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Effect of methylcellulose on the stability of oil-in-water emulsions: influence of the disperse phase

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Abstract

The influence of nature of the disperse phase on the stability of oil-in-water emulsions containing nonionic emulsifiers and methylcellulose 4000 as an auxiliary emulsifier was investigated. One stable and three unstable base emulsions each of olive oil and of mineral oil were formulated with an emulsifier blend of Tween[®] and Span[®]. The stable emulsion (SE) contained 2% emulsifier blend optimized for maximum stability. Three unstable emulsions were formulated from the SE formulation: one with 0.5% emulsifier blend as of the SE formulation (UE1), one with excessive hydrophilic emulsifier (UE2) and one with excessive lipophilic emulsifier (UE3). A series of emulsions was prepared containing increasing amounts of methylcellulose 4000 for each base emulsion. The particle size of all olive oil emulsions was reduced (UE2 > SE > UE3) and the viscosity was increased (UE2 > SE > UE3) on addition of methylcellulose. The stability of these emulsions improved in the presence of methylcellulose. However, the addition of the polymer caused instability in mineral oil emulsions containing lower concentrations of the hydrophilic emulsifier (Tween[®]). These results suggest that: (i) methylcellulose and the hydrophilic emulsifier associate to form a complex; (ii) this complex when present at the mineral oil-water interface would be dislodged from the interface due to less interaction between the non-polar oil and the polyoxyethylene (POE) chain of the hydrophilic emulsifier; and (iii) this complex when present at the olive oil-water interface would stabilize emulsions due to higher interaction between the polar oil and the POE chain of the hydrophilic emulsifier. © 1997 Elsevier Science B.V.

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Natural and synthetic polymers are often used as auxiliary emulsifiers in addition to con-

ventional low molecular weight emulsifiers to enhance the stability of emulsions (Zatz and Ip, 1986; Yilmazer and Kokini, 1991). In our previous study (Gullapalli and Sheth, 1996), the effect

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Table 1

Linear regression analysis of relationship between η_{∞} of methylcellulose solutions and of oil-in-water emulsions

| Emulsion formulation | Concentration of emulsifier (%w/w) | | Slope | r^2 | P-value |
|-----------------------|------------------------------------|----------------------|-------|-------|----------------|
| Olive oil emulsions | Tween [®] 80 | Span [®] 40 | | | |
| SE | 0.80 | 1.20 | 22.11 | 0.991 | 0.0016 |
| UE1 | 0.20 | 0.30 | 18.04 | 0.982 | 0.3334 |
| UE2 | 1.52 | 0.48 | 26.38 | 0.999 | 0.0001 |
| UE3 | 0.30 | 1.70 | 16.59 | 0.979 | — ^a |
| Mineral oil emulsions | Tween [®] 40 | Span [®] 20 | | | |
| SE | 0.40 | 1.60 | 18.24 | 0.998 | 0.3497 |
| UE1 | 0.10 | 0.40 | 17.75 | 0.986 | 0.5432 |
| UE2 | 1.54 | 0.46 | 22.50 | 0.999 | 0.0011 |
| UE3 | 0.00 | 2.00 | 16.87 | 0.965 | — ^a |

^a Reference slope; statistical significance defined at a p -value ≤ 0.05 .

of methylcellulose, as an auxiliary emulsifier, was investigated on the stability of mineral oil-in-water emulsions stabilized with nonionic emulsifiers. It was proposed that methylcellulose would associate with polyoxyethylene (POE) type nonionic emulsifiers (Tween[®]), and that adsorption of the complex at mineral oil-water interface could result in the dislodgment of the complex from the interface and subsequent de-emulsification. This effect was thought to be due to higher hydrophilic nature of the complex, and less interaction between the POE chain of Tween[®] and the non-polar oil (Becher, 1963; Shinoda et al., 1971).

The nature of the disperse phase was known to affect the properties of the emulsifier film at the oil-water interface in an emulsion (Shotton and White, 1960; Florence and Rogers, 1971; Davis and Smith, 1976). The interactions between POE type emulsifiers and a polar oil or a vegetable oil were proposed to result in a portion of the POE chain of the emulsifier immersed in the oil phase (Becher, 1963). This type of behavior was thought to be not possible with a non-polar oil.

The disperse phase in pharmaceutical and food emulsions is often composed of a vegetable oil or more correctly a mixture of triglycerides (Fisher and Parker, 1988; Lobo and Wasan, 1990) with a O/W interfacial tension value different from that of a mineral oil (Fisher et al., 1985). Understanding how various components in an emulsion interact with each other and how these interactions influence the adsorption behavior of the emulsion

components at various O/W interfaces is critical to design stable emulsion formulations (McClements et al., 1993). Therefore, we extended our previous study with olive oil as a model vegetable oil to investigate the influence of nature of the disperse phase on the stability of emulsions containing nonionic emulsifiers and methylcellulose 4000 as an auxiliary emulsifier. Though the emulsifier requirements were known to vary from one oil to another (Shinoda and Freiberg, 1986), the influence of nature of the disperse phase on the stability of emulsions was studied with an arbitrarily chosen emulsifier or emulsifier blend (Florence and Rogers, 1971; Davis and Smith, 1976). It was thought to be more appropriate to select an optimized emulsifier blend for each disperse phase and then study the influence of nature of the disperse phase on the stability of emulsions.

One stable and three unstable base emulsions containing 30% olive oil (Super Refined[™] Croda, Mill Hall, PA) were formulated using Tween[®] 80 and Span[®] 40 as the primary emulsifiers (Table 1). The three unstable emulsions, one with reduced emulsifier concentration (UE1), one with excessive hydrophilic emulsifier (UE2) and another with excessive lipophilic emulsifier (UE3) were selected based on their significantly larger particle size and smaller percent creaming volume than those of the base stable emulsion (SE). A series of emulsions was prepared for each base emulsion containing 0%, 0.29%, 0.88%, 1.18% and 1.47% w/w methylcellulose in the external phase.

Stability of emulsions was evaluated on the basis of creaming and change in particle size distribution of the disperse phase with time for 6 months. The materials and the experimental methods were described in detail in a previous publication (Gullapalli and Sheth, 1996).

The influence of nature of the disperse phase on the particle size stability of base SE formulation containing an optimized emulsifier blend is shown in Fig. 1. Particle size was higher for olive oil SE emulsion ($5.26 \pm 2.8 \mu\text{m}$) than that of mineral oil SE emulsion ($1.97 \pm 1.6 \mu\text{m}$). However, neither the initial particle size nor the nature of disperse phase affected the final stability of emulsions as indicated by the absence of any change in particle size for 6 months.

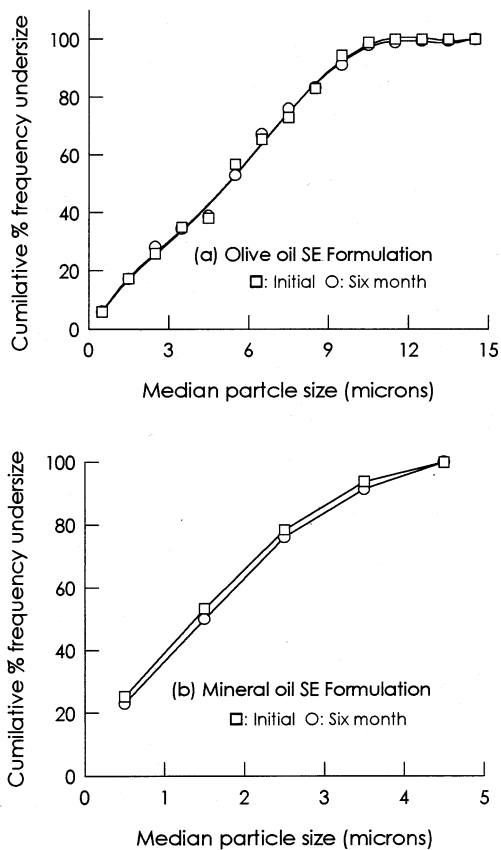


Fig. 1. Changes in particle size distributions of base SE oil-in-water emulsions upon aging.

The general shape of the flow curves for olive oil emulsions was similar to those of mineral oil emulsions. However, olive oil emulsions were more viscous overall than the corresponding mineral oil emulsions. The slopes of the linear relationship between the Structure Equation (Niebergall et al., 1971) viscosity parameter, η_{∞} of emulsions and of the external phase were determined and compared among the four types of emulsions using the regression analysis (Table 1). The increase in η_{∞} value of olive oil emulsions was significantly larger with a higher hydrophilic emulsifier concentration in the emulsions ($\text{UE2} > \text{SE} > \text{UE1} = \text{UE3}$), suggesting an interaction between methylcellulose and the hydrophilic emulsifier.

The viscosity and nature of the disperse phase had no marked effect on the viscosity of the base emulsions of the two oils ($\eta_{\infty} = 4 \text{ cps}$). However, in the presence of methylcellulose, the nature of the disperse phase did affect the viscosity of emulsions. Olive oil UE2 emulsions showed higher η_{∞} values than the corresponding mineral oil emulsions though both the formulations had a similar hydrophilic emulsifier concentration. The particle size distributions of UE2 emulsions for both olive oil and mineral oil were essentially similar ($2.0 < \mu\text{m} < 3.0$) in the presence of methylcellulose. The increase in η_{∞} of methylcellulose solutions on addition of 1.54% Tween[®] 40 was similar to that observed with 1.52% Tween[®] 80. This suggests that factors other than the viscosity and the particle size of the disperse phase, and the interaction between methylcellulose and Tween[®], appear to be responsible for the higher η_{∞} values of olive oil UE2 emulsions. The higher viscosity of olive oil UE2 emulsions than that of mineral oil UE2 emulsions could be attributed to the formation of a thicker and stronger film by methylcellulose–Tween[®] interaction complex at the olive oil-water interface. Substantial increase in emulsion viscosity due to the presence of a stronger and thicker interfacial film and a corresponding increase in volume fraction of the disperse phase was also proposed by others (Shotton and White, 1960; Sherman, 1964; Tadros, 1994). The presence of the complex at the mineral oil-water interface in UE2 emulsions was ruled out in our previous study.

Table 2
Effect of methylcellulose on particle size^a and creaming^b stability of olive oil-in-water emulsions

| Emulsion formulation | Concentration of methylcellulose in external phase (%w/w) | | | | | |
|----------------------------|---|-------------|-------------|-------------|-------------|-------------|
| | 0.00 | 0.29 | 0.59 | 0.88 | 1.18 | 1.47 |
| SE | | | | | | |
| Initial | 5.26 (2.8) | 3.45 (1.9) | 4.36 (2.1) | 3.38 (1.7) | 3.60 (1.8) | 3.91 (1.6) |
| 6 Months | 5.16 (3.4) | 3.45 (2.0) | 3.87 (2.5) | 3.02 (1.9) | 3.01 (2.2) | 3.28 (2.3) |
| V_c | 42 | 42 | 43 | 48 | 47 | 51 |
| UE1 | | | | | | |
| Initial | 10.47 (4.4) | 5.55 (2.5) | 4.81 (2.1) | 5.08 (2.3) | 3.76 (2.0) | 3.91 (2.2) |
| 6 month | 13.62 (6.2) | 4.94 (2.9) | 4.55 (2.9) | 5.24 (2.4) | 4.20 (2.0) | 3.59 (1.9) |
| V_c | 43 | 44 | 44 | 48 | 63 | 72 |
| UE2 | | | | | | |
| Initial | 8.45 (4.1) | 2.66 (1.6) | 2.28 (1.4) | 2.19 (1.5) | 2.18 (1.7) | 2.17 (1.6) |
| 6 Months | 7.91 (4.6) | 2.98 (1.6) | 2.31 (1.2) | 2.46 (1.5) | 2.22 (1.9) | 2.03 (1.3) |
| V_c | 41 | 41 | 45 | 47 | 48 | 53 |
| UE3 | | | | | | |
| Initial | 8.97 (4.4) | 5.80 (2.8) | 5.53 (2.8) | 5.68 (2.6) | 5.67 (2.5) | 5.10 (2.1) |
| 6 Months | 8.47 (4.7) | 5.01 (2.2) | 5.47 (3.3) | 5.22 (2.1) | 5.48 (3.0) | 5.31 (2.6) |
| V_c | 41 | 47 | 59 | 64 | 64 | 71 |
| Polymer^c | | | | | | |
| Olive oil | | 24.03 (9.6) | 21.27 (8.4) | 19.76 (6.5) | 19.96 (6.3) | 21.24 (8.2) |
| Mineral oil | | 23.74 (7.6) | 21.77 (5.9) | 21.19 (5.7) | 20.84 (5.3) | 20.16 (5.8) |

^a Median D_{vol} , μm (standard deviation), mean of three measurements.

^b Percent equilibrium creaming volume (V_c), measured after 6 months.

^c Emulsions with no emulsifiers; measured initially; oil separation.

The addition of methylcellulose caused a significant reduction and narrowing of the particle size distributions of all base olive oil emulsions at 0.29% of the polymer concentration in the external phase (Table 2). Further increase in the polymer concentration above 0.29% exerted only slight changes in the distributions. The extent of particle size reduction with methylcellulose was higher in emulsions with a higher Tween[®] concentration (UE2 > SE > UE3). The concentration of the hydrophilic emulsifier in UE2 formulation (1.52%) was higher than that of the SE formulation (0.8%) and the UE3 formulation (0.3%) and also could be the extent of association of the polymer with the hydrophilic emulsifier in these emulsions. This suggests that methylcellulose–Tween[®] complex could also act as an emulsifier at the olive oil-water interface in addition to the free emulsifiers. The possible presence of the complex at the olive oil-water interface was also indicated

from the flow properties of these emulsions. In contrast, the addition of the polymer caused a proportional reduction in the particle size of mineral oil emulsions only in the absence of a hydrophilic emulsifier.

The creaming stability of all four base olive oil emulsions improved with increasing polymer concentration in the external phase (Table 2). No oil separation was found in any emulsion stored at room temperature for more than 6 months. The improvement in creaming stability was substantially higher in emulsions with a lower hydrophilic emulsifier concentration (UE3 > UE1 > SE = UE2). A similar finding was also observed for mineral oil emulsions (UE3 > UE2). However, unlike mineral oil SE and UE1 emulsions, the addition of the polymer did not cause instability in any of the olive oil emulsions. Furthermore, addition of the polymer improved the particle size stability of olive oil UE1 formulation, which oth-

erwise showed an increase in particle size in the absence of the polymer within two months (Table 2).

The nature of the disperse phase had no effect on the stability of base emulsions formulated with an appropriate emulsifier system. However, methylcellulose improved the stability of emulsions of a polar oil more effectively than those of a non-polar oil. This improvement in the stability of polar oil-in-water emulsions with methylcellulose might be attributed to the association of methylcellulose with the POE type nonionic emulsifier and the interaction between the polar oil and the POE chain of the emulsifier.

References

- Becher, P., Nonionic surface-active compounds. VII. Interfacial tensions of solutions of nonionic surface-active agents. *J. Colloid Sci.*, 18 (1963) 665–673.
- Davis, S.S. and Smith, A., The influence of the disperse phase on the stability of oil-in-water emulsions. In Smith, A.L. (Eds.), *Theory and Practice of Emulsion Technology*, Academic Press, New York, 1976, pp. 325–346.
- Fisher, L.R., Mitchell, E.E. and Parker, N.S., Interfacial tensions of commercial vegetable oils with water. *J. Food Sci.*, 50 (1985) 1201–1202.
- Fisher, L.R. and Parker, N.S., Effect of surfactants on the interactions between emulsion droplets. In Dickinson, E. and Stainsby, G. (Eds.), *Advances in Food Emulsions and Foams*, Elsevier, London, 1988, p. 49.
- Florence, T. and Rogers, J.A., Emulsion stabilization by non-ionic surfactants: experiment and theory. *J. Pharm. Pharmacol.*, 23 (1971) 233–251.
- Gullapalli, R.P. and Sheth, B.B., Effect of methylcellulose on the stability of oil-in-water emulsions. *Int. J. Pharm.*, 140 (1996) 97–109.
- Lobo, L.A. and Wasan, D.T., Thin film stability and interfacial rheology of emulsion systems. In Van, P.J. (Ed.), *Food Emulsions and Foams: Theory and Practice*, Vol. 86, AIChE Symposium Series, 1990, pp. 25–34.
- McClements, D.J., Monahan, F.J. and Kinsella, J.E., Effect of emulsion droplets on the rheology of whey protein isolate gels. *J. Texture Stud.*, 24 (1993) 411–422.
- Niebergall, P.J., Schnaare, R.L. and Sugita, E.T., Nonlinear regression applied to non-Newtonian flow. *J. Pharm. Sci.*, 60 (1971) 1393–1402.
- Sherman, P., The flow properties of emulsions. *J. Pharm. Pharmacol.*, 16 (1964) 1–25.
- Shinoda, K. and Friberg, S., Concepts of HLB, HLB Temperature, and HLB Number. In *Emulsions and Solubilization*, Wiley, New York, 1986, pp. 62–65 and 86.
- Shinoda, K., Saito, H. and Arai, H., The effect of the size and the distribution of the oxyethylene chain lengths of non-ionic emulsifiers on the stability of emulsions. *J. Colloid Interface Sci.*, 35 (1971) 624–630.
- Shotton, E. and White, R.F., Rheology of acacia-stabilized emulsions. *J. Pharm. Pharmacol.*, 12 (1960) 108T–112T.
- Tadros, Th. F., Fundamental principles of emulsion rheology and their applications. *Colloids Surf.*, 91 (1994) 39–55.
- Yilmazer, G. and Kokini, J.L., Effect of Polysorbate-60 on the stability of O/W emulsions stabilized by propylene glycol alginate and xanthan gum. *J. Texture Stud.*, 22 (1991) 289–301.
- Zatz, J.L. and Ip, B.K., Stabilization of oil-in-water emulsions by gums. *J. Soc. Cosmet. Chem.*, 37 (1986) 329–350.