PHARMACY

FORMULATION STUDIES IN MULTIPHASE EMULSION SYSTEMS

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ABSTRACT

The potential of multiple water-in-oil-in-water (w/o/w) emulsions as a drug carrier is dependent upon the extent of multiple droplet formation, the integrity of the multiphase structure formed, and the localisation of the drug or the biologically active agent in the inner-most phase. The studies indicate that predominantly stable multiple w/o/w droplets can be obtained with specific ternary compositions. As the two step method is used in the preparation of these emulsions, a drug can be localised within the internal aqueous phase by incorporating it in the disperse phase of the primary w/o emulsion, and hence these systems can function as vehicles or carriers for drugs.

KEYWORDS

Drug carriers; multiple emulsions; phase-within-a phase-within a phase; ternary phase diagrams; re-emulsification.

INTRODUCTION

Multiple emulsions are emulsion systems whose internal phases contain further dispersed phases. These systems can be simply described as systems consisting of a phase-within-a phase-within-a phase. These systems were accidentally discovered during phase inversion, (Seifritzr, 1925). Such systems however have a great potential in drug delivery since a drug or any biologically active substance can be enclosed in the innermost phase from where it may gradually diffuse out or be controlled to give a prolonged release (Brodin and Frank, 1978). Interest has therefore been shown in these systems as potential drug carriers for prolonged release (Davis, 1976).

Attempts have been made to use these systems to afford protection against micro-environmental hazards in some drug administration. Multiple w/o/w emulsion have thus been tried at the oral administration of insulin (Schichiri et al., 1974, 1978) though this procedure proved less satisfactory to the conventional parenteral insulin administration. These systems have also been found to be potentially useful in enzyme entrapment (Asher et al., 1976). They have equally been found use as liquid membranes for extraction purposes (Matuleviscius and Li. 1975).

The successful use of such systems for drug carrier and the other enumerated uses may however be dependent on the extent of the multiphase droplet formation in the system. Thus formulations yielding maximum multiphase droplet formation should be important for their application as drug carriers. The study therefore seeks to evaluate some of the factors that may lead to the maximisation of multiple droplet formation by means of the ternary phase diagram.

Ternary phase diagrams play a useful role in formulation studies. This approach facilitates the survey of various ternary compositions over an entire area, enabling the location of the exact combinations which best exhibit the desired results.

Burts (1965) using the ternary phase diagram approach evaluated the emulsion stability, relating the o/w stability to an appropriate area contoured in the phase diagram. Similarly, by the use of such, Lachampt and Villa (1967) demonstrated areas where fine, coarse, and unstable emulsions were formed on the phase diagram.

Multiple w/o/w emulsions were formulated and studied based on the phase diagram approach and employing the two step method of preparation (Matsumoto et al., 1976).

EXPERIMENTAL

Materials and Equipment

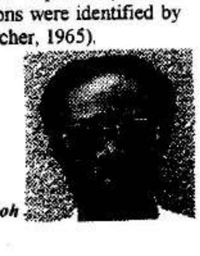
Cotton seed oil purchased from Real Dood Ltd., New Zealand, B. P. grade light liquid paraffin oil purchased from H. F. Stevens Ltd., Christchurch, New Zealand. Polyoxyethylene sorbitan monolaurate (Tween 20) obtained from Sigma Chemical Company, St. Louis, Missouri 63178, USA, and Sorbitan monooleate (Span 80) from Koch-Light Laboratory Ltd., Colnbrook, Burks, England.

Emulsification equipment consisted of a Watson Victor Ltd. Sorvall-Omni-mixer and a Fuyi Optical Co. Ltd., Tokyo, Japan microscope which was used for the examination of the emulsion droplets.

Method

A triangular phase diagram was constructed with the apices representing the internal aqueous phase, the oil phase containing Span 80, and the external aqueous phase containing the Tween 20, the components of the multiple w/o/w emulsion. The proportions of these components (water, oil Span 80 mixture and water Tween 20 mixture) were calculated according to the ternary phase diagram. A total of 54 formulations were examined for each oil phase with the concentrations of these components being varied at 10% intervals. The total weight of these components was 50gms.

Using the two step method of preparation Matsumoto et al (1976), the weighed water was mixed with the oil containing the Span 80 and emulsified for three minutes in a 100ml stainless steel chamber using the Sorvall omni-mixer at 10,000-11,000rpm. The product was then re-emulsified with the water containing Tween 20 at 1,500-1,600rmp for one minute. The emulsions were examined under a light microscope using both low (x100) and high power magnification (x400) for the types of emulsions formed and under the polarised microscope for liquid crystalline formation. Simple o/w and w/o emulsions were identified by phase dilution and conductivity tests (Becher, 1965).



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The observed types of emulsions were contoured on the phase diagram depicting the emulsions associated with those areas.

RESULTS AND DISCUSSIONS

The Figures 1 and 2 indicate the observed systems associated with the specific areas obtained with liquid paraffin and cotton seed oil used as the respective oil phases.

Figures 3 and 4 represent the photomicrographs of the sampled multiphase emulsions. From Figures 1 and 2, the types of emulsions observed from the various formulations are w/o, o/w, mixtures of w/o/w and o/w droplets and, dominantly w/o/w emulsions. Both oils, liquid paraffin and cotton seed oil produced similar emulsion types presumably because both oils easily form emulsions in the presence of surfactants when agitated with water. In the presence of an emulsifying agent, the interfacial tension between the oil and the water is reduced, thus aiding emulsion formation. The surface active agent also stabilised the emulsions.

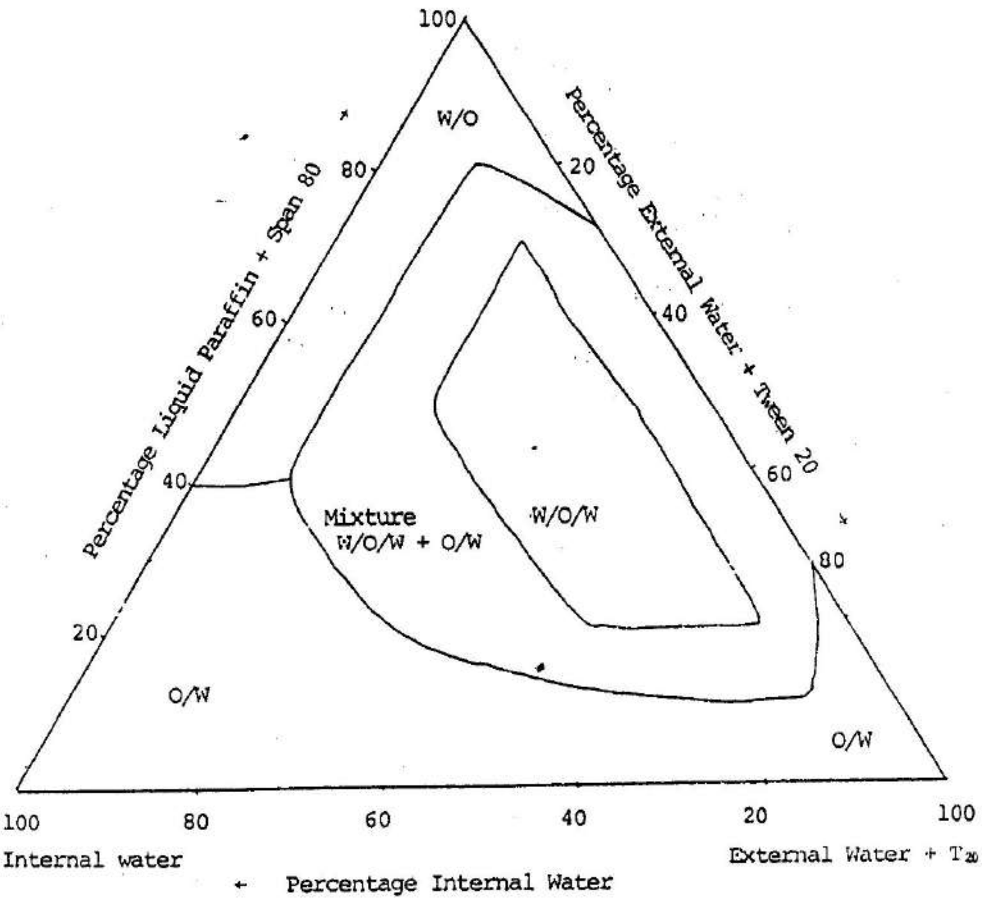

Fig.1. Tenary Phase Diagram Showing Emulsion Types

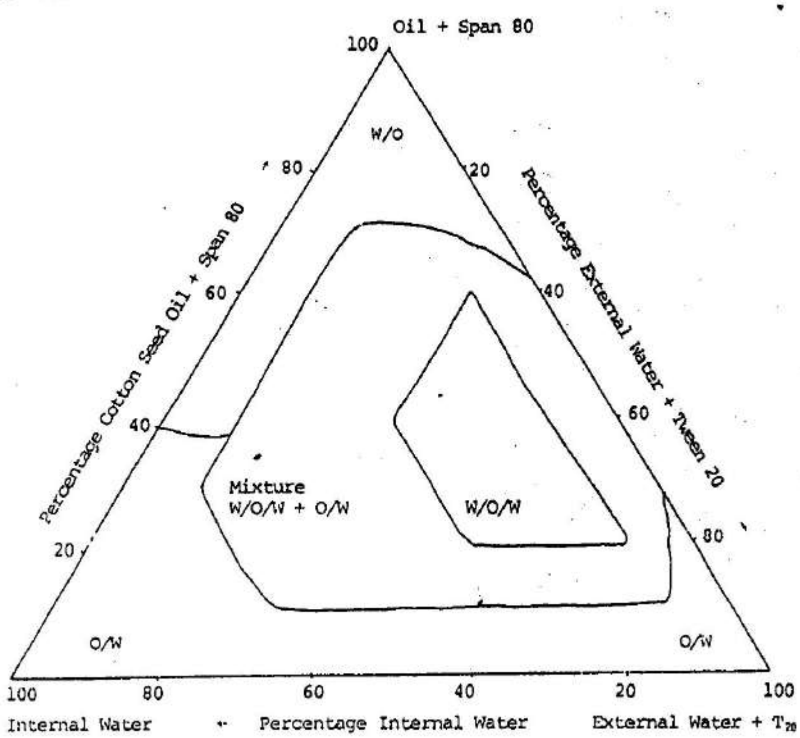

Fig.2. Tenary Phase Diagram Showing Emulsion Types

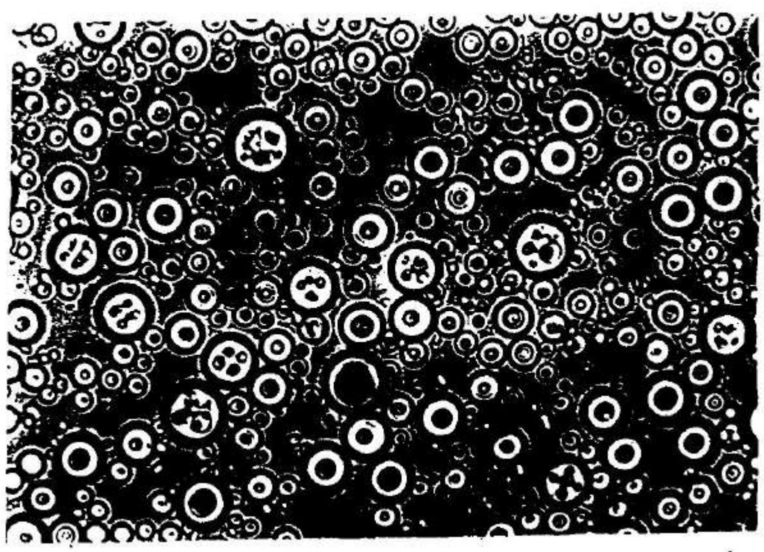

Fig. 3: Multiple w/o/w Emulsions – Oil Phase Liquid Paraffin

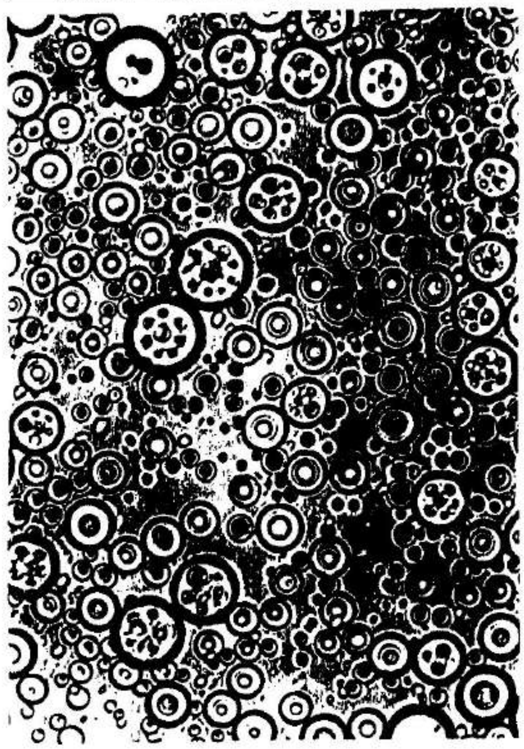

Fig. 4: Multiple w/o/w Emulsions – Oil Phase Cotton Seed

The mixtures of o/w and w/o/w produced surrounding the predominantly w/o/w regions observed in the phase diagrams Figures 1 and 2 may be due to the initial formation of unstable w/o emulsion which upon re-emulsification results in few w/o/w droplets that is some inversion of simple emulsion.

Increasing the proportion of the internal aqueous phase component, tends to produce less multiphase w/o/w droplets. However, when the internal aqueous phase component is between 10-30% v/v multiple w/o/w droplets become predominant. Above this percentage the internal phase in the w/o/w may render the initial primary w/o emulsion unstable because of high disperse phase concentration in the primary w/o emulsion and thus making it prone to reverting to the simple emulsion, during the re-emulsification stage.

Similarly, the oil phase and the external aqueous phase components of the w/o/w may also influence the predominance of the w/o/w in the formular by similar reasoning. From the phase diagram studies, the optimum volume fractions for cotton seed oil phase and secondary aqueous phase that produced predominantly w/o/w emulsions are 20-60% and 30-70% respectively. The volume fractions for liquid paraffin was 20-70% and 20-70% for the secondary aqueous phase.

In multiple (w/o/w) emulsion formulation, the phase volume ratios are of importance in the production of emulsions with predominantly multiphase structure. The internal aqueous phase component is critical in the multiple w/o/w formulation and the range appears narrow 10-30% as shown by the studies.

CONCLUSION

Ternary phase diagrams are useful in formulations and can aid in the formulation of multiphase disperse systems. Various disperse phase systems compositions were obtained in the ternary phase diagram. These include areas of w/o, o/w, mixtures of w/o/w and o/w and predominantly w/o/w areas. Formulations with the internal aqueous phase component between 10-30% produced dominantly w/o/w dispersed systems. Beyond this range there were less w/o/w formation.

The internal aqueous phase component is critical in multiple emulsion (w/o/w) formulation and the range appears to be between 10-30% as indicated by these studies.

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