. Castor oil was purchased from G. Heess, Stuttgart, Germany. Water was of bidistilled quality.

2.2. Methods

2.2.1. Emulsion preparation

Ethylcellulose was dispersed in 2-octyldodecanol and stirred for 60 min at 95 °C until the polymer dissolved completely. Subsequently, the solution was cooled to room temperature and equilibrated for 24 h. Then, the oil and water phase were separately brought to 15 or 30 °C, respectively, and emulsified using a rotor-stator homogenizer (Ultra Turrax, Janke & Kunkel, Staufen, Germany) at 10 000 rpm for 10 min. Finally, emulsions were poured into appropriate glass vessels and were stored at 20 °C.

2.2.2. Measurements of Interfacial tension

Samples were equilibrated for 30 min at 20 ± 0.1 °C. The interfacial tension between the oil phase and water was measured using a Prozessor Tensiometer K12 (Krüss, Hamburg, Germany) equipped with a Pt-Ir ring. Measurements were performed using the pull mode. Results are mean values of ten repetitive measurements.

2.2.3. Light microscopy

Investigations were performed with a Zeiss Photomicroscope III (D-Oberkochen).

2.2.4. Transmission electron microscopy (TEM)

After shock-freezing in melting nitrogen (−210 °C), samples were either freeze-fractured or they were cut with a sharp-edged knife in a BAF 400 (Balzers, Wiesbaden, Germany) at −100 °C. If required, replicas were etched for 60 s at −100 °C and 10^{-7} mbar. Shadowing was performed with platinum/carbon at 45° and replicas were stabilized by vertical deposition of 20 nm pure carbon. After cleaning with a methanol/chloroform mixture (1:1), the replicas were viewed in a transmission electron microscope (EM 300, Philips, Kassel, Germany; EM 902, Zeiss, Oberkochen, Germany), operated at 80 kV.

3. Results and discussion

3.1. Interfacial activity

The IUPAC Commission for nomenclature defines an emulsifier as “a surfactant which is positively adsorbed at interfaces and lowers the interfacial tension. It facilitates when present in small amounts the formation of an emulsion, or enhances its colloidal stability by decreasing either or both of the rates of aggregation and coalescence” [10]. Thus, measurements of the o/w interfacial tensions in the presence of ethylcellulose indicate the ability of this substance to act as an emulsifier. Fig. 1 displays the interfacial-tension results for water and ethylcellulose in various lipids. The ethylcellulose concentration ranged from 0.2 to 2%. With all the lipids used, ethylcellulose reduced the interfacial tension with water substantially when its concentration was increased. Thus it can be concluded that the polymer was positively adsorbed at the oil/water interface. In all cases interfacial tension leveled off at approx. 8 mN/m when the ethylcellulose concentration exceeded 0.5%, indicating that a saturated interfacial layer is formed.

3.2. Structural characterization

Further investigations on the ability of EC to act as an emulsifier were performed using octyl dodecanol as the oil phase. This lipid was used due to its unique solution properties for EC. Details have been described elsewhere [11,12].

The standard manufacturing process yielded uniform milky-white emulsions. However, the consistency of these emulsions varied enormously depending on the processing temperature. Emulsification at 30 °C produced liquid-like systems. Preparations at 15 °C, however, delivered a semi-solid cream.

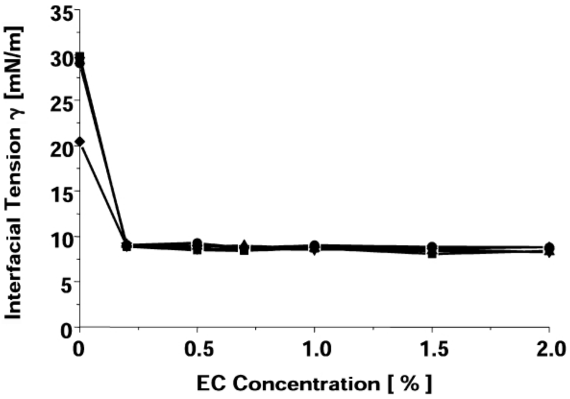

Fig. 1. Interfacial tension isotherm between water and different oils containing various amounts of ethylcellulose. (■) Octyldodecanol, (●) hexyldodecanol, (▲) octyldodecanol/hexyldodecanol (1:1), (▼) octyldodecanol/medium-chain triglycerides (1:1), (◆) octyldodecanol/castor oil (1:1).

Similar effects were described for other disperse systems where the differences in consistency could be correlated to differences in the colloidal structure [13]. Accordingly, microscopic techniques were applied to characterize the structure of the ethylcellulose stabilized emulsions.

Fig. 2 shows a typical photo-micrograph of a fluid lotion. It is characterized by numerous small individual droplets, each surrounded by the coherent phase. No flocculation can be observed and the particle size distribution is very narrow.

In contrast, the semisolid cream exhibits an extremely wide particle size distribution (Fig. 3). The voids between the larger droplets are filled sequentially with ever smaller droplets leaving almost no free space between the individual droplets. This leads to a close-packed system without significant droplet deformation. The continuous phase is reduced to only a thin film between the droplets of the internal phase. This is a typical representation of a so-called Fuller distribution [14]. Taking into consideration that the oil volume fraction of the model emulsions was 0.8, it is likely that the cream-like systems can be referred to as super-fatted emulsions or high-internal-phase-ratio emulsions (HIPREs). Such emulsions are characterized by an internal phase ratio $\Phi > 0.74$ [15].

More details can be obtained from freeze-cut and etched samples where fracture occurred directly through the droplets. Fig. 4 shows a transmission electron micrograph of a fluid emulsion which was prepared at 30 °C. It represents a typical image of a w/o emulsion where droplets of the disperse water phase are separated by a continuous lipid phase. The droplet size can be roughly estimated to be in the range of 0.6 to 1.2 μm.

The electron micrograph of a semi-solid sample prepared at 15 °C depicts droplets of extremely different size (Fig. 5). Their diameters vary from 3 up to 7 μm. All droplets are in close contact or even touch each other.

At a higher magnification, the structure and the dimensions of the interfacial film can be visualized (Fig. 6). The interfacial skin of the droplets measures approximately 220 nm and contains particulate matter 90 nm in diameter. In the two-dimensional perspective, these particles are lined up similar to a string of pearls.

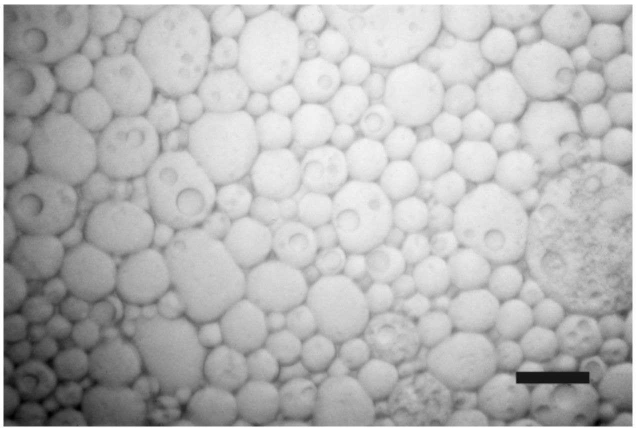
Fig. 3. Photo-micrograph of an ethylcellulose stabilized emulsion prepared at 15 °C. Scale bar = 9.23 μm.

TEM images from freeze-fractured and replicated samples show the surface of the dispersed phase (Fig. 7). It is characterized by an unusual rough and grainy surface texture which can be attributed to lots of very small particles which were deposited on it.

These findings suggest that colloidal ethylcellulose was adsorbed in a ‘solid form’ onto the droplets and thus improve their stability by mechanical action.

Interfacial precipitation was proven as the mechanism for the formation of colloidal ethylcellulose particles using a very simple experimental setup. In a test tube, a solution of 2% ethylcellulose in octyldodecanol was layered over water. After the two phases have been in contact for 1 week, the interfacial layer became macroscopically turbid. With increasing storage time the thickness of this turbid layer between oil and water increased. Microscopic examination revealed that the

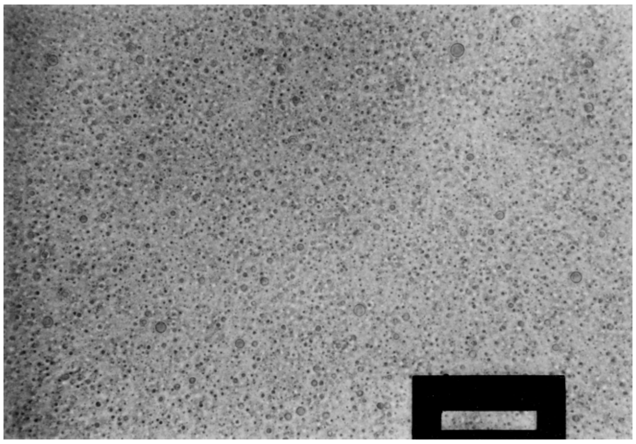
Fig. 2. Photo-micrograph of an ethylcellulose stabilized emulsion prepared at 30 °C. Scale bar = 9.23 μm.

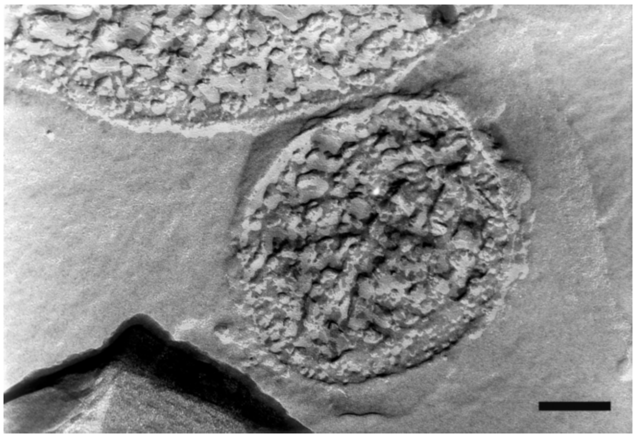
Fig. 4. TEM micrograph of an ethylcellulose stabilized emulsion prepared at 30 °C. Scale bar = 196 nm.

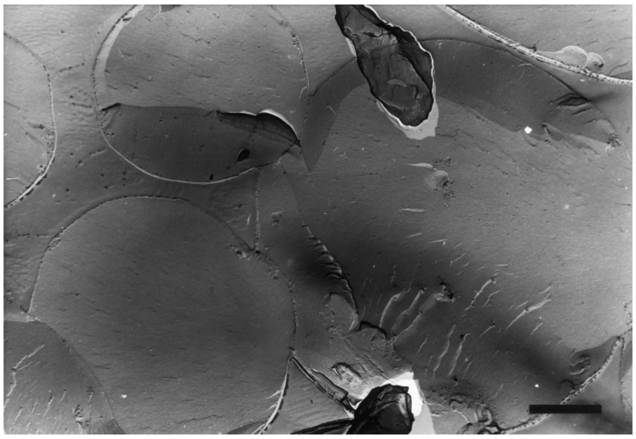

Fig. 5. TEM micrograph of an ethylcellulose stabilized emulsion prepared at 30 °C. Scale bar = 1.47 μm.

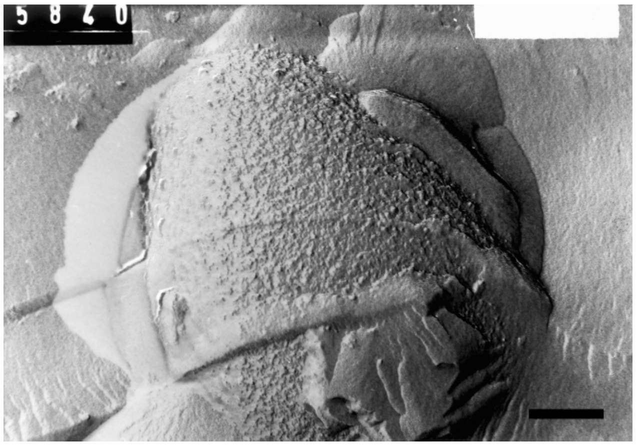

Fig. 7. TEM micrograph of an ethylcellulose stabilized emulsion prepared at 30 °C. Scale bar = 305 nm.

interfacial layer now contained small irregular formed solid particles (Fig. 8) which could be clearly identified as consisting of ethylcellulose. The following mechanism is proposed: Water is able to diffuse into the polar lipid phase. This causes a decrease in solvent 'goodness'. Thus polymer–polymer contacts are favored and ethylcellulose precipitates.

Although ethylcellulose has a pronounced interfacial activity, the stability of emulsions prepared with this polymer is not only due to the adsorption of the polymer to the oil/water interface as described for the hydrophilic cellulose ethers. Additionally precipitated colloidal particles act as another class of emulsifying agent. The fact that finely divided solid particles can act as a stabilizer in emulsions has been known since the beginning of the last century. This phenomenon was first described by Pickering, hence the term 'Pickering emulsions' [16]. The essential properties of such emulsions have been reviewed recently [17]. A key issue is that particles are strongly held at the interface. This is commonly the cause of the high stability of water-in-crude oil emulsions [18] as well as various food emulsions [19]. The type of emulsion, oil-in-water or water-in-oil, which is stabilized depends mainly on the wettability of the solids [20]. Particles which are wetted more by water than by oil act as emulsifiers for oil-in-water emulsions. In the case of colloidal ethylcellulose particles their affinity to water and lipid obviously depends on the temperature. With increasing temperature ethylcellulose becomes better soluble in the lipid, thus increasing the affinity of the precipitated colloidal particles for the oil phase. Thus, according to Bancroft's law a water-in-oil emulsion will be stabilized. At temperatures below 20 °C the affinity for the lipid is significantly reduced and w/o-systems are formed. Surprisingly, emulsion stability is not negatively influenced by the high oil volume fraction of these systems. This indicates that stabilization of emulsions with solid particles partitioning between oil and water phases is highly effective and provides an interesting alternative to conventional emulsion stabilization.

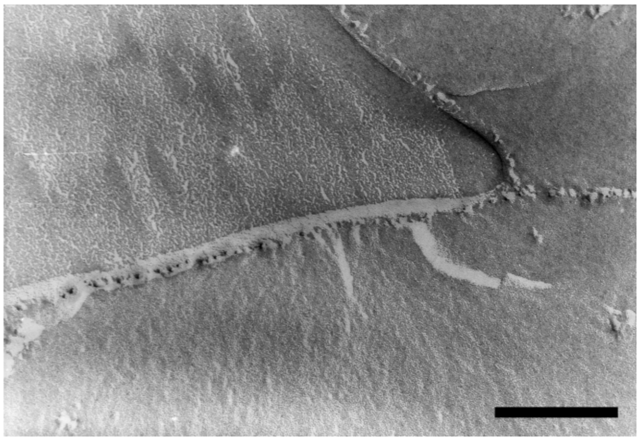

Fig. 6. TEM micrograph of the interfacial layer in an ethylcellulose stabilized emulsion prepared at 15 °C. Scale bar = 251 nm.

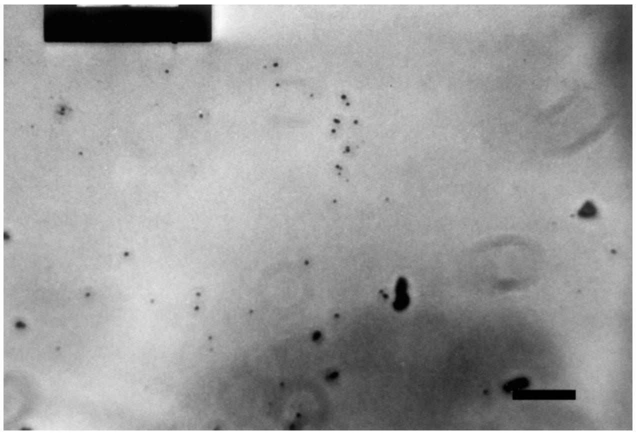

Fig. 8. Photo-micrograph of the interface between water and 2% ethylcellulose in octyldodecanol (dark spots are solid particles). Scale bar = 9.23 μm.

3.3. Conclusions

Due to its interfacial activity, ethylcellulose can be used as a polymeric emulsifier. Its stabilizing action was identified to be in part due to the formation of a colloidal precipitate which occurs at the o/w interface. Thus the resulting systems can be classified as solid-stabilized emulsions. The oil-linking tendency of these particles varies with the solubility of ethylcellulose in the lipid which increases with increasing temperature. This explains the unexpected phase inversion phenomenon at low temperature, where highly concentrated oil-in-water emulsions are obtained whereas at 30 °C w/o emulsions are formed. This unexpected behavior of ethylcellulose might be of interest for the formulation of a new class of multiple emulsions which should prove of great benefit in the field of drug delivery. Therefore the preparation of surfactant-free multiple emulsions will be the scope of another paper.

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