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# Effect of phospholipid emulsifiers on physicochemical properties of intravenous fat emulsions and/or drug carrier emulsions

FUMIYOSHI ISHII, ICHIRO SASAKI, HIROYASU OGATA, *Meiji College of Pharmacy, 1-22-1 Yato, Tanashi, Tokyo 188, Japan*

**Abstract**—The physicochemical properties of soybean oil emulsions stabilized with purified egg lecithins (phosphatides) of various concentrations have been examined. The zeta potential of the emulsion droplets and the mean particle size of oil droplets in 10% (w/w) o/w-type emulsion decreased with increasing emulsifier concentration and then levelled off at more than 1·2% (w/w). In rheological measurements, at the initial stage, the viscosity of 10% (w/w) o/w-type emulsion gradually increased with increasing purified egg lecithin concentration, at the next stage, a plateau was reached at about 1·0–1·4% (w/w), and at the final stage, the viscosity curve showed a dramatic increase. These results indicate that emulsions stabilized by purified egg lecithin at more than 1·2% (w/w) are likely to be sufficiently stable.

The choice of lecithins (phosphatides) from egg yolk or soybean as emulsifiers for parenteral emulsions has been advocated since these materials can be metabolized. However, little attention has been given to the fundamental properties of submicronized emulsions stabilized with lecithins (phosphatides) for parenteral formulations. Schuberth & Wretlind (1961) studied various emulsifying agents for fat emulsions, at a constant concentration of egg yolk phosphatides (1·2%), and Benita et al (1986) reported the effect of concentration of phospholipids and a non-ionic surfactant, polyoxyethylene-polyoxypropylene block copolymer (Pluronic F68), on the physicochemical properties of o/w emulsions prepared using a stirrer and mixer without high-pressure homogenization.

This paper reports the effect of phospholipid emulsifiers on the physicochemical properties of soybean oil emulsions prepared using a high-pressure homogenizer.

## Materials and methods

Purified egg lecithins (phosphatides) were kindly provided by Asahi Chemical Industries Co. Ltd, Japan. The lipids consisted of phosphatidylcholine (79·8%), lysophosphatidylcholine (0·6%), phosphatidylethanolamine (17·2%), phosphatidylserine (0·4%), phosphatidylinositol (0·4%), sphingomyelin (0·7%) and others (0·9%). All other ingredients were of reagent grade. Deionized-distilled water was used.

*Preparation of emulsions.* Typical oil-in-water emulsions were prepared containing 10% (w/w) soybean oil, various concentrations (0·6–2·0% (w/w)) of egg lecithins (phosphatides), and 2·5% (w/w) glycerol in a sufficient amount of distilled water to make 500 mL. Furthermore, 5–40% oil-in-water emulsions with 1·2% (w/w) egg lecithins were also prepared. The emulsifiers (egg lecithins) were dissolved in the oil phase, heated to 80 °C in a tank, and water which had been preheated to 80 °C was added to the solution. The agitator used was an autohomomixer, a high-shear mixer (Type IM, Tokushukika Co. Ltd, Osaka, Japan): the temperature of the mixture was maintained at 80 °C for 30 min after the start of agitation in the tank. The impeller speed was kept at 10000 rev $min^{-1}$. To make fine emulsions, coarse emulsions were introduced rapidly into a two-stage pressure homogenizer (Model 15M-8TA, Gaulin Co. Ltd, Mass, USA) operating at 4500 psi. Fig. 1 shows the effect of shear application on the mean diameter of emulsion droplets in the prepared emulsions. As the number of shear applications increased, the mean diameter of the emulsion droplets decreased sharply and reached a minimum constant value at ten cycles. Therefore, this number of shear applications was used subsequently.

Correspondence to: F. Ishii, Meiji College of Pharmacy, 1-22-1 Yato, Tanashi, Tokyo 188, Japan.

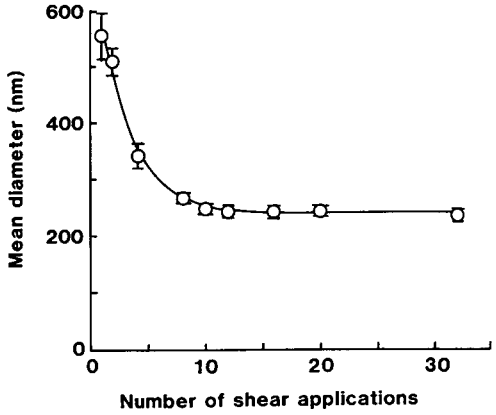


FIG. 1. Effect of shear application on the mean diameter of droplets in emulsion containing 1·2% (w/w) egg lecithin and 10% (w/w) soybean oil.

*Measurements.* Emulsion viscosities were measured with concentric cylinders using a Rheomat 30 viscometer (Contravas, Zurich, Switzerland). The diameters of the bob and cup were 11·0 and 12·0 mm, respectively, so that the gap width was 0·5 mm. The measurement temperature was controlled to 20 ± 0·1 °C with a circulating water bath. The zeta potential (Laser Zee Model 500, Penkem Inc., New York) was calculated from the mean electrophoretic mobility of the oil droplets. Measurements of zeta potential were performed in the same continuous phase. The mean diameter of oil droplets in the emulsion was determined with a Coulter Nanosizer (Type N4, Coulter Electronics Inc., Hialeah, Fla, USA) by laser light scattering.

## Results and discussion

Emulsifying agents form good mechanical and/or electrical barriers to emulsion droplet coalescence. The surface potentials on the oil droplets play an important role in o/w emulsion stability through electrostatic repulsion. Fig. 2 shows the change in zeta potential of oil droplets in the emulsions stabilized by egg lecithins at various concentrations. The zeta potential decreased as the emulsifier concentration increased and then levelled off at more than 1·2% (w/w). These results show that an increase in the amount of negatively charged phospholipid (contained in the egg lecithins) brings about a decrease in the zeta potential which reaches a plateau region when the oil droplets in the emulsion are completely coated by the lecithin molecules. At a pH value of around 7, the emulsion carries a negative charge because of ionization of the various minor components in the lecithins (Bangham 1968), i.e. phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol. Emulsions stabilized by more than 1·2% (w/w) egg lecithin are likely to be sufficiently stable with respect to these electrical barriers.

Mean particle size and particle size distribution are the most important physicochemical characteristics of colloidal carrier systems such as emulsions, liposomes, micro- and nanocapsules, and micro- and nanospheres. Small particle size in an emulsion is associated with good stability during storage and low toxicity in the body. Fujita et al (1971) reported that particles larger than 6 $\mu$m in emulsions can cause serious side effects such as emboli. Yokoyama et al (1975) considered that small-particle-size emulsions are eliminated from the bloodstream more slowly than large-particle-size emulsions. Fig. 3 shows the change in the mean particle size of oil droplets in the emulsions stabilized by egg lecithins at various concentrations. The mean particle size decreased as the emulsifier concentration increased and then levelled off at more than 1·2% (w/w).

It is interesting to compare the results of zeta potential (Fig. 2) with the mean particle size (Fig. 3). The curve of the zeta potential and the curve of the mean particle size show a similar tendency as the egg lecithin concentration increases. The plateau region of these curves appears at the saturation stage of egg lecithin adsorption on the oil droplets.

The above results suggest that it is necessary to use a lecithin at more than 1·2% (w/w) as an emulsifier in order to prepare a stable parenteral emulsion. Although the commercially available fat emulsion, Intralipid, contains a 10% or 20% (w/w) oil phase, the concentration of egg lecithins as the emulsifier is 1·2% (w/w) for both preparations. Burnham et al (1983) indicated that the mean diameters for 10 and 20% (w/w) Intralipid were 250 and 410 nm, respectively. Therefore, we examined whether

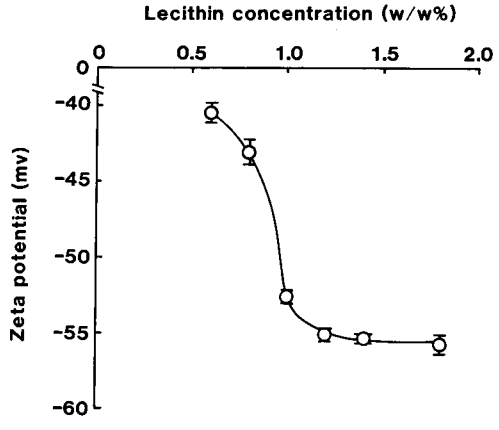


FIG. 2. Effect of egg lecithin concentration on zeta potential of emulsion droplets in emulsion containing 10% (w/w) soybean oil.

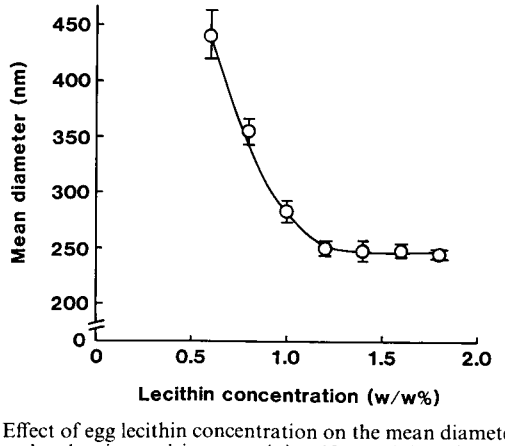


FIG. 3. Effect of egg lecithin concentration on the mean diameter of emulsion droplets in emulsion containing 10% (w/w) soybean oil.

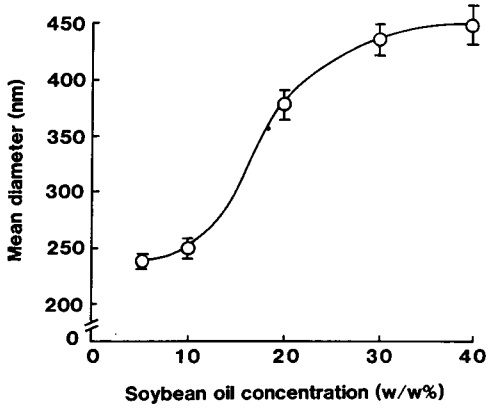


FIG. 4. Effect of oil phase volume on the mean diameter of emulsion droplets in emulsion prepared with 1·2% (w/w) egg lecithin.

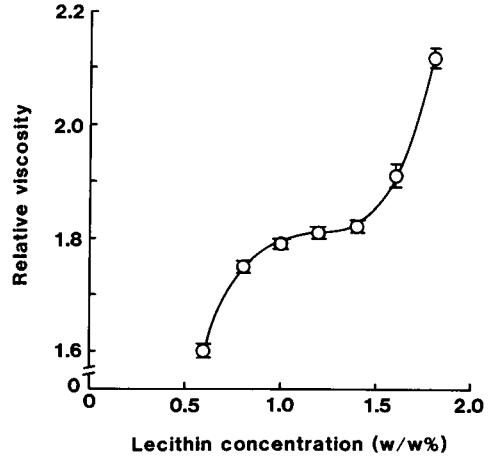


FIG. 5. Effect of egg lecithin concentration on relative viscosity of emulsions containing a 10% (w/w) oil phase.

emulsions containing an oil phase at more than 10% (w/w) could be prepared with 1·2% (w/w) egg lecithin. Fig. 4 shows the effect of the oil phase on the mean diameter of the emulsion droplets. As can be seen, this parameter increased as the volume fraction of the oil phase increased; the mean diameters of emulsions containing 10% and 20% (w/w) oil phases were 248 and 390 nm, respectively. The results obtained here are similar to those reported by Burnham et al (1983): the larger the size of the emulsion droplets, the lower the stability of the emulsion system. Accordingly, with respect to the oil phase at a constant concentration (1·2 % (w/w)) of egg lecithin, the optimal condition for a stable oil-in-water emulsion preparation was found to be a 10% (w/w) oil phase.

Rheological properties are factors affecting the flow of parenteral emulsions through a needle or a catheter, the removal of emulsions from a bottle or vial, and the behaviour of emulsions in pharmaceutical preparations. Fig. 5 shows the effect of egg lecithin concentration on the relative viscosity of an emulsion product. At the initial stage, the curve shows a gradual increase, then reaches a saturation value (1·0–1·4% (w/w)), and at a higher concentration of egg lecithin, it shows a dramatic increase. Previously we reported that a decrease in mean particle size contributes to an increase in viscosity (Takamura et al 1983). A smaller particle size increases the total interface in an emulsion, resulting in an increase in the number of interparticle interactions. Moreover, it is generally known that the higher the volume ratio of the dispersed phase, the higher the viscosity of

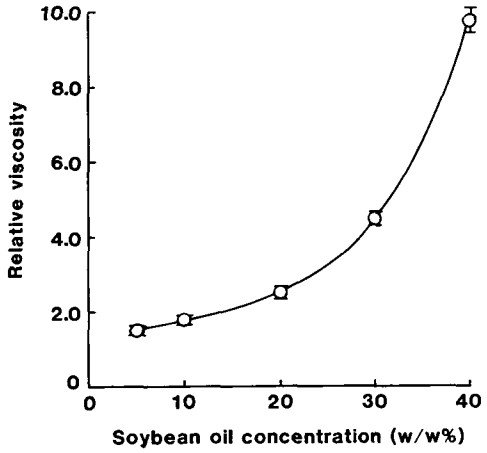


FIG. 6. Effect of oil phase volume on relative viscosity of emulsion prepared with 1·2% (w/w) egg lecithin.

the system. As demonstrated in Fig. 3, at lower concentrations of 0·6–1·2% (w/w) egg lecithin, the adsorbed layer around the emulsion droplets formed, decreasing the particle size. At higher concentrations of egg lecithin (above 1·6% (w/w)), the surplus egg lecithin molecules associated to form micelles or vesicles, increasing the volume ratio between the dispersed phase and the continuous phase.

Intravascular administration of a viscous preparation is associated with pain (Korttila et al 1976); accordingly, we investigated the rheological properties of emulsions by changing the oil volume ratio of the dispersed phase. Fig. 6 shows the effect of oil phase volume on the relative viscosity of emulsions. This increased as the oil phase volume ratio to the continuous phase increased. These results strongly suggest that the interaction between oil droplets in emulsions increases due to their closer approach in the continuous phase.

In conclusion, it appears that lecithin as an emulsifier is effective at 1·2% (w/w) for the preparation of intravenous fat emulsions, at least in terms of the physicochemical parameters and surface properties determined here.

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# The effect of chronic captopril administration on hepatic blood flow of the rat

SIMON BAR-MEIR, HAIA PRIGOJIN, RAFAEL BRUCK, ZIPORA KREPEL, YONA AVNI, *Department of Gastroenterology, Edith Wolfson Hospital, Holon and Sackler School of Medicine, Tel Aviv University, Israel*

**Abstract**—The effect of chronic captopril administration on indocyanine green (ICG) clearance and hepatic extraction has been studied in the rat using the intact liver for ICG clearance and the isolated perfused liver for ICG extraction. The captopril was added to the drinking water to give a calculated daily intake from 0·45 mg $kg^{-1}$. Hepatic clearance of ICG was dose related from $16·5 \pm 2·4$ (control) to $7·2 \pm 1·6$ mL $min^{-1}$ $kg^{-1}$, respectively. The hepatic extraction of ICG was not significantly different ($37 \pm 6\%$) from the control value in groups on 4 and 45 mg $kg^{-1}$ daily. Since ICG clearance and extraction are dependent on hepatic blood, a change in ICG clearance without a change in the extraction reflects a similar change in the hepatic blood flow. This remained unchanged at daily captopril intakes of 1 and 4 mg $kg^{-1}$ and decreased when the daily intake was 10 mg $kg^{-1}$ or higher. If these results in the rat are applicable to man, the chronic administration of therapeutic doses of captopril (0·5–2 mg $kg^{-1}$) will not affect the hepatic blood flow.

Correspondence to: S. Bar-Meir, Department of Gastroenterology, Edith Wolfson Hospital, Holon 58100, Israel.

Captopril, an oral angiotensin converting enzyme inhibitor, is used in the treatment of hypertension and congestive heart failure (MacGregor et al 1979). Clinical and experimental studies suggest that it lowers total systemic vascular resistance by inducing selective vasodilatation in regional vascular beds (Cavras et al 1978; Faxon et al 1980, 1981). Animal studies have shown that it increases renal, cerebral and coronary blood flow at the expense of hepato-mesenteric, cutaneous and skeletal muscle perfusion (Cavras et al 1978).

Crossley et al (1984) found a decrease in hepatic blood flow following the administration of 50–100 mg of captopril to hypertensive patients while Eriksson et al (1984) and Shepherd et al (1985) did not find any effect of the drug on hepatic blood flow in patients with liver cirrhosis and in normal volunteers. In those three studies only single doses of captopril were given; no information is available on the effect of chronic administration of captopril on hepatic blood flow. We have investigated the effect of chronic captopril administration in the rat.