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Characterization of Oil-in-Water Emulsions Prepared from Solid-State Emulsions: Effect of Matrix and Oil Phase

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Emulsions (o/w) were prepared from solid-state emulsions comprised of various matrix materials and oils and the resultant particle size properties determined. Results suggest that for those matrices that can form solid-state emulsions, the droplet size decreased as a function of time, as previously observed. The final droplet size was dependent on the oil utilized but was independent of the matrix material. The use of mineral oil resulted in the smallest droplet diameter (~1.5 μm) while isopropyl myristate resulted in the largest droplet diameter (~3 μm). With the exception of mineral oil, the oil/water interfacial tension was found to be directly proportional to the droplet diameter. The rate of emulsification appeared to be biphasic. The initial emulsification phase appeared to be independent of the matrix material while the terminal phase was a function of the matrix material. Most importantly, it was found that solid state emulsions could be prepared from a diverse, yet specific, list of matrices.

KEY WORDS: microemulsion; drug delivery; reconstitutable emulsions; particle size.

INTRODUCTION

Solid-state emulsions are solids, in some cases metastable solids, that, upon the addition of an aqueous phase, form dispersions. The procedure to prepare solid-state emulsions, to form either oil-in-water (o/w) or water-in-oil-in-water (w/ow) emulsions, has been previously reported by this laboratory (1). The utility of o/w and w/o/w emulsions for the administration of oil-soluble and water-soluble medicinals, respectively, is well established (2,3). Although the utility of disperse systems has been repeatedly demonstrated using conventional surfactant based systems. The inherent physical instability of conventional surfactant-based systems has, in many cases, prevented the commercialization of emulsion systems. In addition to storing solid-state emulsions as solids, solid-state emulsions are prepared without emulsifying agents. Due to the lack of emulsifying agents within solid-state emulsions, common toxicities and environmental concerns are not problematic, e.g., pH, temperature, tonicity. The lack of emulsifying agents has, however, meant that conventional theories of emulsification do not completely describe these systems.

The size distribution of the dispersion as a function of the matrix-to-oil composition (w/w) and time postemulsification has been reported (4). In this initial study (4), it was reported that the droplet size decreased and the initial trimodal distribution became unimodal as a function of time. Based on these early results it was evident that emulsions prepared from solid-state emulsions exhibited properties of both conventional emulsions and microemulsions. The observed particle size is analogous to that observed for conventional emulsions (5,6), while the kinetic properties appear analogous to microemulsions (7). Based on the ability of the droplet size to decrease as a function of time, emulsions prepared from solid-state emulsions appear to behave similar to microemulsions (8). Since solid-state emulsions do not contain emulsifying agents, the thermodynamic principles that describe microemulsions are not directly obvious.

Before it is possible to design a methodical study to investigate potential emulsification mechanisms and matrix/oil interactions, the characteristics of emulsions prepared from solid-state emulsions must first be evaluated. Questions still exist whether other matrix materials and oils can be utilized to prepare solid-state emulsions and how the properties of the aqueous emulsion will be changed.

The purpose of this study is therefore to determine if solid-state emulsions can be prepared with different matrices and oils and determine if there is any relationship between the properties of the dispersion and those of the matrices and oils.

MATERIALS AND METHODS

Potential matrix materials evaluated consisted of polyvinylpyrrolidone, PVP C-15 (USP, GAF Chemicals Corp., USA), lactose (hydrous, USP/NF, Paddock Laboratories, Inc., USA), maltose (monohydrate, Sigma Chemical Co., USA), sorbitol (70% USP, FCC, Pfizer Chemical Division, USA), mannitol (ACS reagent grade, Sigma Chemical Co., USA), dextrose (analytical grade, Mallinckrodt, Inc., USA), corn starch (food grade, CPC International, USA), sodium cyclamate (NF, City Chemical Corp., USA), Dipac (Amstar Corp., USA), sodium saccharine (Purified, Fisher Scientific Co., USA), xylitol (USP/NF FCC, crystalline, American Xyrofin, Inc.), maltodextrin (Grain Processing, Inc., USA), and sucrose (reagent grade, EM Science, USA). All reagents were used as supplied. Oil phases such as cod liver (City Chemical Corp., USA), corn (MCB Manufacturing Chemists, USA), isopropyl myristate (anhydrous, Sigma Chemical Co., USA), heavy mineral (USP/FCC, Fisher Scientific, USA), and olive oil (super refined, Croda Inc., USA) were used as supplied. Double-distilled deionized water was used throughout.

Preparation of Solid-State Emulsion. Solid-state emulsions were prepared by adding a matrix material (75–95%, w/w) and an oil phase (25–5%, w/w) to a round-bottom vacuum flask. The total batch size ranged from 4 to 6 g. Double-distilled deionized water (approximately 10 mL) was then added to the flask. The flask was fitted to a rotary evaporator and partially immersed in a water bath (approximately 60°C), while vacuum was applied (approximately 5 mm Hg). The mixture was slowly rotated until a dry film or foam was produced. The resulting solid was stored in a desiccator containing calcium carbonate at room temperature.

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Determination of Emulsion Particle Size. The final aqueous O/W dispersions were prepared by the addition of an aqueous phase to the prepared solid-state emulsion. For each composition, 50 mg of the respective solid-state emulsion was added to 10.0 mL of water. Preliminary experiments indicated that the resulting O/W emulsion should not be stored in glass or vigorously agitated, e.g., greater than 300 rpm. It was therefore necessary to prepare the samples in plasticware and not use any mixing that would impart high rates of shear or inertia.

The droplet size of the resultant oil-in-water emulsion was determined at room temperature with a Microtrac FRA (Leeds and Northrup, USA). Approximately 9.5 mL of water was added to the sample cell (10.0-mL capacity). The respective emulsion was then added, in a dropwise manner, to the sample cell until the proper sample loading was achieved (2). The particle size distribution was then determined as a function of time postemulsification.

Determination of Interfacial Tension. All Interfacial tension measurements were determined using a thermostated interfacial tensiometer (K-8, Kruss USA). Double-distilled water was added to a carefully cleaned sample vessel. The ring ($R = 5.935$ cm, $R/r = 53.166$) was lowered into the water, followed by the addition of the respective oil phase. The sample temperature was allowed to equilibrate to 25°C. The interfacial tension was determined to be that force required to move the ring from the aqueous phase to the oil phase. The interfacial tensions reported are the means (±SD) of three determinations.

RESULTS AND DISCUSSION

Numerous materials were evaluated based on physical and structural similarities for their ability to form solid-state dispersions or glasses. Of those materials evaluated, PVP, sodium cyclamate, sodium saccharine, maltodextrin, xylitol, and sucrose were able to form solid-state emulsions. It is interesting to note that while sucrose can be used to prepare solid-state emulsions, lactose, maltose, and dextrose cannot form solid state emulsions. The same observation can be made for the sugar alcohols in which xylitol formed solid-state emulsions but mannitol and sorbitol did not form solid-state emulsions. The fact that not all molecules of a given chemical class form solid-state emulsions suggests that other factors such as geometry or stereochemical factors may determine the ability to form solid-state emulsions, e.g., cyclamate and saccharine. No specificity was observed for the oil phase, however. All oils utilized to date can be utilized to prepare solid-state emulsions with any of the above acceptable matrix materials.

In order to determine the effect of the oil phase on the properties of an o/w emulsion, given a constant matrix material (PVP), solid-state emulsions were prepared using mineral, cod liver, corn, and olive oil as well as isopropyl myristate. The resulting average droplet sizes (±SD) of the respective aqueous emulsions are shown in Fig. 1. The size distribution for each composition was unimodal. According to Fig. 1, the average droplet diameter, in ascending order, was mineral oil, corn oil, olive oil, and isopropyl myristate. It is interesting that the size variability seen with mineral oil-based systems was much less than that observed for heterogeneous natural oils. Although the average diameters were significantly different (two-tailed t test, $P \leq 0.05$) between mineral oil and isopropyl myristate, the average droplet diameters were observed to vary by less than 1.5 μm.

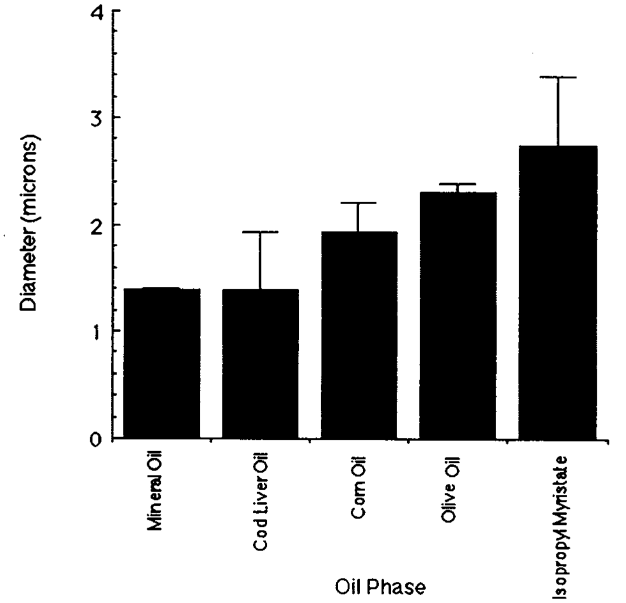

Fig. 1. Average droplet size (±SD) as a function of oil phase ($N = 3$). PVP-to-oil phase was 3 to 1 (w/w) for each composition. Samples evaluated 6 hr post addition of water to the respective solid-state emulsion.

Although the range of droplet sizes between mineral oil and isopropyl myristate emulsions was smaller than expected, real differences were observed. In order to gain some insight as to what oil properties might effect the emulsification process, the various oil/water interfacial tensions were investigated (Fig. 2). Analysis of Fig. 2 indicates that, with the exception of mineral oil, the oil–water interfacial tension is directly related to the average droplet diameter.

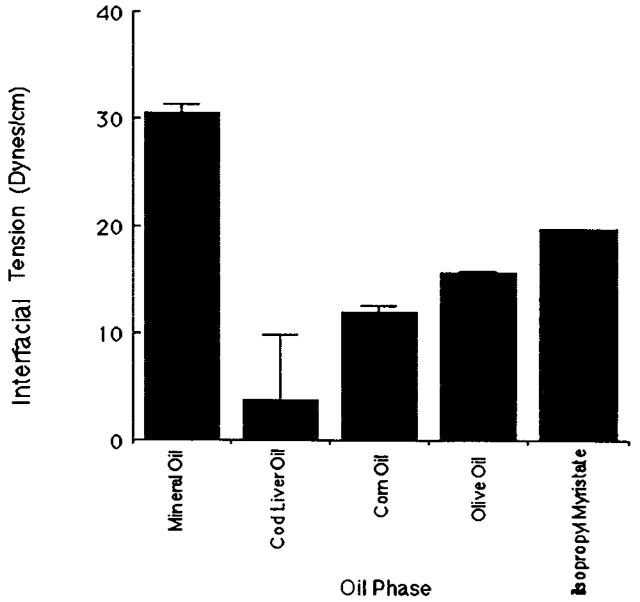

Fig. 2. Average (±SD) oil/water interfacial tension ($N = 3$) as a function of the oil phase at 25°C.

Isopropyl myristate had the largest interfacial tension and the largest droplet diameter, while cod liver oil had the smallest interfacial tension and the smallest droplet diameter.

A similar phenomenon has been observed by El-Nokaly *et al.* (9) for w/o microemulsions utilizing triglycerides. The following hypothesis, analogous to that of El-Nokaly *et al.* (9), is proposed to explain the unusual results observed for mineral oil. Mineral oil, a petroleum by-product, is essentially 100% hydrocarbon based and does not contain low molecular weight fractions that are soluble in water. In contrast, natural oils are comprised of numerous components, some of which may be partially water soluble and thus capable of diffusing into the water phase. In the event that water-soluble components do diffuse into the aqueous phase, the optimal HLB conditions change. If the hydrophilic/lipophilic balance changes as a result of the diffusion of water-soluble components but the matrix system remains unchanged, one would predict the formation of an emulsion with different physical characteristics, e.g., droplet diameters or physical stability.

Due to the chemical and physical diversity of the matrix materials, the effect of the matrix material on the emulsification process was evaluated with a constant oil phase. Solid-state emulsions were prepared with sucrose, saccharine, PVP, cyclamate, and mineral oil. In each case, the solid-state emulsion was prepared with a matrix-to-oil ratio of 3 to 1 (w/w). Six hours after the addition of water to the respective solid-state emulsions, the droplet distribution was determined (Fig. 3). Analysis of Fig. 3 indicates that the modal droplet diameter was 1.5 μm, for each matrix material. According to Fig. 3, the matrix material does not appear to be a major determinant of the final droplet diameter. Due to the bimodal nature of the saccharine distribution profile and the broad shape of the PVP profile, Fig. 3 also suggests that the various self-emulsifying systems may be at different stages of the emulsification process. Although the matrix materials, utilized in this study, do not dramatically influence the final average droplet diameter, these data suggest that the rate of self-emulsification may be a function of the matrix material.

To investigate further the emulsification process, the above experiment was repeated as a function of time. The extent of self-emulsification was determined by calculating the ratio of the percentage of droplets in the 10-μm channel to the percentage of droplets in the 1-μm channel as a function of time. The above ratio will subsequently be referred to as the self-emulsification ratio. The results for three representative matrix materials, i.e., sucrose, saccharine, and PVP, are shown in Fig. 4. Figure 4 indicates that the self-emulsification ratio as a function of time was biphasic. The initial rates observed for each matrix material appear to be extremely rapid ($t_{1/2}$ = 30 min), while the terminal rates for the various matrix materials appear to be significantly slower ($t_{1/2}$ = 2 to 12 hr) and dependent on the particular matrix material utilized. In addition, Fig. 4 indicates that the self-emulsification ratio for sucrose goes to zero after approximately 6 hr, while that for saccharine goes to zero after 20 hr. The self-emulsification ratio for PVP-based systems is intermediate between that of sucrose and that of saccharine. These results clearly indicate that the matrix material is a determining factor in the rate of self-emulsification.

In summary, our results indicate that the average droplet diameter may be altered by utilizing various oil phases. Given the oil phases utilized in this study, the droplet diameter was observed to range from 1.5 to 3 μm. With the exception of mineral oil, the oil/water interfacial tension appears to be directly related to the droplet diameter. Based on our results, there does not appear to be any relationship between the matrix material and the average droplet diameter. Although the mechanism is unclear at this time, the choice of matrix material does appear to affect the rate of emulsification. Further studies are in progress to determine if drugs incorporated within the oil phase change the rate of emulsification of droplet distribution.

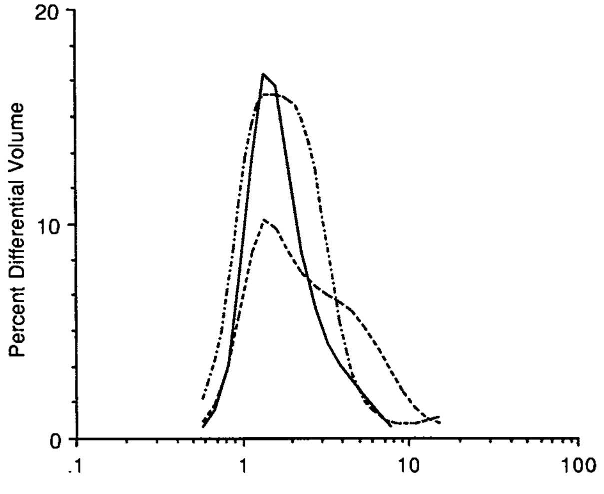

Fig. 3. Droplet distribution as a function of the matrix material at 25°C. Mineral oil was utilized as the oil phase in each case. Droplet size distribution was determined after the distribution became unimodal (except for saccharine; see Fig. 4). (——) Sucrose; (– – –) saccharine; (- · · - -) PVP.

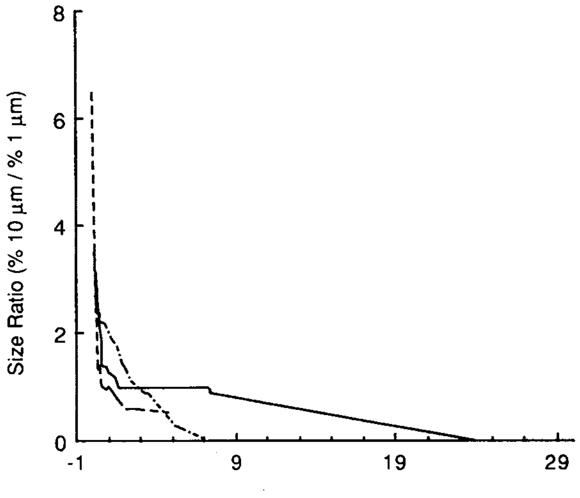

Fig. 4. The ratio of the percentage of sample having a diameter of 10 μm to that having a diameter of 1 μm at 25°C. (- · · - -) Sucrose; (——) saccharine; (– – –) PVP.

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