

Optimisation of electrical conductance measurements for the quantification and prediction of phase separation in o/w-emulsions, containing hydroxypropylmethylcelluloses as emulsifying agents

F. Kiekens^a, A. Vermeire^a, N. Samyn^b, J. Demeester^b, J.P. Remon^{b,*}

^aLaboratory of Pharmaceutical Technology, University of Gent, Harelbekestraat 72, B-9000 Gent, Belgium

^bLaboratory of Biochemistry and Physical Pharmacy, University of Gent, Harelbekestraat 72, B-9000 Gent, Belgium

Received 11 October 1996; accepted 5 December 1996

Abstract

Different hydroxypropylmethylcelluloses, Methocel E and K, and one methylcellulose, Methocel A (Colorcon, Kent), were evaluated for their emulsifying properties. Eight o/w emulsions were prepared with 20% (w/w) arachidic oil and 80% (w/w) aqueous phase containing the emulsifying agent in different concentrations. Methocel K100-LV, Methocel E50-LV and Methocel A4C were used in a 2% (w/w) concentration, while Methocel A15-LV was used in a 1, 2, 3 and 4% (w/w) concentration. The stability of the emulsions was assessed with four different techniques: visual inspection, electrical conductance, droplet size (Coulter counter) and viscosity measurements. The Methocel A15-LV 1% emulsion showed a visual instability after only 3 days, followed by the 2% emulsion (6 days) and the E50-LV (2%) emulsion (55 days). The Methocel A15-LV 3 and 4%, the Methocel K100-LV (2%) emulsion and the A4C (2%) emulsion showed no visual instability after 90 days. For all emulsions, the difference in electrical conductance between the upper and lower part of the conductance cell, especially designed for the stability study, gradually increased with ageing. Droplet size measurements showed no major differences in droplet size as a function of time, probably due to the fact that before measurements the emulsions had to be gently shaken before sample taking. The conclusion of this study is that the electrical conductance measurements in the specially designed cells can be used to quantify and predict the phase separation in o/w-emulsions. © 1997 Elsevier Science B.V.

Keywords: Emulsions; Hydroxypropylmethylcellulose; Stability; Conductance

* Corresponding author. Tel.: +32 9 2648056; fax.: +32 9 2228236; e-mail: JeanPaul.Remon@rug.ac.be

1. Introduction

Emulsions are thermodynamically unstable systems and will separate to minimize the interfacial area between the aqueous and the oil phase. The rate of this separation will be the criteria for characterisation of a 'stable' or 'unstable' emulsion and will be strongly influenced by additives, e.g. surfactants and colloids. Low molecular weight surfactants are commonly used to stabilise emulsions but allergic reactions have been reported in many cases (Ashton et al., 1986). The emulsifying properties of cellulose derivatives were investigated by Daniels and Barta (1993, 1994) by the use of surface tension determination, electrical conductance measurements and scanning electron microscopy. They suggested that cellulose ethers containing methoxy and hydroxypropyl groups are promising candidates as emulsifying agents. In this study, the emulsifying properties of some methyl- and hydroxypropylmethylcellulose derivatives were evaluated with four different techniques: visual evaluation, electrical conductance, droplet size and viscosity measurements. The evaluation of the emulsion stability using the electrical conductance measurements is emphasized.

2. Materials and methods

2.1. Emulsion production

Arachidic oil (Federa, Belgium, G1914CA) was used as the oil phase and water containing propyl- and methylparahydroxybenzoate was used as the aqueous phase. Methylcellulose (Methocel A15-LV and A4C) and hydroxypropylmethylcellulose (Methocel E5, E50-LV and K100-LV), all from Colorcon (Kent, UK) were used as emulsifying agents. Methocel A15-LV was used in four concentrations 1, 2, 3 and 4% (w/w). The other cellulose derivatives were used in only one concentration: 2% (w/w). In all cases an o/w emulsion was prepared according to a standardised production protocol. The emulsifier was dispersed in the water phase with a spatula, next the arachidic oil was added and the emulsion was mixed with the

Silverson mixer (Silverson Machines, Waterside, UK). The emulsion was then degassed with a Stephan vacuum pump (Stephan und Sohne, Hameln, Germany). Immediately after production, 500 ml of the emulsions were stored in specially designed glass containers for the conductance measurements and evaluated for their stability under constant temperature conditions ($23 \pm 2^\circ\text{C}$). The remaining 500 ml were divided into glass bottles of 250 ml and used for the viscosity and the droplet size measurements and were kept under the same constant temperature conditions.

2.2. Emulsion stability evaluation

2.2.1. Droplet size measurements

The droplet size distribution of the emulsions was determined with a Coulter counter (Coulter

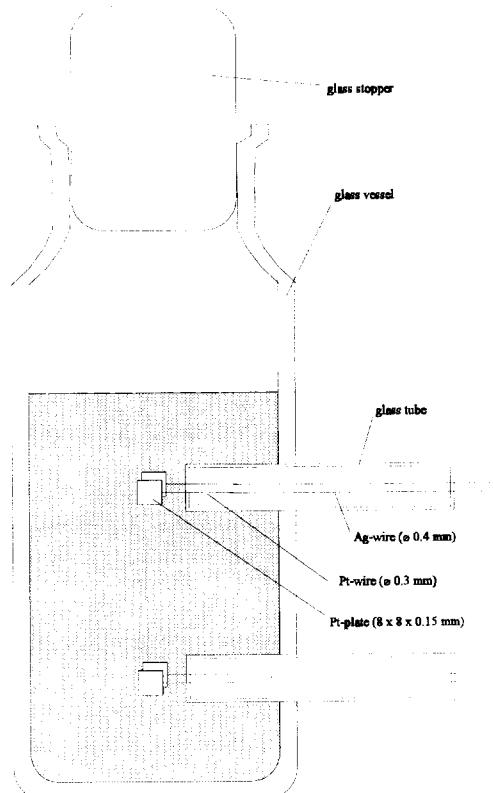


Fig. 1. Schematic view of a measuring cell with fixed platina electrodes.

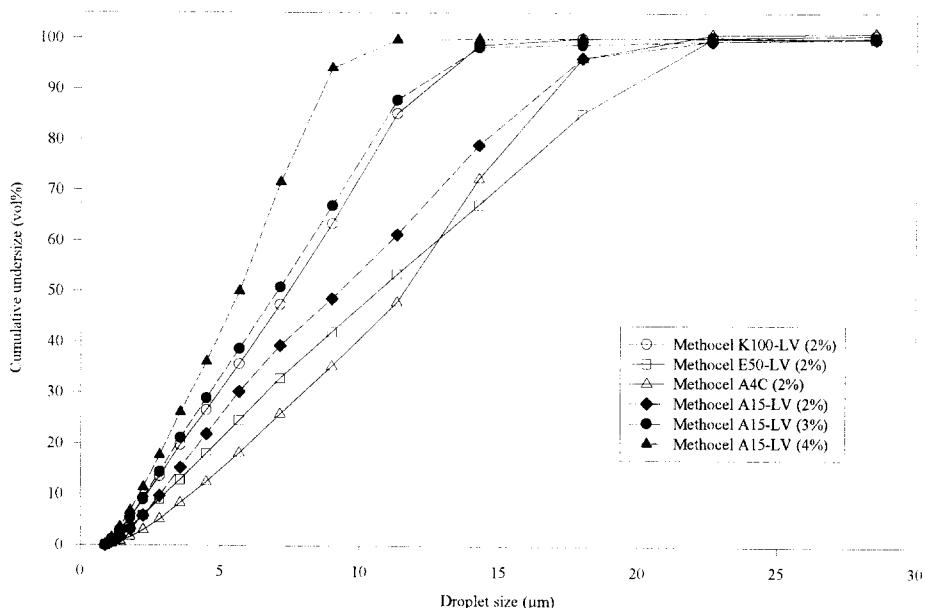


Fig. 2. Cumulative undersize distributions of initial droplet size of the emulsions prepared with different types and concentrations of MCs and HPMCs.

Electronics, Hertz, England), immediately after the emulsion preparation and weekly, during 3 months. Before the measurements, the emulsions were subjected to a 3-step dilution process (1–88 000 (v/v)): 400 μ l of the emulsion were diluted in 20 ml of a 0.9% NaCl solution and gently shaken. Next, 350 μ l of this dilution, were diluted in the same way and finally 650 μ l was taken of dilution II and diluted in 20 ml of a 0.9% NaCl solution. For this dilution, the coincidence index (C.I.) did not pass the '4%-maximum' value and therefore coincidence corrections were not necessary. With the applied instrument settings, a globule count for a sample volume of 0.5 ml diluted emulsion was performed.

2.2.2. Viscosity measurements

The emulsion viscosity was determined weekly using a Haake viscosimeter (Rotovisco RV 12, Haake, Germany) during a period of 5 weeks. The experimental parameters were kept constant during the measurements: rotating device MV I, attenuation 1, rotational speed 128 rev/min, resolution factor 10, shear rate 29.95 s^{-1} and a temperature of 23°C.

2.2.3. Visual evaluation

A visual evaluation of the emulsion stability was performed until phase separation was seen.

2.2.4. Electrical conductance measurements

After production, the emulsions were stored in specially designed conductance measuring cells (Fig. 1). Two electrodes were fixed: one at 1/5th of the bottom and one at 1/5th of the top emulsion level. These electrodes were developed according to Fig. 1. The 16 electrodes (2 per measuring cell) were connected to a 16-channel switchboard with an output to a conductometer (LF 39, WTW, D812, Weilheim). A 0.1 M KCl-solution (0.012856 S/cm) was used to calibrate the electrodes inside the cells at 23°C, allowing the calculation of the specific conductance. As emulsion instability progressed, the specific electrical conductance (L) in the upper part of the cell decreased due to the increasing volume fraction of oil while in the lower part of the cell, the specific electrical conductance increased. The difference between the two conductances (ΔL), in terms of percentage, was calculated using the following equation:

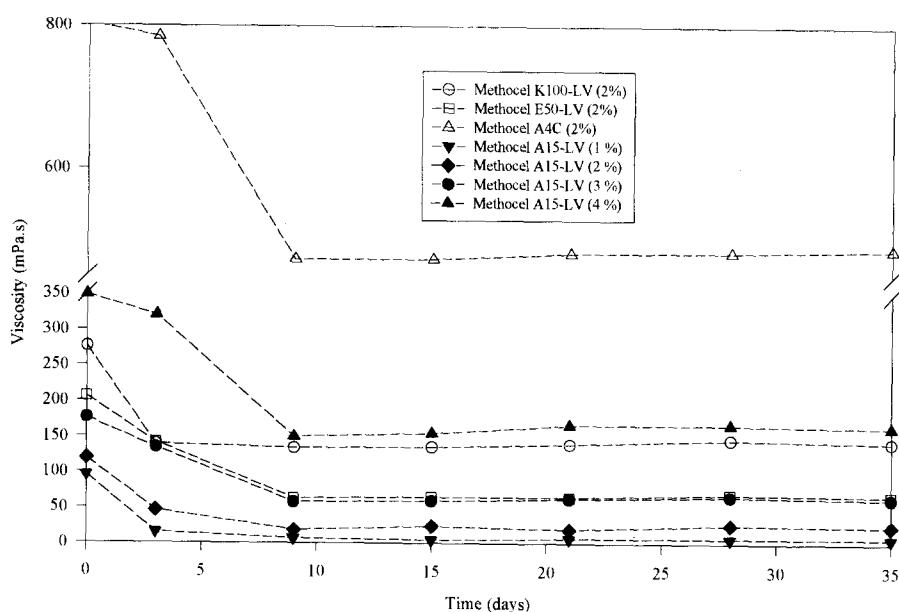


Fig. 3. Rheologic behaviour of the emulsions prepared with different types and concentrations of MCs and HPMCs while ageing.

$$\Delta L = (L_{\text{lower}} - L_{\text{upper}})/L_{\text{lower}} \times 100$$

The difference in electrical conductance was examined every 5 min during the first 2 h after preparation of the emulsions, every 30 min during the next 6 h and from then on, on a daily basis. The increase in conductance difference between the upper and the lower phase of the emulsions was evaluated as a function of time and expressed quantitatively by calculating the slope of the first linear part of the curve by linear regression analysis. In this way the phase separation rate was determined.

3. Results and discussion

3.1. Coulter counter analysis

The initial droplet size distribution of the different emulsions is showed in Fig. 2. As the Methocel A15-LV concentration was increased from 2 to 4% (w/w), the mean droplet volume diameter by number decreased from 3.8 to 3.1 μm . These mean droplet volume diameters were reciprocally equivalent to the initial emulsion viscosity, being 119 and 348 mPa.s and this supports

the data reported by Ferdous (1993). These droplet size distributions did not change as a function of time. This observation can be explained by the fact that the phenomenon of flocculation, in which the droplets form clusters or flocculates, starts long before phase separation can visually be seen. When the droplet size distribution is determined, these flocculates are broken up into the original droplets during the dilution phase. The droplet size measurements using the Coulter counter revealed that this technique cannot be used to determine changes in droplet size distribution while ageing of the emulsions. This problem of determining droplet sizes in concentrated pharmaceutical emulsions, has been reported by Whateley et al. (1984) who recommended careful sample handling and method selection for droplet size distribution measurements in emulsions.

3.2. Viscosity measurements

Fig. 3 shows the change in viscosity as a function of time for all emulsions tested. In all cases the viscosity decreased during the early storage period and reached a plateau value within 10

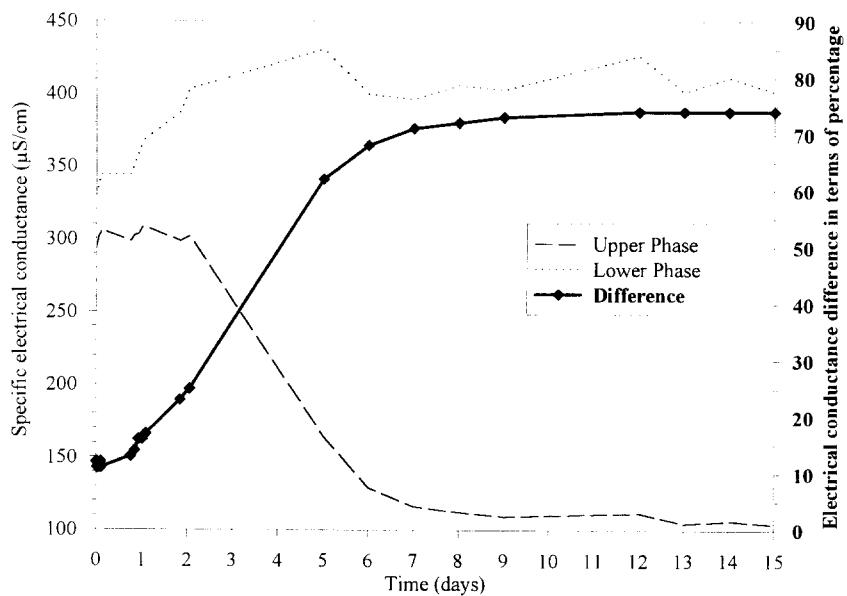


Fig. 4. The specific electrical conductance of the two phases and the difference in terms of percentage versus time in the 2% Methocel A15-LV emulsion.

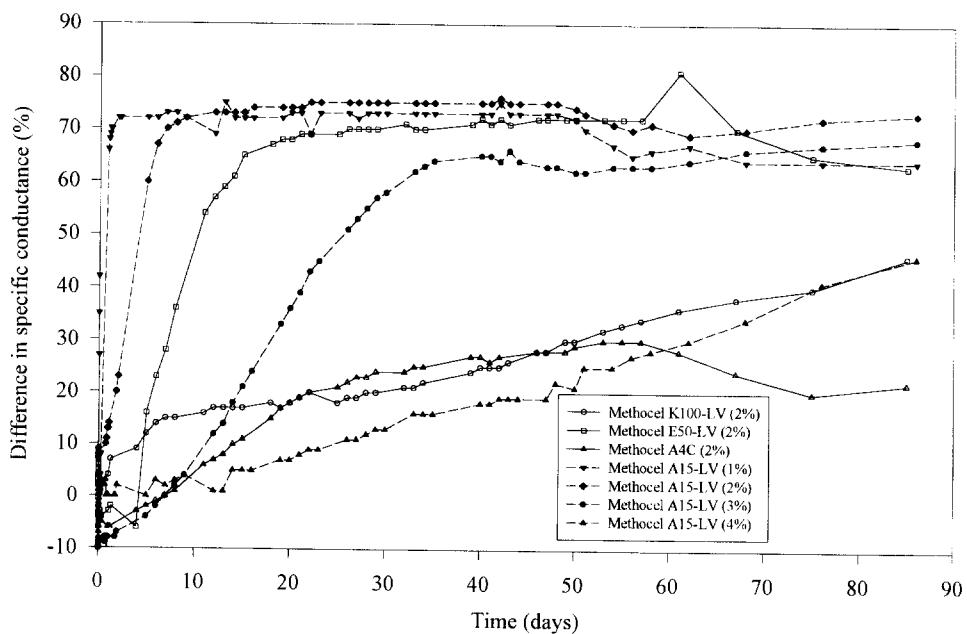


Fig. 5. The difference in electrical conductance between the upper and the lower phase as a function of time for different types and concentrations of MCs and HPMCs.

Table 1
Evolution of the electrical conductance and the viscosity of the emulsions^a

Emulsifier	Concentration (%) (w/w)	Specific conductance (μ S/cm) Under (initial → 90 days)	Specific conductance (μ S/cm) Upper (initial → 90 days)	Slope	Initial viscosity (mPa.s)	Viscosity after 35 days (mPa.s)
Methocel K100- LV	2	244 → 316	230 → 164	0.45	282	142
Methocel E50- LV	2	226 → 399	218 → 153	6.6	206	67
Methocel A4C	2	364 → 419	358 → 313	0.59	804	487
Methocel A15- LV	1	114 → 360	170 → 128	97.64	96	6
Methocel A15- LV	2	334 → 532	293 → 137	8.67	119	24
Methocel A15- LV	3	437 → 634	465 → 195	2.99	176	62
Methocel A15- LV	4	592 → 803	631 → 462	0.58	348	163

^aEvolution as a function of time compared with the creaming velocity expressed as the slope of the increase in conductance difference vs. time curves.

days. The proportional decrease in viscosity was for all types of emulsifier reciprocally equivalent with the initial viscosity.

3.3. Electrical conductance measurements

The results of the conductance measurements are shown in Figs. 4 and 5. Fig. 4 shows that the specific conductance ($\mu\text{S}/\text{cm}$) of the upper phase (oil) was always lower than that of the aqueous phase. Although these values should initially be equal, small differences were seen; these are probably due to some equilibrium which had to be obtained after pouring the emulsions in the measuring cells. After a few minutes of stabilization, these values intercrossed and the difference in conductance between upper and lower phase progressively increased. From Table 1 it is clear that the difference in electrical conductance between the two phases increased as a function of time. Fig. 5 shows that the phase separation rate was equivalent with the emulsifier concentration. For the Methocel A15-LV emulsions (1, 2, 3 and 4% (w/w)) it was shown that the increase in conductance difference (represented in Table 1 by the slope of the first linear part of the curve) was reciprocally equivalent with the emulsion viscosity and proved that the viscosity had an important influence on the emulsion stability. According to the conductance measurements, the emulsions prepared with Methocel A15-LV (4%), A4C (2%) and K100-LV (2%) had almost a similar stability profile. The slopes of the curves being 0.58, 0.59 and 0.45, respectively. The main distinction between the K100-LV emulsion and the A15-LV and A4C emulsions was the difference in increase of conductance (expressed in terms of percentage) during the first 8 days (Fig. 5). After that time, a similar increase in the difference in conductance could imply that the Methocel K100-LV (2%) emulsifier required more time to migrate to the surface of the oil droplets because of its higher molecular weight. The emulsions prepared with methylcelluloses of analogue molecular weight (A4C and A15-LV) showed a very similar profile. Daniels and Barta (1993) also used electrical conductance for the determination of emulsion stabil-

ity but the electrodes were not fixed perpendicularly but were aligned with the length of the measuring cell axis. In that way, the alignment of the electrodes benefitted the cleaning of the cell but showed a clear disadvantage in terms of the quality of the measurements as the mutual position of the upper- and lower electrode was crucial for reproducible measurements.

4. Conclusion

The electrical conductance technique is an accurate method for the evaluation of emulsion stability and can be used to quantify and predict the phase separation in o/w-emulsions. Hydroxypropylmethyl- and methylcelluloses can be used as emulsifying agents.

Acknowledgements

We are grateful to Mr J. Hermans from Philips Lighting Glassworks, (Lommel, Belgium) for supplying the glass tubes type 291 to produce the electrodes. We want to thank Mrs B. Socolic from Metroglas (Affoltern a. Albis, Switzerland) for the supply of the platinum wires and plates.

References

- Ashton, P., Hadgraft, J. and Walters, K.A.. Effects of surfactants in percutaneous adsorption, *Pharm. Acta. Helv.*, 61 (1986) 228–235.
- Daniels, R. and Barta, A., Pharmacopoeial cellulose ethers as oil-in-water emulsifiers, *Eur. J. Pharm. Biopharm.*, 40(3) (1994) 128–133.
- Daniels, R. and Barta, A., Preparation, characterization and stability assessment of oil-in-water emulsions with hydroxypropylmethylcellulose as emulsifier, *12th Pharma. Technol. Conf.*, Vol 3, April 1, 1993, 51–60.
- Ferdous, A.J., Viscosity and stability studies of liquid paraffin emulsions prepared by hydroxypropyl methylcellulose, *Drug Dev. Ind. Pharm.*, 19(9) (1993) 1083–1088.
- Whateley, T.L., Steele, G., Urwin, J. and Smail, G.A., Particle size stability of Intralipid® and mixed total parenteral nutrition mixtures, *J. Clin. Hosp. Pharm.*, 9 (1984) 113–126.