ELSEVIER

International Journal of Pharmaceutics 183 (1999) 17–20

international journal of pharmaceutics

Short communication

The effect of controlled osmotic stress on release and swelling properties of a water-in-oil emulsion

S. Bjerregaard [a,*], I. Söderberg [b], C. Vermehren [a], S. Frokjaer [a]

[a] *Department of Pharmaceutics, The Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark*
[b] *Pharmaceutical Development, H. Lundbeck A/S, Ottiliavej 9, DK-2500 Valby, Denmark*

Received 18 December 1998; accepted 14 January 1999

Abstract

The purpose of this study was to investigate the effect of osmotic gradients in a water-in-oil (w/o) emulsion on release properties in order to control the release of hydrophilic drugs. The magnitude and direction of the osmotic gradient was shown to have a pronounced effect on the apparent permeability of the hydrophilic marker, [^{3}H]glucose. The apparent permeability coefficient of glucose could be varied between 1.0×10^{-8} and 5.0×10^{-8} cm s^{-1} using osmotic gradients. The release rate of glucose was related to the swelling properties. The larger the degree of swelling, the lower the release rate. Furthermore the present w/o emulsion has a low viscosity and a long-term physical stability. This makes the emulsion a promising parenteral drug delivery system in which the release of hydrophilic drugs such as peptides, can be controlled.

Keywords: Water-in-oil emulsion; Emulsion stability; Prolonged release; Osmotic behaviour

1. Introduction

Water-in-oil (w/o) emulsions have a very attractive potential as prolonged release systems for hydrophilic drugs with the oil phase and surfactant layer acting as a release barrier. Davis et al. (1985) has previously reviewed the use of emulsions as drug delivery systems. The applications mainly include topical and parenteral administrations. With respect to parenteral administration, w/o emulsions have the potential to increase the therapeutic efficacy of drugs such as proteins with short elimination half-lives and high potency. The frequency of administration can be reduced with w/o emulsions. In addition the oil phase protects drugs in the internal water phase against degrada-

* Corresponding author. Fax: +45-3537-1277.

0378-5173/99/$ - see front matter
PII: S0378-5173(99)00052-6

tion in a harsh enzymatic environment. Recent work regarding parenteral prolonged release of hydrophilic drugs with emulsions has mainly focused on multiple water-in-oil-in-water (w/o/w) emulsions (Omotosho et al., 1989; Miyakawa et al., 1993; Kim et al., 1995; Nakhare and Vyas, 1997). Multiple emulsions are much more complex and less stable than simple w/o emulsions (Florence and Whitehill, 1982), and simplicity often increases the freedom to modify a formulation without breaking the emulsion. The emphasis on w/o/w emulsions is mainly based on a low viscosity relative to w/o emulsions thereby improving injectability (Omotosho et al., 1989; Kim et al., 1995; Cole and Whateley, 1997). However, in this study we have been able to formulate a w/o emulsion with good injectability, i.e. low viscosity and with a long-term physical stability by using a low viscosity oil and a polymeric surfactant.

Several studies of multiple w/o/w emulsions have reported that osmotic gradients between the internal and external water compartment have a pronounced effect on stability and release properties of the emulsions (Brodin et al., 1978; Florence and Whitehill, 1981; Hino et al., 1995; Jager-Lezer et al., 1997). The aim of this study was to investigate the effect of osmotic stress of a w/o emulsion on release properties of a hydrophilic marker ([^{3}H]glucose).

2. Methods

The w/o emulsion was prepared with an aqueous volume fraction of 28%. Fractionated coconut oil (Delios V, Grünau, Germany) was used as the oil phase with 5.0% (w/w) polyglycerol polyricinolate (Danisco Ingredients, Denmark) and 1.4% (w/w) sorbitan monooleate (Sigma, USA) as the lipophilic surfactants. The water phase contained 278 mM D-glucose labelled with D-[6-^{3}H]glucose (New England Nuclear, USA) as a marker molecule in 0.05 M phosphate buffer pH 7.4. The phosphate buffer was adjusted to an osmotic strength of 1650 mOsm kg^{-1} with NaCl. The preparation was homogenised with an Ultra Turrax (Janke and Kunkel, Germany) and subsequently treated with an ultrasound probe (Branson, USA) using ice-cold water for cooling. Photon correlation spectroscopy was used to determine the mean droplet size using a Malvern Zetasizer 4 (Malvern, UK). The emulsion droplets obtained had an initial mean droplet diameter of 165 nm.

The physical stability of the w/o emulsion was studied while following the mean droplet size in samples stored in closed glass ampoules under nitrogen at 4 and 25°C, respectively. Although some increase in the mean droplet size was observed especially during the initial storage period, it levelled off with time (Fig. 1). In addition, no visual signs of physical destabilisation, e.g. phase separation, was noticed during the observation period indicating good physical stability of the formulation.

The rheological characteristics were examined with a Carri-med CLS^2 100 rheometer (TA Instruments, UK) at 25°C. The emulsion exhibited a simple Newtonian flow and the dynamic viscosity was measured as 78 mPa s.

To study the effect of osmotic gradients, glucose was released into buffers with various osmolarities using a Hanson transdermal diffusion cell system (Hanson Research, USA). A weighed amount of emulsion (approximately 200 mg) was placed on 3.7 ml 0.05 M phosphate buffer pH 7.4 without any membrane separating the emulsion and buffer. The acceptor buffer was adjusted to various osmolalities with NaCl ranging from 300

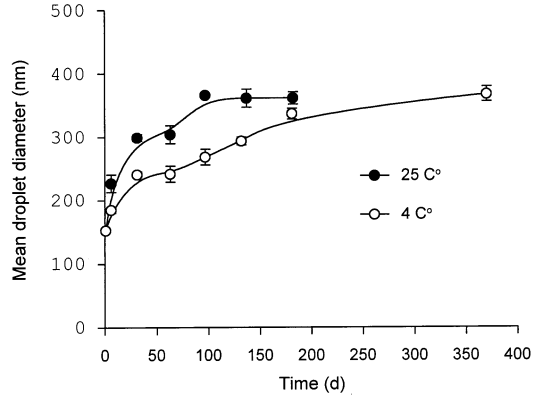

Fig. 1. Effect of storage temperature on increase in mean droplet diameter of the w/o emulsion.

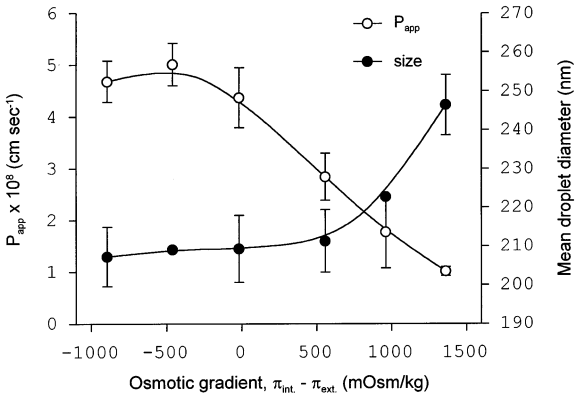

Fig. 2. Effect of osmotic gradients on glucose release and swelling properties of a w/o emulsion at 37°C. Droplet size was measured at the termination of the release experiments after 72 h.

to 2500 mOsm kg^{-1} (Osmomat 030-D, Gonotec, Germany) and contained 0.05% NaN_3 as a preservative. Serial sampling was performed and the amount of glucose released was determined by liquid scintillation. The swelling properties of the emulsion were investigated by measuring droplet sizes at the termination of release experiments.

3. Results and discussion

The maximum accumulated release of [^{3}H]glucose after 72 hours was 14%. The release of glucose from the droplet phase was reduced when the droplets were hypertonic relative to the receptor buffer. In fact, a good linearity was achieved with flux of glucose versus the osmotic gradient as shown in Fig. 2 as long as the emulsion droplets were hypertonic ($R^2 = 0.9949$), but no significant effect on flux of glucose was observed when the emulsion droplets were hypotonic. Furthermore no significant shrinkage of hypotonic emulsion droplets was observed compared to isotonic conditions. The resistance to shrinkage might be explained by both Laplace pressure due to the interfacial tension of the droplets and the mechanical properties of the interface, i.e. interfacial elasticity.

Similar results have been reported with w/o/w emulsions. Adding salt to the internal water phase in multiple w/o/w emulsions reduces the release rate of hydrophilic drugs (Brodin et al., 1978; Omotosho et al., 1989; Hino et al., 1995; Jager-Lezer et al. 1997). This phenomenon is usually explained as a salting out effect of the surfactant layer which rigidifies the oil–water interface. In this study, the reduction in release rate was achieved by reducing the osmotic strength in the receptor buffer indicating another effect of salt. This suggests the existence of a relationship between the osmotically induced swelling of the water droplets, i.e. mean droplet diameter, and release rates. The higher the degree of swelling, the lower the release rate of glucose. Another study (Cunha et al., 1997) finds that the release rate of insulin from hypertonic w/o/w emulsion droplets is accelerated due to an osmotically induced breaking up of the emulsions at an osmotic gradient of 300 mOsm kg^{-1}. This shows that the effect of osmotic gradients on swelling and release properties is not trivial. More studies will be conducted to elucidate the swelling properties of the w/o emulsion.

Acknowledgements

The authors would like to thank Danisco Ingredients for providing polyricinolate polyglycerol.

References

Brodin, A.F., Kavaliunas, D.R., Frank, S.G., 1978. Prolonged release from multiple emulsions. Acta Pharm. Suec. 15, 1–12.

Cole, M.L., Whateley, T.L., 1997. Release rate profiles from theophylline and insulin from stable multiple w/o/w emulsions. J. Controlled Release 49, 51–58.

Cunha, A.S., Grossiord, J.L., Puisieux, F., Seiller, M., 1997. Insulin in w/o/w multiple emulsions: preparation, characterization and determination of stability towards proteases in vitro. J. Microencapsulation 14, 311–319.

Davis, S.S., Hadgraft, J., Palin, J.K., 1985. Medical and pharmaceutical applications of emulsions. In: Becher, P (Ed.), Encyclopedia of Emulsion Technology, vol. 2. Marcel Dekker, New York, pp. 159–238.

Florence, A.T, Whitehill, D., 1981. Some features of breakdown in water-in-oil-in-water multiple emulsions. J. Colloid Interface Sci. 79, 243–256.

Florence, A.T., Whitehill, D., 1982. Formulation and stability of multiple emulsions. Int. J. Pharm. 11, 277–308.

Hino, T., Takeuchi, H., Niwa, T., Kitagawa, M., Kawashima, Y., 1995. Analysis of drug release from diluted water/oil/water emulsions by a model of the rupture of oil membrane. J. Pharm. Pharmacol. 47, 1–7.

Jager-Lezer, N., Terrisse, I., Bruneau, F., et al., 1997. Influence of lipophilic surfactant on the release kinetics of water-soluble molecules intrapped in a w/o/w multiple emulsion. J. Controlled Release 45, 1–13.

Kim, C.K., Kim, S.C., Shin, H.J., et al., 1995. Preparation and characterization of cytarabine-loaded w/o/w multiple emulsions. Int. J. Pharm. 124, 61–67.

Miyakawa, T., Zhang, W., Uchida, T., Kim, N.S., Goto, S., 1993. In vivo release of water-soluble drugs from stabilized water-in-oil-in-water (w/o/w) type multiple emulsions following intravenous administrations using rats. Biol. Pharm. Bull. 16, 268–272.

Nakhare, S., Vyas, S.P., 1997. Multiple emulsion based systems for prolonged delivery of rifampicin: in vitro and in vivo characterization. Pharmazie 52, 224–226.

Omotosho, J.A., Whateley, T.L., Florence, A.T., 1989. Release of 5-fluorouracil from intramuscular w/o/w multiple emulsions. Biopharm. Drug. Dispos. 10, 257–268.