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EFFECT OF NON-IONIC SURFACTANT CONCENTRATION AND TYPE ON THE FORMATION AND STABILITY OF W/O/W MULTIPLE EMULSIONS: MICROSCOPIC AND CONDUCTOMETRIC EVALUATIONS

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ABSTRACT

W/O/W multiple emulsions with sodium salicylate as a model drug were prepared and evaluated for the effect of surfactant concentration and type on stability using microscopic and conductometric methods. Primary (W/O) emulsions were prepared with lipophilic surfactants (2-31% W/W relative to the oily phase). W/O/W emulsions were formed by mixing the primary emulsions with solutions containing 0.5 to 2% W/V hydrophilic surfactants. Optimum concentration of the lipophilic surfactant was 26% W/W. The optimum hydrophilic surfactant concentration was 1% W/V. Best stability was achieved with HLB 3.7 lipophilic and HLB 15.6 hydrophilic surfactants.

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INTRODUCTION

Multiple emulsions are complex systems that have been found promising as prolonged drug delivery systems (1,2,3), in drug overdose treatment (4), in separation science (5), and in the cosmetics industry (6). However, the inherent instability associated with these systems has baffled researchers (7,8,9,10). S. Magdassi et al. (11) correlated surfactant type and multiple emulsion stability using a titration method for the analysis of sodium chloride released from the internal phase, however, the surfactant concentration was not related to the globule size, and microscopic evaluation of the emulsions was not documented. The effect of emulsifier blend in the external phase of the emulsion on the yield of the emulsions was investigated by Magdassi and colleagues (12). T.K. Law et al (13,14) investigated the stabilization of W/O/W multiple emulsions by interfacial complexation of macromolecules and nonionic surfactants, and concluded that both the HLB values and surface activities of the surfactant have to be considered in the optimization of stable multiple emulsion formulation. The aims of this study were to evaluate the formation and breakdown of W/O/W emulsions, monitor the release of the drug from the internal phase by microscopic and conductometric evaluation and to improve the stability of emulsions by optimization of the concentration and type (HLB value) of the surfactants.

EXPERIMENTAL

Method of Preparation

The general formulations for the W/O primary and W/O/W multiple emulsions are shown below.

W/O Primary Emulsions

Mineral Oil	100 g
Lipophilic Surfactant	2-31% W/W
Dextrose Monohydrate	0.338% W/V
Sodium Salicylate	1% W/V
Deionized Water	100 ml

W/O/W Multiple Emulsion

Primary Emulsion	200 ml
Hydrophilic Surfactant	0.5-2.0% W/V
Deionized Water	100 ml

The W/O/W multiple emulsions were prepared by a two-step emulsification procedure. The internal phase of the W/O primary emulsion was slowly incorporated into the oily phase over a period of 5-8 minutes. The mixture was then passed through a colloid mill (Colby #2 1/2, Speco, Inc., Beverly, MA 01915) using a rotor-stator distance of 100 um. After passage through the mill, the emulsion was allowed to cool to room temperature. The primary emulsion was then stirred with 100 ml aqueous solution of the secondary surfactant for 2-3 minutes to produce the multiple emulsion.

Lipophilic Surfactants

Different formulations were prepared which contained 2%, 6.5%, 13%, 20%, 31% W/W relative to the oily phase of the following surfactants: sorbitan sesquioleate (Span 83) HLB 3.7, sorbitan monoleate (Span 80) HLB 4.3 and octyl polyoxyethoxyethanol (Triton Type X-15) HLB 3.6 One percent polyoxyethylene sorbitan monopalmitate (Tween 40) hydrophilic surfactant was employed in the external phase. Drug release into the external phase was determined two hours after preparation. Time of study for release of drug in the emulsions prepared with 20%, 26%, 31% of Span 83 was extended for 30 days.

Hydrophilic Surfactants

The effect of 0.5%, 1%, 1.5%, 2% W/V concentration of polyoxyethylene sorbitan esters - Tween 40 (HLB 15.6), Tween 84 (HLB 11) and Tween 81 (HLB 10) on the immediate release of drug was determined conductometrically. Sorbitan sesquioleate was used as the lipophilic surfactant in these formulations. The release of the drug from the internal phase of the Tween 40 formulations was studied for 30 days.

Conductometry

To measure the amount of sodium salicylate transferred from the internal to the external phase of the emulsion, the change in electrical conductivity with time was measured using a conductance meter (YSI model 32, Yellow Springs Instrument Co., Yellow Springs, Ohio 45387). One gram of W/O/W emulsion was

suspended in 100 ml external phase hydrophilic surfactant solution (.05 mg surfactant/ml). The mixture was allowed to settle for 15 minutes, after which the top oily layer was aspirated. The aqueous phase was analyzed with a conductance meter for the sodium salicylate released. The average of three readings was recorded for each determination and the corresponding concentration calculated from the calibration curve.

Micrography

All the emulsions were observed microscopically following preparation and throughout the time of study. For microscopic study, the emulsion samples were diluted about 20-fold with the continuous phase. Photomicrographs were taken at magnifications between 100x and 400x.

RESULTS AND DISCUSSION

The effect of lipophilic surfactant concentration on the release of drug after two hours is shown in Figure 1. Triton type X-15 formulations are not represented because the emulsions separated into two phases immediately after preparation. At the highest (31%) and lowest (2%) surfactant concentrations, more than 70% of the drug content was released immediately following emulsification - an indication that the emulsions were unstable. Phase reversal was observed in formulations prepared with 31% lipophilic surfactant. The concentration limits suggest that when there is excess or insufficient surfactant,

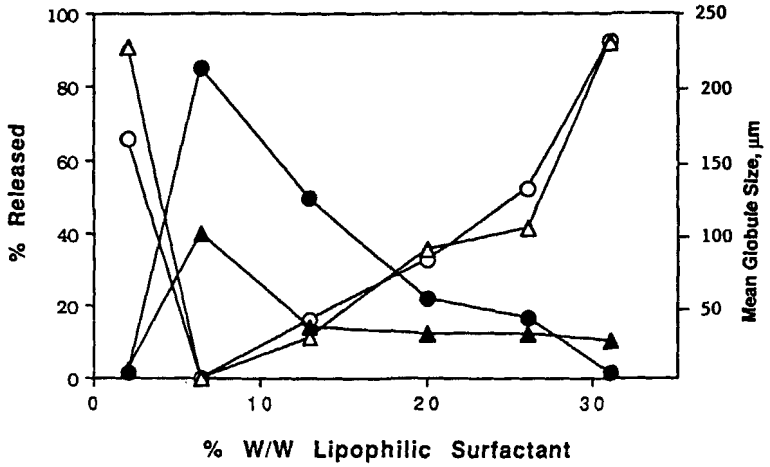

FIGURE 1

Effect of Lipophilic Surfactant HLB and Concentration on Mean Globule Size and Release of Sodium Salicylate from the Internal Aqueous Phase of W/O/W Emulsiions Two Hours after Preparation

O ● == Span 80 (HLB 4.3) Open Symbols = % Drug Released

Δ ▲ == Span 83 (HLB 3.7) Filled Symbols = Mean Globule Size (µm)

breakdown occurs. With 6.5% W/W lipophilic surfactant concentration, no drug was released.

Relating these observations to the mean globule size of the emulsions (also shown in Figure 1), at the upper and lower limit of surfactant concentration, the mean globule size was smallest (2 µm) because only simple, two phase emulsions resulted. At 6.5% lipophilic surfactant with no immediately drug release, the globule size was largest (250 µm) and rapidly coalesced. In simple two phase emulsions, smaller particle size is desirable for stablity, but in W/O/W emulsions, very small particle size

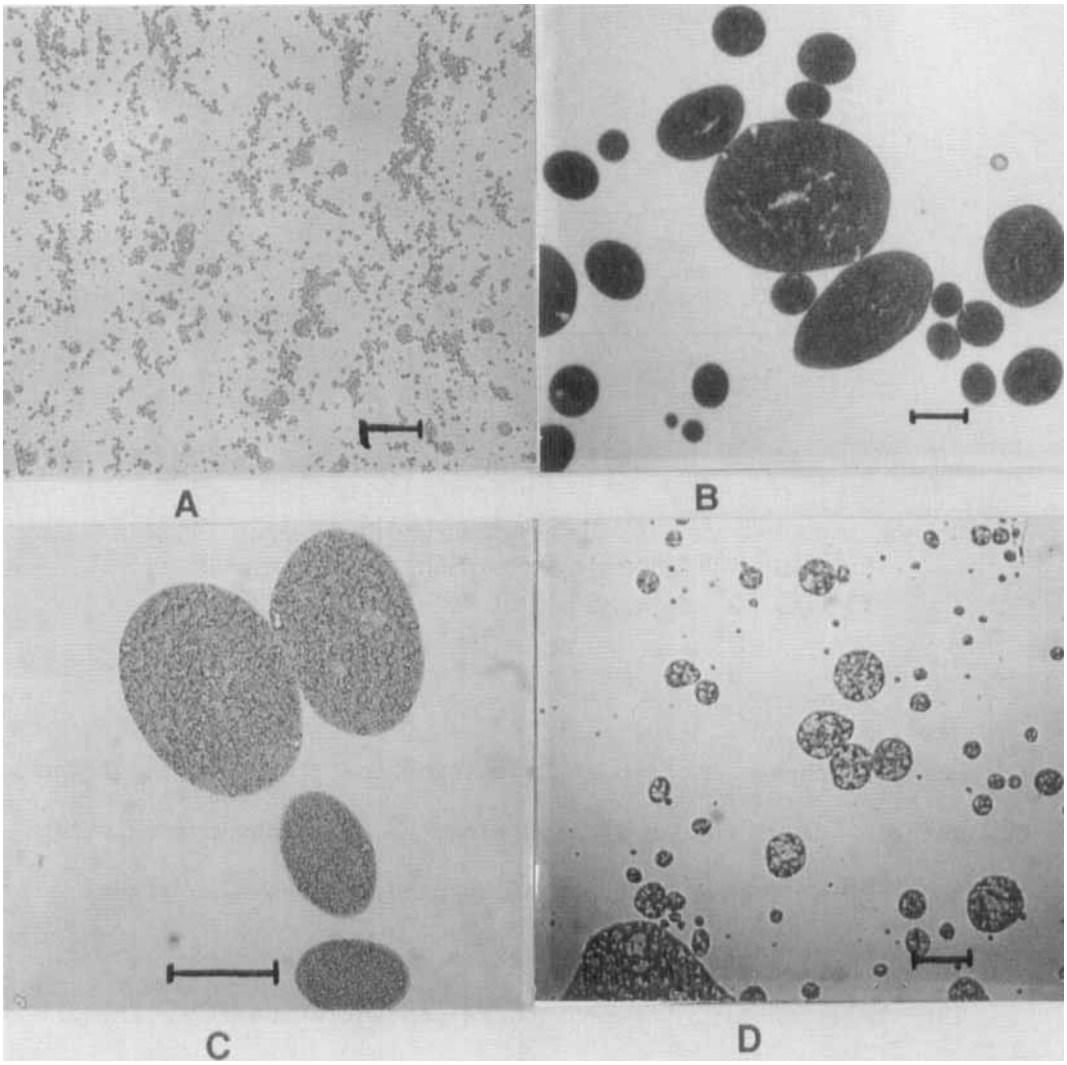

FIGURE 2

Photomicrographs of W/O/W Emulsions Containing Span 80 (A) 2%, (B) 6.5%, (C) 13%, (D) 26% W/W Immediately after Preparation
Bar (A) = 20 μm, (B, C, D) = 100 μm

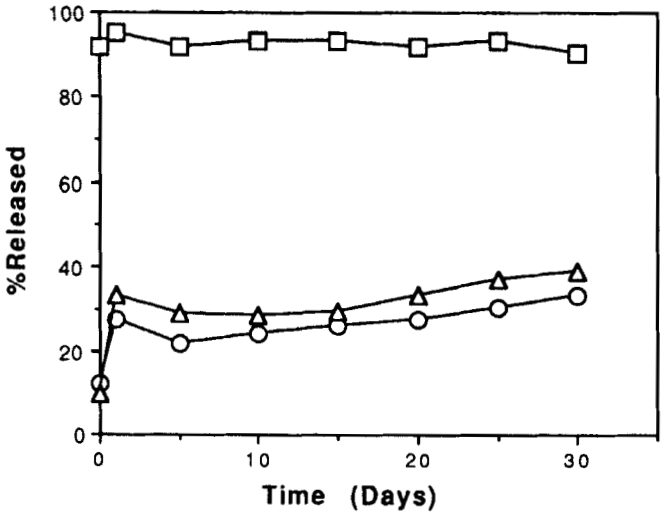

FIGURE 3

Effect of Age on the Release of Sodium Salicylate into the External Phase of W/O/W Emulsions with Different Lipophilic Surfactant Concentrations
❐ = 31%, Δ = 26% O = 20% Span 83

in the oily phase is often an indication that the W/O/W emulsion has broken down to an O/W emulsion. Micrographs representing four different concentrations of Span 83 are shown in Figure 2. Emulsions prepared with Span 80 have a similar appearance.

The relationship between three concentrations (20, 26, 31% W/W) of the lipophilic surfactant, Span 83, and the release patterns of the drug from aging emulsions is shown in Figure 3. At concentrations of 20 and 26% of the lipophilic surfactant, the release pattern was nearly identical, but when the lipophilic surfactant concentration was increased to 31% W/W, almost all the sodium salicylate was released immediately. The

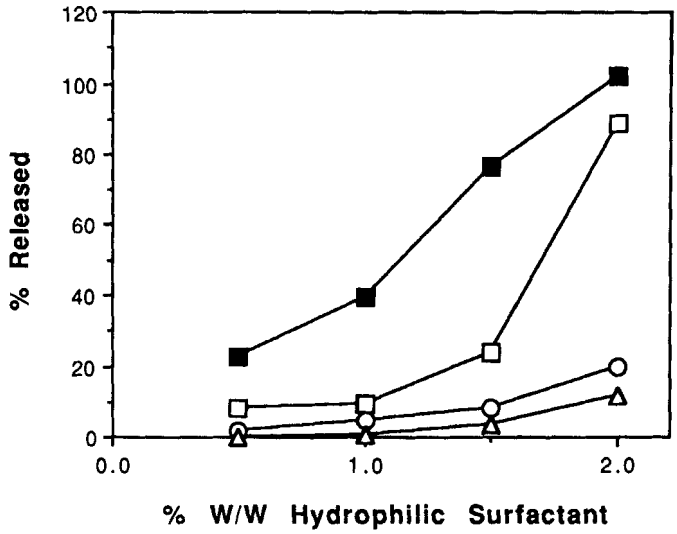

FIGURE 4

Effect of Hydrophilic Surfactants on the Release of Sodium Salicylate from the Internal Aqueous Phase of W/O/W Emulsions

❐ TWEEN 40 = Immediate Release

O TWEEN 85 = Immediate Release

Δ TWEEN 81 = Immediate Release

■ = Release from Emulsions made with TWEEN 40 after 30 days

optimum concentration for Span 80 was 13% but, generally, this surfactant produced less stable emulsions, perhaps because the relatively higher HLB value is more likely to favor O/W emulsions in the presence of a hydrophilic surfactant.

The relationship between hydrophilic surfactant HLB and the release of drug is represented in Fig. 4. The initial release of drug was greatest with Tween 40 (HLB 15.6), followed by Tween 85 (HLB 11) and Tween 81 (HLB 10). However, Tween 40 was the most suitable for longer studies because Tween 85 produced

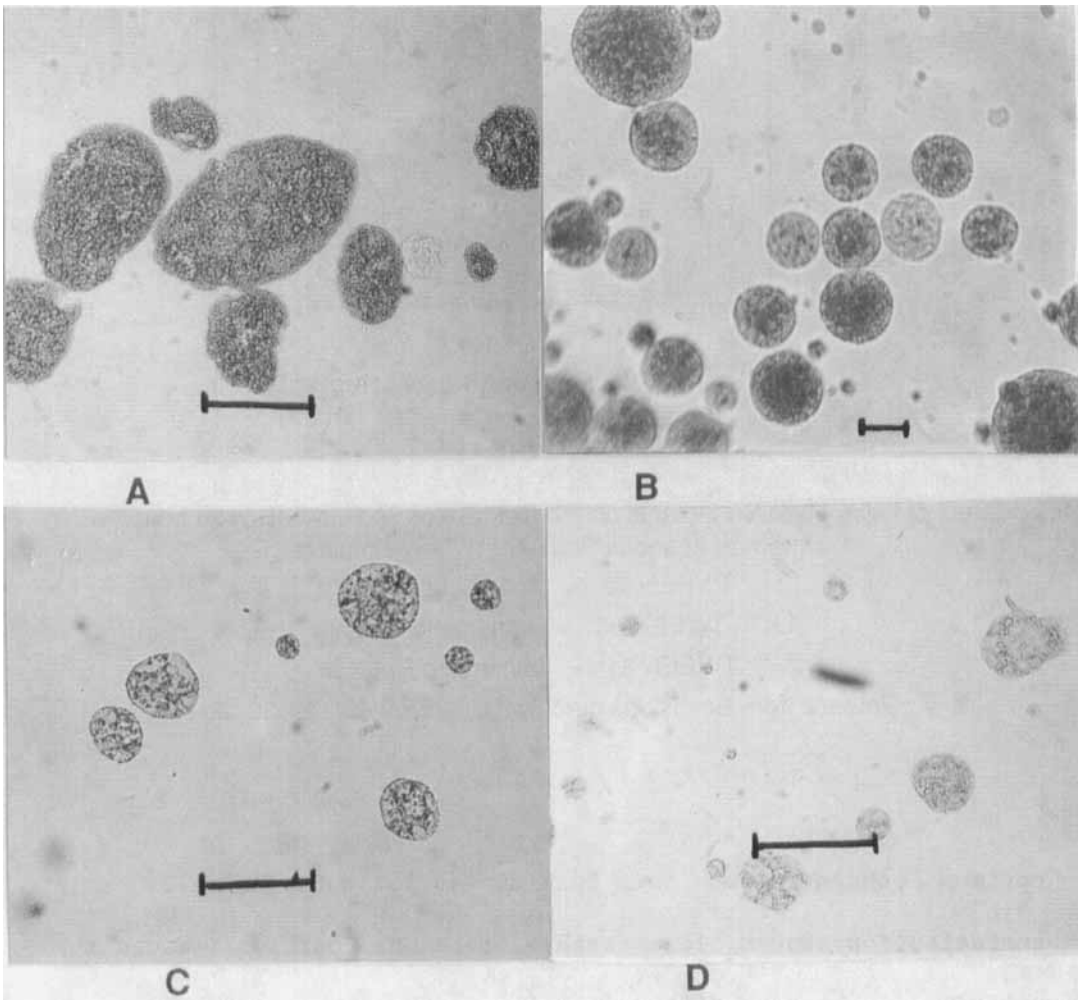

FIGURE 5

Photomicrgraphs of W/O/W Emulsion Containing TWEEN 40. (A) 0.5%, (B) 1%, (C) 1.5%, (D) 2% W/V Immediately after Preparation. Lipophilic Surfactant Concentration was 26% W/W. Bar (A, C, D) =100 µm, B = 20µm

unstable oil phase globules that could not be followed for more than 2 hours after preparation due to the separation of the two phases. Tween 81 also produced unstable oil phase globules despite the good initial drug retention.

The effect of the hydrophilic surfactant, Tween 40, on sodium salicylate released to the external phase after 30 days is also shown in Fig. 4. The higher the concentration, the greater the amount of drug released. At concentrations of 0.5%, 1%, 1.5%, 2% W/V, the percentages of drug released after 30 days were 18.2, 32,9, 65.5, 98.5%, respectively. Formulations with 0.5% Tween 40 had the least drug release, but the oil globules were less stable compared to formulations prepared with 1% Tween 40. Hence, 1% W/V hydrophilic surfactant was considered the optimum concentration. Micrographs of the emulsions immediately after preparation are shown in Figure 5.

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