International Journal of Pharmaceutics, 65 (1990) 133–136
Elsevier

IJP 02200

Notes

Retard release from a flocculated emulsion system

R.S. Okor

Department of Pharmaceutics, University of Benin, Benin City (Nigeria)

(Received 5 January 1990)
(Modified version received 7 May 1990)
(Accepted 1 June 1990)

Key words: Emulsion; Retard release; Flocculated emulsion system; Emulsion globule structure

Summary

Coarse oil-in-water (o/w) emulsions stabilized by glycerol monostoarate have been converted (by addition of polysorbate 20) to a flocculated structure consisting of a cluster of fine oil globules and narrow, tortuous aqueous channels. The mean apparent interglobular space in the glycerol monostearate emulsion (A) was 26 ± 11 μm, and in the glycerol monostearate-polysorbate emulsion (B) the mean space was 1 ± 0.8 μm. In vitro release rates of chloroquine phosphate from the emulsions at 37°C were 1.5 mg h^{-1} (A) and 0.5 mg h^{-1} (B). Oral bioavailability in rats in 3 h was 10.3 ± 2 and 7.5 ± 1.1 μg/ml, respectively. The retard release effect observed in B relates to the greater tortuosity of aqueous diffusion channels in its structure, and its low rate of diffusive mixing with aqueous fluids.

Solutes may be entrapped in the internal aqueous phase of water-in-oil (w/o) emulsions for sustained release applications, however, the irritancy of the oil dispersion medium limits their usage. Redispersion of the w/o emulsion in an aqueous medium forms a multiple w/o/w emulsion which is safer for biological application, but at the same time less stable. For instance, osmotic water influx causes swelling and eventual rupture of medicated internal aqueous droplets in w/o/w multiple emulsions (Florence and Whitehill, 1981; Okor, 1988). Now, oil globules in a simple oil-in-water (o/w) emulsion constitute barriers which obstruct the diffusive flow of water-soluble molecules. In certain o/w emulsions, the oil phase can be reduced to numerous fine globules which are clustered together (i.e. a flocculated structure). Release of a water-soluble drug from such a flocculated system occurs via the tortuous aqueous channels. In certain situations where the emulsion is not stirred (to prevent mixing with the biological fluid), this approach may be explored for retard and sustained release applications. Such an approach has not been reported in the literatures, and hence the present study was undertaken.

In this investigation, two types of emulsion identical in content of oil phase (25% v/v) but varying in globule structure (size, number, and packing) were prepared as follows: 1.25 g glycerol monostearate (BP grade, supplied by Hallewood Chemicals, U.K.) was dissolved in arachis oil (25 ml). The oil had an acid value of 0.46 and saponification value of 193, weight/ml at 30°C, 0.892 g, and was obtained locally and filtered before use. The oil was added gradually to tragacanth mucilage (1.5% w/v aq., 75 ml) containing the drug

Correspondence: R.S. Okor, Department of Pharmaceutics, University of Benin, Benin City, Nigeria.

chloroquine phosphate (20 mg/ml). The preparation was stirred continuously (10 min at 1500 rpm) using a Silverson emulsifier (model V5104) fitted with a dispersator head; this emulsion was designated A. In another formulation (B), arachis oil (25 ml) containing glycerol monostearate (1.25 g) was emulsified in 75 ml tragacanth mucilage (1.5% w/v aq.) containing 2% v/v polysorbate 20 (Merck, Schuchardt) and the drug (20 mg/ml). Both emulsions were of the o/w type, as verified by staining tests.

Drug release tests on the emulsions and the tragacanth mucilage were carried out using dialysis methods. The dialysis membrane derived from an acrylate-methacrylate copolymer (trade name; Eudragit RL 100, Rhom Pharma, Darmstadt) was applied on a porous support (Whatman No. 1 filter paper) by immersion of the paper in a 5% w/v solution of the polymer in ethanol (i.e. absolute alcohol BP) for 10 s, followed by drying at 70 °C for 10 min. This coating procedure was repeated, yielding membranes of thickness 10 ± 1.5 μm; the membrane area exposed to drug solution in the dialysis cell was 5 cm^2. The cell was similar in design to the apparatus described by Luttinger and Cooper (1967), however, the donor fluid in the cell was left unstirred to simulate the in vivo situation where mixing with aqueous biological fluids would be minimal, e.g. intradermal, intramuscular sites, and the rectum. To measure drug release, the drug solution (10 ml, 20 mg/ml) in tragacanth mucilage or a sample of the medicated emulsion (10 ml) was filled into the cell which was then immersed in the leaching fluid (800 ml water maintained at 37 ± 0.5 °C and stirred at 150 rpm with a Gallenkamp single-blade stirrer). At a number of intervals, samples (5 ml) were withdrawn from the leaching fluid and analysed for content of chloroquine at λ_{max} 257 nm using a Unicam SP500 spectrophotometer. The experiment was carried out in quadruplicate; individual results were reproducible to $\pm 9.5\%$ of the mean.

A preliminary oral bioavailability test was also carried out on the medicated emulsions and the mucilage using rats (Wistar strain, average body wt 0.2 kg) as models. Five rats (previously fasted 24 h) were each given emulsion A via a stomach tube (1.3 ml). A second set of five rats were each given emulsion B (1.3 ml), while a third set received the medicated mucilage (1 ml). These volumes were equivalent to a 20 mg dose of chloroquine phosphate. 3 h after oral administration of the drug, the rats were killed, and 1 ml blood withdrawn from each rat via cardiac puncture. The blood samples were alkalinized, heated to lyse the red blood cells and then extracted first with chloroform and the chloroform layer re-extracted with dilute (0.1 N) HCl. Details of the extraction procedure have been described elsewhere (Okor and Nwankwo, 1988). The absorbance of the extracts was determined at λ_{max} 257 nm. A detailed pharmacokinetic study was not carried out at this stage of the work; the 3 h sample point was selected on the basis of a previous report (Owoyale et al., 1981) that oral chloroquine reached peak blood levels in the rabbit within 2–4 h.

The structure of the emulsions, including globule size and number, and the apparent interglobular space (i.e. the apparent distance of closest approach of two adjacent oil globules) were studied using photomicroscopy as described earlier (Okor, 1988). The channels in a close-packed emulsion will be multidimensional, hence the term 'apparent' was applied to the measured interglobular spaces. To evaluate mean globule size and number, a sample of emulsion B only was diluted 1/20 with the mucilage before photomicroscopy. Dilution of emulsion A was not necessary as globules were considerably less numerous in this emulsion. Assessment of apparent interglobular space was carried out using undiluted emulsion samples; 50 such spaces were randomly sized. For each structural analysis three representative photomicrographs were examined. The mean globule size or apparent interglobular space ($\bar{x}$) was obtained from the expression;

$$\bar{x} = \frac{\sum f_x}{\sum f}$$

where f is the frequency of each size x. Possible dilution of the emulsion by diffusive mixing with biological fluids at the site of administration was simulated as follows: water (10 ml) was added

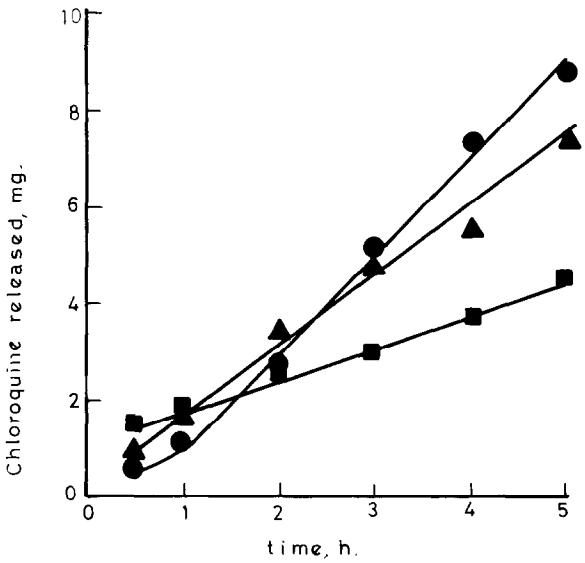

Fig. 1. Amounts of chloroquine released from emulsions A (▲), B (■), and tragacanth mucilage (●) having equivalent drug concentration (20 mg/ml of the mucilage).

gently to the emulsion sample (10 ml) and vice versa in a 25 ml glass measuring cylinder and allowed to stand for 5 h at 37 °C. The % increase in the emulsion volume was noted and taken as an index of diffusive mixing.

The results of the in vitro release experiment (Fig. 1) showed that the drug (chloroquine phosphate) was released at a faster rate from the mucilage compared with the emulsions, the release from emulsion A being in turn faster than the rate from B. The amount released vs time plots were generally linear over the 5 h test period, indicating a zero-order flux, The release rates obtained from the slopes of the plots were as follows (in units of mg h^{-1}): 2.2 (mucilage), 1.5 (emulsion A), 0.5 (emulsion B). Viscosity affects solute diffusivity in an inverse manner (Flynn et al., 1974); the viscosities of the preparations decreased in the order: emulsion B > A > musilage. Nevertheless, the dispersion medium (i.e. the mucilage) was also the diffusion medium in the three preparations, therefore, the differences in drug release rates cannot be attributed to the differences in viscosity, but rather, to structural differences. The mucilage was of course structureless; as can be seen in Table 1, the oil globules in emulsion A were few in number, and sparsely distributed leaving wide aqueous channels. In B, the globules were fine, numerous, and clustered, leaving narrow and tortuous aqueous channels (i.e. a flocculated structure). About 80% of the apparent interglobular spaces in emulsion B were below measurable sizes. The oil volume fraction remained constant (0.25) but the increased globule number and hence increase in surface area in B led to the clustering of the oil globules and the formation of narrow, tortuous aqueous channels.

TABLE 1

Structural properties of the emulsion globules

Emulsion	Globule size (μm) (mean ± SD)	Globule number per field	Apparent distances for closest approach (μm)
A	46 ± 5	42 ± 3	26 ± 11
B	3.8 ± 0.2	887 ± 124	1 ± 0.8

Based on this structrual feature, a model for the retard release from emulsion B is given in Fig. 2. Under conditions where stirring was omitted, a depletion zone was formed at the emulsion-membrane interface after the initial release of drug from this zone. In B, the structural feature of this zone will be characterized by narrow and tortuous channels (due to the cluster of fine globules), whereas A will feature relatively wide aqueous

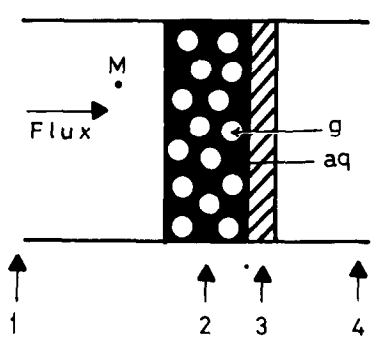

Fig. 2. Hypothetical model for the diffusion layer controlled drug release from an o/w emulsion, A molecule (M) is released from the emulsion bulk (1) by diffusion first through the tortuous aqueous channels (aq) in the zone of depletion (diffusion layer (2)) and then through the membrane (3) before exiting into the leaching fluid (4); g, oil globule.

channels (owing to the large globules being sparsely distributed). This zone of depletion forms part of the diffusion barrier and may contribute to the overall resistance significantly. For instance, molecular flux (J) through the diffusion layer is governed by the theory (Flynn et al., 1974):

$$J = \frac{\partial M}{\partial t} = D\frac{(1-Q)}{H}C_0 \quad (1)$$

and

$$H = hz_0 \quad (2)$$

where M is the amount of drug transferred in time t, C_0 the initial donor concentration, D the diffusion coefficient, Q the disperse (oil) phase volume fraction, H the path length of tortuous aqueous channels, h the thickness of the diffusion layer, and Z_0 the tortuosity factor. The latter is not readily quantifiable, but in the system studied it relates directly to the globule number. The slower release from B is therefore explained on the basis of increased tortuosity of aqueous channels in the diffusion layer.

Dilution of the o/w emulsion with biological fluids in vivo will lead to a loss of the retard release effect. In the in vitro test no measurable diffusive mixing of the emulsion with water was observed during a period of 5 h, suggesting that this tendency may also be low at biological sites. In the G1 tract gut movement was expected to cause some degree of mixing of the emulsion sample with G1. Fluid, but even here retard release from emulsion B was still evident, based on the data for 3 h oral bioavailability listed in Table 2.

The results suggest that diffusive mixing of the test emulsion with biological fluids was negligible and that the retard release of a water-soluble drug may be realised in vivo. On the other hand, the excessive subdivision and flocculation of oil globules have important implications on drug release and bioavailability from topical formulations utilizing the o/w base.

TABLE 2

Chloroquine blood level in rats, 3 h after oral administration of the emulsion samples and mucilage

Rat No.	Mucilage	Chloroquine level (μg/ml)	
		Emulsion A	Emulsion B
1	14.5	12.5	6.2
2	9.0	10.0	9.5
3	15.1	8.5	6.5
4	10.2	13.2	8.2
5	12.5	7.5	7.2
Mean	12.3±2	10.3±2	7.5±1.1

Dose administered, 20 mg; average body weight of rats 0.2 kg.

References

Florence, A.T. and Whitchill, D., Some features of breakdown in water-in-oil-in-water multiple emulsions. *J. Coll. Interface Sci.*, 79 (1981) 243–256.

Flynn, G.L., Yalkowsky, S.H. and Roseman, T.J., Dispersed phases and barrier property in mass transport phenomena and models: Theoretical concepts. *J. Pharm. Sci.*, 63 (1974) 479–510.

Luttinger, M. and Cooper, C.W., Improved dialysis membranes for the artificial kidney. *J. Biomed. Mater. Res.*, 1 (1967) 67–81.

Okor, R.S., Effect of chloroquine on the globule structure of certain water-in-oil-in-water (w/o/w) multiple-emulsions. *Pharm. World. J.*, 5 (1988) 312–316.

Okor, R.S. and Nwankwo, M.U., Chloroquine absorption in children from polyethylene glycol base suppositories. *J. Clin. Pharm. Ther.*, 13 (1988) 219–223.

Owoyale, J.A., Ayodele, J.T. and Aliu, Y.O., Influence of Vernonia amygdalina on chloroquine blood level in the rabbit. *Nigeria J. Pharm.*, 12 (1981) 13–15.