International Journal of Pharmaceutics, 63 (1990) 183–188
Elsevier

IJP 02116

Research Papers

Polymeric and emulsion carriers—interaction with antiflocculants and ionic surfactants

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(Received 30 December 1989)
(Accepted 4 February 1990)

Key words: Antiflocculant; Fat emulsion; Polystyrene particles; Stability; Zeta potential

Summary

A factor determining the physical stability of polymeric and fat emulsion drug carriers is the electrostatic repulsion of the particles/droplets. An increased repulsion (and subsequently increased stability) was achieved by the addition of antiflocculants to suspensions of polystyrene latex particles used as model carriers. Sodium citrate and sodium pyrophosphate proved to be most efficient by increasing the zeta potential to about −100 mV. This effect was less distinct with emulsions and was overlapped by a simultaneous zeta potential increase due to pH shifts. Eliminating the pH effect, sodium pyrophosphate could still enhance the net zeta potential of fat emulsions by −38 mV compared to −65 mV on polymeric particles. Antiflocculants could thus be selected with similar strong charge enhancing effects as ionic surfactants [sodium dodecyl sulphate, cetyl pyridinium chloride] but with a higher toxicological acceptance.

Introduction

Colloidal polymeric particles and parenteral fat emulsions are possible carrier systems for the controlled delivery of drugs (Davis, 1981, 1982). Particles made from biodegradable materials can be administered as aqueous suspensions, the fat emulsions are generally systems of the O/W type. The absence of particle flocculation or droplet coalescence leading to aggregates or large droplets with possible changes in drug release or organ distribution is important for the physical stability of these systems. The organ distribution of intravenously administered systems is for example strongly dependent on their size (Davis et al., 1986). The stabilizing factor in both systems is the electrostatic repulsion of similarly charged particles and droplets (Lagaly, 1984); in emulsion systems the rigidity of the emulsifier layer is an additional factor. As a measure of particle charge (and electrostatic stabilization) the zeta potential of the particles can be used (James, 1979). A range of particles made from biodegradable materials such as polyhydroxybutyrate (PHB) carriers possess a relatively low zeta potential (Koosha, 1989). The incorporation of drugs oppositely charged to the particles or emulsion droplets can also lead to a zeta potential reduction. In addition, drug incorporation can reduce the rigidity (microviscosity) and therefore stability of the emulsifier

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film. These two effects could be compensated by increasing the zeta potential, e.g. by addition of ionic surfactants which adsorb on the particles. However, the use of ionic surfactants is limited due to their toxicity (Attwood and Florence, 1983). Antiflocculants are described to efficiently enhance the zeta potential and thus the stability of inorganic suspensions (Lucks et al., 1988, 1990; Müller et al., 1990). Most of these antiflocculants are naturally occurring metabolic compounds of the body and therefore of low toxicity, e.g. sodium citrate. The aim of this paper is to investigate their possible use for the stabilization of colloidal drug carriers. As model carriers, polystyrene standard latex particles and a drug-free soya oil emulsion were selected.

Materials and Methods

Polystyrene latex particle suspensions (2.5% w/v) were purchased from Polysciences (Northampton, U.K.), mean diameter 0.93 μm. A commercial fat emulsion, Intralipid, was a gift by Pfrimmer Kabi (Erlangen, F.R.G.). This fat emulsion consisted of 10% (w/w) soya oil and 1.2% (w/w) egg lecithin (emulsifier) dispersed in water containing 2.5% (w/w) glycerol to achieve isotonicity. All salts (sodium dihydrogen phosphate, sodium citrate, sodium chloride, sodium pyrophosphate) and surfactants (cetyl pyridinium chloride (CPC), sodium dodecyl sulphate (SDS)) were purchased from Sigma (F.R.G.). Egg lecithin was donated by Lipoid KG (F.R.G.), soya oil was purchased from Sainsburys (U.K.).

Photon correlation spectroscopy (PCS) (Cummins and Pike, 1974) was employed for particle size determinations below 1 μm using a Malvern Spectrometer in connection with a 4-Bit K7025 Correlator (Malvern Instruments, U.K.). Particle charge was determined by electrophoresis measurements and expressed as zeta potential (Lucks et al., 1990; Müller et al., 1990). The electrophoretic velocity was measured by laser doppler anemometry (LDA) using a Malvern Zetasizer II (Müller et al., 1986a) or by amplitude weighted phase structuration (AWPS) (Schätzel and Merz, 1984; Müller et al., 1986b; Müller et al., 1990). The experiments were performed in a 4 mm glass capillary cell whereby intermittent measurements were necessary at high salt concentrations of 10^{-1} M using the LDA system (Zetasizer) due to heating effects. The AWPS system allowed continuous measurements because of the lower field strength which could be applied. This avoided thermal heating of samples containing high electrolyte concentrations. Sample preparation: Polymeric particles and emulsion were added to the salt and surfactant solutions resulting in a final concentration of the disperse phase of 10^{-4}% (w/w). The salt and surfactant concentrations ranged from 10^{-6} to 10^{-1} mol/l.

An experimental fat emulsion containing soya oil (10% (w/w)), egg lecithin (1.2% (w/w)), and water was produced by microfluidization (Washington and Davis, 1988) applying two cycles and 500 bar (Microfluidizer M 110, Microfluidics Corp., U.S.A.).

Results and Discussion

Polymeric particles

Inorganic suspensions could be stabilized by addition of selected antiflocculants in concentrations ranging from 10^{-3} to 10^{-2} M (Lucks et al., 1990). To study the effect on polymeric particles, sodium dihydrogen phosphate, sodium pyrophosphate and sodium citrate solutions were mixed with polystyrene latex suspensions. An adsorption onto the particle surface was observed for all antiflocculants as indicated by the increase in zeta potential (Fig. 1). Charge maxima were obtained at identical concentrations previously described for inorganic suspensions (Lucks et al., 1990). However, the antiflocculants adsorbed to a different extent as indicated by the differences in zeta potential. Least adsorption and increase in zeta potential were found for sodium dihydrogen phosphate, a very distinct adsorption however for sodium pyrophosphate and sodium citrate. This resulted in a large increase of the zeta potential from -30 mV to about -100 to -120 mV at 1 mM (Fig. 1). Such increased electrostatic repulsion can be utilized to enhance the physical stability of drug carrier suspensions. In inorganic sus-

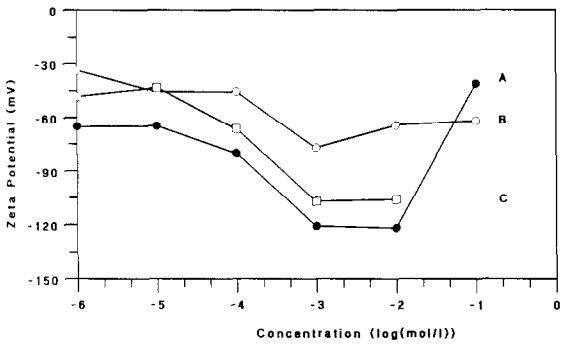

Fig. 1. Zeta potential of polystyrene particles as a function of the concentration of different salts. (A) sodium citrate, (B) sodium dihydrogen phosphate, (C) sodium pyrophosphate.

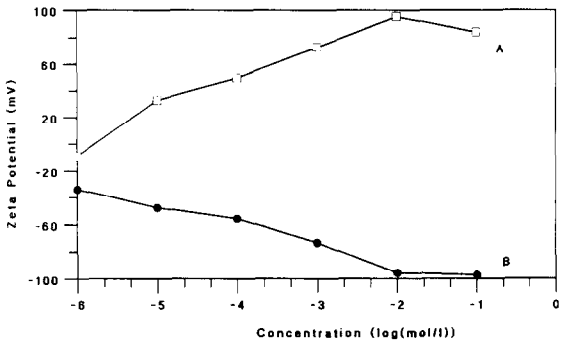

Fig. 2. Zeta potential of polystyrene particles as a function of the concentration of different surfactants. (A) Cetyl pyridinium chloride, (B) sodium dodecyl sulphate.

pensions, sodium citrate was less effective than sodium pyrophosphate (Lucks et al., 1990) indicating that the properties of the particle surface determined affinity and degree of adsorption. At high salt concentrations of 10^{-1} M a reduction in zeta potential and therefore reduced stability occurred. The same effect was described previously (Lucks et al., 1990) and could be explained by the compression of the diffuse layer. Too high antiflocculant concentrations can cause a de-stabilization. Therefore, optimum conditions need to be assessed for each drug carrier system considering affinity, degree of adsorption and concentration of antiflocculant.

Antiflocculants had therefore a stabilizing effect similar to ionic surfactants (e.g. sodium dodecyl sulphate (SDS)) or ionic surfactants used as preservatives (e.g. cetyl pyridinium chloride (CPC)). The negatively charged SDS was as effective as sodium pyrophosphate and created a zeta potential of -100 mV at 10^{-2} M (Fig. 2). In contrast to sodium citrate, SDS has the advantage of maintaining this charge even at higher concentrations (10^{-1} M). A similar effect but with reversed charge could be created by mixing the polymeric particles with CPC solutions. The zeta potential increased to $+100$ mV and showed little reduction at high CPC concentrations. The strongly surface active cetylpyridinium ion would surely lead to a positive charge by adsorbing directly to the particle surface. It would displace the double layer. The charged groups are located outside the diffuse layer leading to the remaining high zeta potential (Lucks et al., 1990).

Emulsion carriers

Ionic surfactants added to emulsions created the same distinct zeta potential increases as in particle suspensions. Incorporation of the ionic surfactant into the emulsifier layer of the oil droplets and less adsorption is regarded as the responsible mechanism. The maximum potentials were -82 mV (SDS) and $+85$ mV (CPC), again no zeta potential reduction occurred at high surfactant concentrations (Fig. 3). These surfactants are not suitable with regard to toxicological aspects and need to be replaced by charged compounds with similar structure but reduced toxicity, e.g. fatty acids for which a penetration into the surfactant layer has been described (Washington and Davis, 1987). The increase in the emulsion droplet charge might have some impact on the

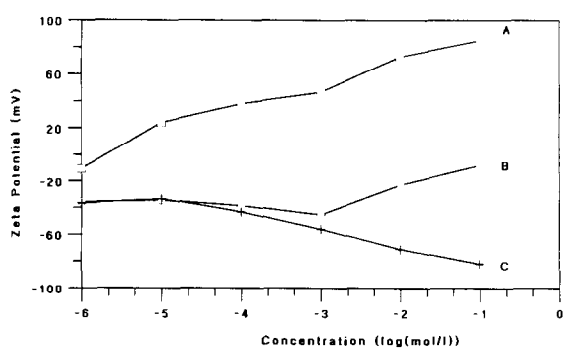

Fig. 3. Zeta potential of Intralipid particles as a function of the concentration of different salts and surfactants. (A) Cetyl pyridinium chloride, (B) sodium chloride, (C) sodium dodecyl sulphate.

organ distribution. The uptake of intravenously injected particles by liver and spleen macrophages increases with particle charge (Wilkins and Myers, 1966). Emulsion carriers administered intravenously with increased charge are therefore expected to comprise a shorter half-life in the blood and increased clearance by liver and spleen (Illum et al., 1989). Such a change in organ distribution could also affect drug pharmacokinetics.

The interaction of toxicologically more acceptable antiflocculants with emulsions was studied using Intralipid and compared to the effect of the salt sodium chloride. In contrast to antiflocculants, the neutral salt sodium chloride led only to a minor increase of the zeta potential in the investigated concentration range. The zeta potential-concentration profile was characterized by the compression of the diffuse layer leading to a distinct potential decrease at concentrations above 10^{-3} M (Fig. 4). The antiflocculant sodium dihydrogen phosphate stabilized the polymeric particles but had no potential increasing effect on the emulsion at all. In contrast, above 10^{-3} M a charge reduction occurred as observed with sodium chloride. An identical decay of the potential was found for sodium citrate but a distinct charge increase and therefore stabilization could be created at lower concentrations (10^{-4}–10^{-3} M). A very large increase in the zeta potential to −83 mV could however be obtained with sodium pyrophosphate (Fig. 4) which proved to be the most

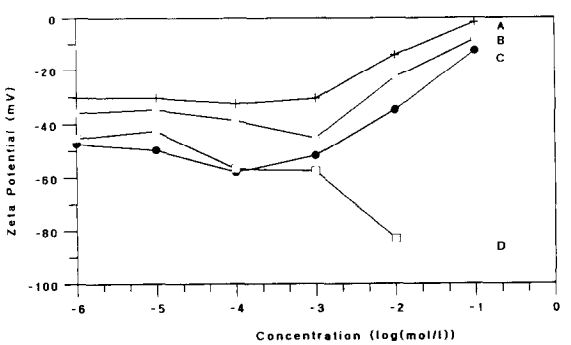

Fig. 4. Zeta potential of Intralipid as a function of the concentration of different salts. (A) Sodium dihydrogen phosphate, (B) sodium chloride, (C) sodium citrate, (D) sodium pyrophosphate.

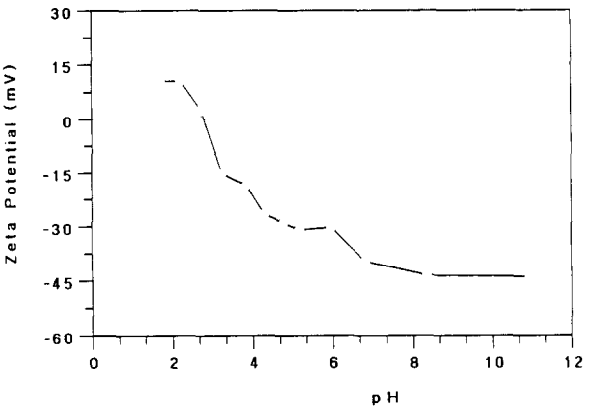

Fig. 5. Zeta potential of Intralipid as a function of the pH.

efficient additive. The zeta potential could not be determined at 10^{-1} M due to the high conductivity of the solution.

A possible shift in the pH of the emulsions needs to be considered to assess the net increase in charge due to the adsorption of antiflocculants. Addition of sodium pyrophosphate shifts the pH of the emulsion from 5 to about 10. This change in the pH increases the zeta potential of antiflocculant-free emulsions from −30 mV to about −45 mV (Fig. 5, measured by AWPS, pH adjusted with NaOH, HCl). The net increase of charge in the sodium pyrophosphate-containing emulsion is therefore −38 mV (at 10^{-2} M, pH 10). Such a pH causes problems with regard to the chemical stability of the emulsion and cannot be used for parenteral administration. Antiflocculants need therefore to be selected which cause minimum pH shift and create a maximum net increase at a suitable pH (e.g. pH 7.4).

To investigate the effect of the increased zeta potential on the long term stability of fat emulsions, the mean droplet size of an antiflocculant-free emulsion (pH 5.1) and emulsions containing sodium citrate and sodium pyrophosphate (10^{-4} M respectively, pH 9.4) was monitored over 6 months. To assess the effect of the pH shift, an emulsion was prepared with the pH adjusted to 9.5 by addition of NaOH. The emulsion was produced by Microfluidizer at low pressure with a small number of cycles (Lucks et al., 1989). This resulted in a physically less stable system as indi-

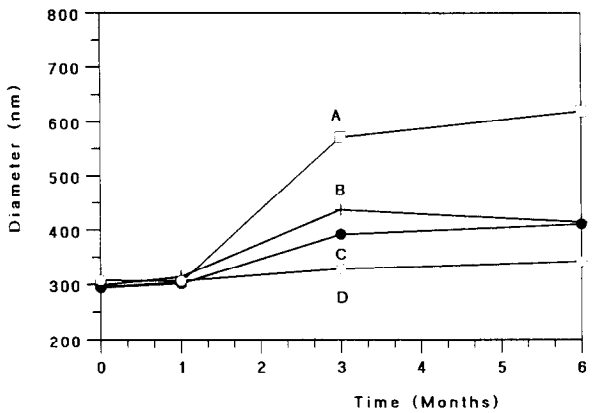

Fig. 6. Mean droplet diameter of fat emulsions containing antiflocculants as additives during storage. (A) No additive (pH 5.1); (B) 10^{-4} M sodium pyrophosphate; (C) 10^{-4} M sodium citrate; (D) no additive (pH 9.5).

cated by the increase in the mean PCS diameter after 3 months (Fig. 6). The possible stabilizing effects were expected to be more obvious in a less stable system. Indeed, the emulsions containing antiflocculants showed a distinctly reduced increase in the mean droplet diameter (Fig. 6). However, the antiflocculant-free emulsion with pH adjusted at 9.5 was at least of similar stability. From these results it was concluded that antiflocculant addition had no stability enhancing effect at the investigated pH. The data demonstrate the need to consider such effects during the screening for suitable additives in a more physiological pH range.

Conclusions

Polymeric colloidal particles can be stabilized by addition of antiflocculants and ionic surfactants. Ionic surfactants have the advantage of maintaining the stabilizing effect even at higher surfactant concentrations. This mechanism can be utilized to enhance the physical stability of polymeric drug carrier suspensions whereby from toxicological considerations antiflocculants such as sodium citrate are preferable. The number of antiflocculants suitable to stabilize emulsion is limited and the effect is less distinct compared with polymeric particles. Possible shifts in the pH can mimic an affinity of the antiflocculant and might also influence the chemical stability. Selection of an antiflocculant requires consideration of net charge increase, effects of pH shift and toxicological acceptance.

Acknowledgement

We would like to express our sincere thanks to Professor S.S. Davis, University of Nottingham, for the opportunity to conduct parts of this work in his laboratories.

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