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Note

The effect of acacia, gelatin and polyvinylpyrrolidone on chloroquine transport from multiple w/o/w emulsions

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Summary

The formation of multiple w/o/w emulsions with improved stability due to the formation of interfacial complex films between acacia, gelatin, polyvinylpyrrolidone and sorbitan monooleate is described. The long-term stability of the emulsions as assessed by microscopy showed no significant changes in w/o/w emulsions prepared with acacia in the internal phase, indicating good stability in these systems. Multiple emulsions containing chloroquine phosphate in the internal phase and which had been stored for 2 weeks surprisingly showed a reduced rate of release of chloroquine phosphate as compared with freshly prepared emulsions, suggesting that the release of chloroquine phosphate from these systems occurs by the process of diffusion as opposed to the physical breakdown of emulsions. It is suggested that the intramuscular administration of chloroquine in the form of w/o/w emulsions could reduce the frequency of administration, improve patient compliance and increase the therapeutic efficacy of chloroquine. The drug can be formulated as a single dose system in which the starting dose is incorporated into the external phase while the maintenance dose is encapsulated in the internal phase of the emulsion.

Multiple w/o/w emulsions are complex systems in which both types of emulsions (i.e., w/o and o/w) exist simultaneously and require at least two stabilizing surfactants, one having a low HLB to form the primary emulsion, the other having a higher HLB to achieve secondary emulsification (Frenkel et al., 1983; Florence et al., 1989). The migration of surfactant from one interface to the other on formation of the completed multiple system is one of the causes of instability. A stabilising film can be formed through the interfacial interaction between macromolecules such as albumin or a polyanion such as polyacrylic acid in the internal aqueous phase and lipophilic non-ionic surfactant in the oil phase (Law et al., 1984, 1986).

Previously, we reported results on the stabilization of w/o/w emulsions via interfacial interaction between bovine serum albumin in the internal aqueous phase and Span 80 in the oil phase (Omotosho et al., 1986a,b). Multiple w/o/w emulsions with enhanced stability were prepared with a range of oil phases, viz., octane, dodecane, hexadecane, cyclohexane, toluene and isopropyl myristate. However, since the use of multiple w/o/w emulsions shows most promise in the area of pharmaceutical sustained release preparations, the present investigation was undertaken in order

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to examine the potential of the more acceptable pharmaceutic oil for preparing w/o/w emulsions stabilised by interfacial interaction between sorbitan monooleate (Span 80) and acacia (Hopkin and Williams, U.K.), gelatin (BDH, U.K.) and polyvinylpyrrolidone (Aldrich, U.K.).

The w/o/w emulsions were prepared via a two-stage emulsification procedure with the aqueous phase containing 10 mg/ml of chloroquine phosphate (B.P grade) and 2% w/v of each of the macromolecules (acacia, gelatin, polyvinylpyrrolidone). Soybean oil containing 10% w/v Span 80 (Honeywell-Atlas, U.K.) served as the oil phase. Emulsification was carried out using a Rotamixer (Hook and Tucker Instruments) to produce the w/o emulsions. One part (by vol.) of the primary w/o emulsions was further emulsified with one part of water containing 1% Tween 80 (Honeywell-Atlas) as the secondary emulsifier.

The emulsions were prepared and stored in sealed glass vials at room temperature. Preliminary work showed no significant drug absorption by the Visking dialysis tubing in drug release experiments and the glass vials during storage of emulsion. Immediately after preparation and for various storage times, samples of emulsions were analysed by microscopy through measuring the alteration in internal aqueous and multiple oil droplet size distributions and the change in number of multiple to simple oil drops. Before sizing, samples were diluted 10 times with the external phase and about 500 droplets were counted and sized.

A DT type dissolution rate apparatus (Erweka-Apparatabau) was used for the study of release rates. Visking dialysis tubing was washed several times with distilled water and left to soak in distilled water before use. Immediately after preparation and following 2 weeks of storage, 5 ml of w/o/w emulsions containing chloroquine phosphate were pipetted into a bag which was made from the dialysis tubing, tied double at each end, and placed in 700 ml dialysis medium (distilled water) maintained at 37 °C with constant stirring at 150 rpm. The amount of chloroquine phosphate released was determined from the absorbance at $\lambda_{max} = 345$ nm using a UV spectrophotometer (Varian series 634). Controls were determined as described below. Each release rate was calculated from the mean of at least 3 experiments.

The multiple oil droplets varied in size depending on which macromolecules were present in the internal phase. The mean number diameter of multiple oil droplets of w/o/w emulsions prepared with acacia as the complexing macromolecule was found to be 36.7 μm. The corresponding values for gelatin and PVP emulsions were 44.8 and 27.3 μm, respectively (Table 1). There appeared to be no significant change with time in the number of multiple drops of w/o/w emulsions prepared with 2% w/v acacia in the internal phase, indicating good stability for these systems. Although the number of multiple drops decreased on storage for emulsions stabilised by gelatin and PVP in the internal phase, these systems were found to be more stable than emulsions prepared

TABLE 1

Changes in the mean number diameters of the internal and multiple oil droplets of w/o/w multiple emulsions

Time of preparation (weeks)	Mean droplet diameter (μm)					
	Acacia		Gelatin		PVP	
	Internal droplet	Multiple oil droplet	Internal droplet	Multiple oil droplet	Internal droplet	Multiple oil droplet
0	2.4	36.7	2.5	44.8	1.6	27.3
1	2.4	37.3	2.7	43.6	1.7	27.4
2	2.6	37.5	2.6	45.3	1.9	27.8
4	2.7	38.7	2.7	46.1	1.9	28.3
6	2.8	38.4	2.8	46.9	2.0	28.9
8	2.9	39.2	3.1	47.0	2.0	29.5

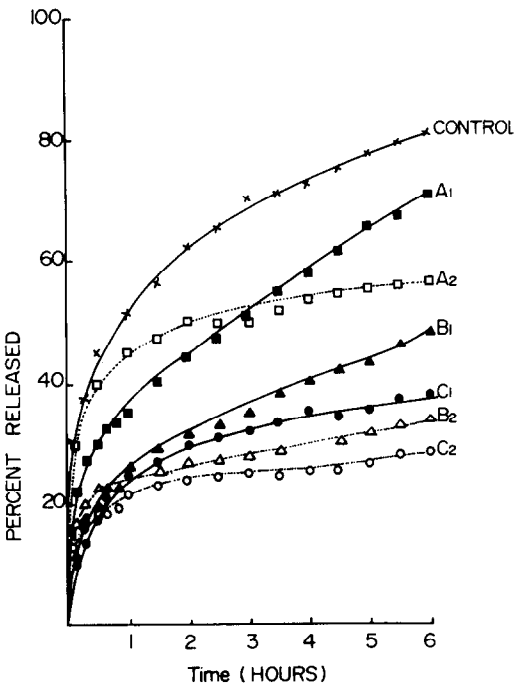

Fig. 1. Profile of chloroquine phosphate release from w/o/w multiple emulsions. A_1, freshly prepared PVP emulsions; A_2, PVP emulsions stored for 2 weeks; B_1, freshly prepared gelatin emulsions; B_2, gelatin emulsions stored for 2 weeks; C_1, freshly prepared acacia emulsions; C_2, acacia emulsions stored for 2 weeks.

with free Span 80 as the primary emulsifier. The enhanced stability of w/o/w emulsions stabilised by interfacial complexation between non-ionic surfactants and macromolecules may be attributed to complex formation at the interface which results in a rigid film from which the droplets rebound and remain free after collision.

The results obtained on in vitro release of chloroquine phosphate from freshly prepared w/o/w emulsions and emulsions stored for 2 weeks are shown in Fig. 1. The release of encapsulated solute from w/o/w emulsions and its subsequent transport through the dialysis membrane were, as expected, slower as compared to those of the aqueous solution used as reference. Chloroquine phosphate was released more rapidly from multiple emulsions formulated with PVP in the internal aqueous phase due either to the effects of instability of the emulsion or enhanced rate of diffusion because of the small droplets (large surface area) of these emulsions (Omotosho et al., 1989a).

The release rates of chloroquine phosphate were extended from multiple w/o/w emulsions. However, emulsions prepared with acacia in the internal aqueous phase and Span 80 in the oil phase sustained release of chloroquine phosphate more effectively than in the case where gelatin or PVP was in the internal phase. The reduced release rates of chloroquine phosphate from w/o/w emulsions imply interfacial barrier-controlled release in which the drug contained in the internal phase would be released at a rate governed by its ability to partition into and diffuse through the interfacial film and the oil membrane separating the two aqueous phases. The factors that determine the differences in rates of release for these systems appear to be the droplet size of the internal aqueous phase and the mechanical strength of the interfacial film at the w/o interface.

Multiple emulsions stored for 2 weeks surprisingly showed a lower rate of release of chloroquine phosphate as compared with those freshly prepared. The reduced rate of chloroquine phosphate transport from stored emulsions may theoretically be attributable to two main factors: (i) the interfacial film resulting from the interfacial interaction between Span 80 and the macromolecule might become more rigid with time, thereby forming a more efficient barrier against the transport of encapsulated chloroquine phosphate; (ii) the coalescence between droplets, which would lead to an increase in droplet size, reduction in interfacial area available for drug transport and reduced release rate for chloroquine phosphate. However, as shown in Table 1, no significant increase was observed in the mean droplet size, suggesting that chloroquine phosphate is released from these systems via the process of diffusion across the liquid membrane as against the physical breakdown of emulsions.

Chloroquine phosphate is one of the most effective and widely used antimalarial drugs. However, there are now reported cases of chloroquine-resistant parasites and increase in recurrent infections due partly to the intervals between doses becoming too widely spaced as a result of non-compliance with the dose regimen. The result of

this investigation is of practical significance as it may be possible to improve the therapeutic efficacy of chloroquine by formulating it as a single dose parenteral intramuscular injection with the starting dose incorporated into the external phase and the maintenance dose encapsulated in the internal phase of the emulsion. In the treatment of acute malaria, the primary aim is to eliminate rapidly the erythrocytic forms of plasmodia from the circulation by means of schizontocidal agents such as chloroquine. The drug incorporated into the external phase will provide free chloroquine for rapid release into the blood (Omotosho et al., 1989b) and this can be sustained by the maintenance dose encapsulated in the internal phase of the emulsion which will be released slowly at a rate governed by its diffusivity and the partition coefficient in the oil layer. It is suggested that the formulation of chloroquine in the form of w/o/w emulsions may be capable of replacing daily administration of the drug, enhancing patient compliance and increasing the therapeutic efficacy of the drug.

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