PDA Journal of Pharmaceutical Science and Technology

1995

March / April

Volume 49

Number 2

PDA

An International Association For Pharmaceutical Science And Technology

March–April 1995 Vol. 49, No. 2

PDA Journal of Pharmaceutical Science and Technology

EDITOR: Joseph B. Schwartz

Philadelphia College of Pharmacy & Science
600 South 43rd Street
Philadelphia, PA 19104-4495
Phone: (215) 596-8590
STAFF: Susan M. McCoy, Henrietta Zimm

CIRCULATION OFFICE:
PDA, Inc.
7500 Old Georgetown Rd
Suite 620
Bethesda, MD 20814
Phone: (301) 986-0293

ADVERTISING/CIRCULATION: Margaret Wanca
Phone: (301) 986-0293

PDA Journal of Pharmaceutical Science & Technology (ISSN 1076-397X) is published bimonthly by the PDA, Inc., 7500 Old Georgetown Rd., Suite 620, Bethesda, MD 20814.

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Printed in the U.S.A.

Formerly the
"Journal of Parenteral Science and Technology"

ISSN 1076-397X

RESEARCH ARTICLE

Particle Size Reduction of Emulsions by Formulation Design-II: Effect of Oil and Surfactant Concentration

GURMUKH D. CHANANA* and BHOGI B. SHETH†

Parenteral Medications Laboratories, Department of Pharmaceutics, University of Tennessee, Memphis, Tennessee

ABSTRACT: The objective of this study was to investigate the effect of the concentration of surfactant and oil on particle size reduction and stability of oil-in-water emulsion formulations containing polyhydroxy alcohols. Emulsions were prepared using an emulsifier system consisting of Tween 80® and Span 80® with 5%, 10%, 15% and 20% soybean oil and containing 50% w/w of either propylene glycol (PG) or glycerol (GLY) in the external phase. At each oil concentration, four emulsions were formulated with increasing surfactant concentration to provide emulsions with surfactant to oil (S/O) ratios of 0.1, 0.2, 0.3 and 0.4. Three parameters were evaluated, particle size reduction, particle size stability upon dilution, and viscosity. It was found that increase in S/O ratio resulted in substantial decrease in particle size in all cases. But there was a difference in the particle size reduction pattern between PG and GLY. Increase in oil concentration at the same S/O ratio caused particle size reduction for emulsions with PG but not for emulsions with GLY. The reduction in particle size was also greater for emulsions containing PG. Further, particle size of emulsions containing PG was found to be stable over 24 hours after dilution. However, a slight increase in particle size was observed in emulsions containing GLY. It was also found that the viscosity of emulsions increased with an increase S/O ratio as well as the concentration of the oil.

Introduction

The use of oil-in-water emulsions as drug delivery systems has been widely recognized, and considerable research has been focused on emulsions in recent years. These systems can be used for the delivery of poorly water-soluble drugs via the parenteral route (1). The typical method of preparation of intravenous O/W emulsions requires the use of high shear or high energy equipment (2–4). An alternate method for particle size reduction is by formulation design. In this method, a fourth component, referred to as the cosurfactant, is added to emulsion formulations to achieve a decrease in particle size (5, 6).

In a previous study, we reported on the effect of the addition of glycerol (GLY) and propylene glycol (PG) on particle size reduction of oil-in-water emulsions of soybean oil (7). These polyhydroxy alcohols appeared to act as cosurfactants when added at concentrations ranging from 30% to 70% in the external phase, causing a substantial reduction in the particle size. The minimum particle size obtained in the study was approximately 2.0 μm. However, the particle size of emulsions intended for intravenous administration needs to be below 1 μm (8).

Therefore, it was an objective of this study to investigate if further particle size reduction could be achieved by either decreasing the amount of oil or increasing the amount of surfactant. Soybean oil emulsions were formulated containing 50% w/w GLY or PG in the external phase. This was the concentration of polyhydroxy alcohol at which maximum particle size reduction was observed (7). Emulsions were prepared containing increasing oil concentration as well as increasing surfactant concentration. The parameters evaluated were particle size reduction, particle size stability upon dilution, and viscosity. Particle size stability was evaluated in emulsions diluted with commonly used Large Volume Parenteral Solutions (LVPs).

Materials and Equipment

Glycerol (GLY) and propylene glycol (PG) were obtained from J. T. Baker (Phillipsburg, NJ). Soybean oil was obtained from Croda Inc. (Mill Hall, PA). Polyoxyethylene sorbitan monooleate (Tween 80®) and sorbitan monooleate (Span 80®) were obtained from Emulsion Engineering, Inc. (Sanford, FL). Sterile Water for Injection, USP (SWFI) was obtained from Abbott Laboratories (North Chicago, IL), 10% Mannitol Injection, USP was obtained from American McGaw (Irvine, CA) and 0.9% Sodium Chloride Injection was obtained from Travenol Laboratories Inc. (Deerfield, IL). A single lot of each material was used in preparation of all emulsions. Equipment used to make emulsions included: propeller mixer, Model RW 20 DZM, (Ika-Werk, Germany), and homogenizer, Model Omni 2000, (Omni International, CT). Particle size was determined with a Horiba Particle Size Analyzer, Model CAPA 700, (Horiba Corporation, Irvine, CA). Viscosity was mea-

Received November 22, 1993. Accepted for publication September 16, 1994.

* Present Address—American Drug Development Inc., 9100A Yellow Brick Road, Baltimore, MD 21237.

† Author to whom correspondence should be addressed: 38163.

sured using a Brookfield Cone and Plate Viscometer, Model DV-II, (Brookfield Engineering Laboratories, Stoughton, MA).

Methods

In a study reported previously, it was found that the emulsifier blend with HLB value of 8.0 gave the most stable emulsion (7). It was also found that emulsifier concentration of 2% w/w (10 percent of the oil phase) gave the minimum particle size. Increase in emulsifier concentration beyond 2% w/w did not result in further decrease in the particle size of the emulsion. Therefore, this concentration of the emulsifier blend, corresponding to surfactant to oil (S/O) ratio of 0.1, was chosen as the minimum concentration used in this study. Formulations with higher surfactant concentrations were prepared to provide emulsions with S/O ratios ranging from 0.1–0.4.

We had also reported that the particle size of soybean oil decreased with an increase in polyhydroxy alcohol concentration in the external phase (7). It was found that polyhydroxy alcohol level of 50% w/w in the external phase caused maximum reduction in particle size. The particle size of emulsions containing 50% w/w of either GLY or PG was found to be approximately 2.0 μm. Therefore, this level of polyhydroxy alcohol was selected.

A stable base O/W emulsion without any polyhydroxy alcohol was first formulated. This base emulsion was formulated to contain 20% w/w soybean oil and a surfactant system consisting of an emulsifier blend of 35% Tween 80® and 65% Span 80®. The amount of emulsifier blend used was 10% of the oil phase, giving an S/O ratio of 0.1. The procedures used in formulation development have been previously described (7). Four series of emulsions were prepared with this emulsifier blend containing 5%, 10%, 15% and 20% w/w oil, respectively. For each series of emulsions, four formulations were prepared at each oil concentration with increasing amounts of the emulsifier blend. The increase in emulsifier concentration was designed to provide S/O ratios of 0.1, 0.2, 0.3 and 0.4, respectively. Table I shows the sixteen emulsions prepared for this investigation. The method of preparation of emulsions was as follows: the oil phase containing the surfactants, heated to 60°C, was added to aqueous phase (50% w/w polyhydroxy alcohol solution) heated to 60°C and mixed with the homogenizer at 30,000 rpm for 5 minutes. Particle size determination of the emulsions was carried out within 24 hours after their preparation. The procedure used in the particle size determination has been described previously (7).

The investigation of particle size stability of admixtures of emulsions with LVPs was done with 20% soybean oil emulsion at two S/O ratios of 0.1 and 0.4, respectively. The following procedure was used: the sample tube containing the emulsion was gently inverted 10 times to get a homogeneous sample. A sample of 2

TABLE I
Formulations Prepared to Study the Effect of Surfactant and Oil Concentrations on the Particle Size and Viscosity of Emulsions Containing Propylene Glycol or Glycerol

Surfactant to Oil (S/O) Ratio	Ingredient Concentration, % w/w				
	Soybean Oil	Tween 80®	Span 80®	PG[a] or GLY[b]	Water
0.1	5	0.17	0.33	47.25	47.25
	10	0.35	0.65	45.50	45.50
	15	0.50	1.00	41.75	41.75
	20	0.70	1.30	39.00	39.00
0.2	5	0.35	0.65	47.00	47.00
	10	0.70	1.30	44.00	44.00
	15	1.05	1.95	41.00	41.00
	20	1.40	2.60	38.00	38.00
0.3	5	0.50	1.00	46.75	46.75
	10	1.05	1.95	43.50	43.50
	15	1.60	2.90	40.25	40.25
	20	2.10	3.90	37.00	37.00
0.4	5	0.70	1.30	46.50	46.50
	10	1.40	2.60	43.00	43.00
	15	2.10	3.90	39.50	39.50
	20	2.80	5.20	36.00	36.00

[a] Propylene Glycol.
[b] Glycerol.

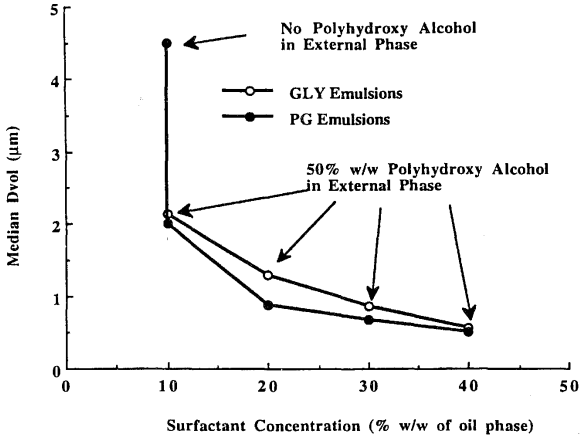

Figure 1—Effect of surfactant concentration on the particle size of O/W emulsions with 20% w/w soybean oil.

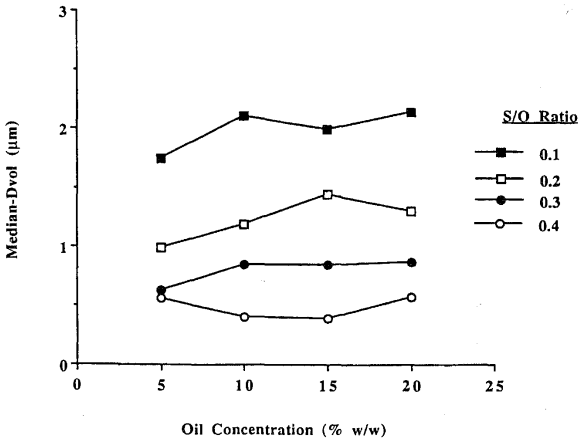

Figure 2—Effect of surfactant and oil concentrations on the particle size of soybean oil emulsions containing 50% w/w glycerol.

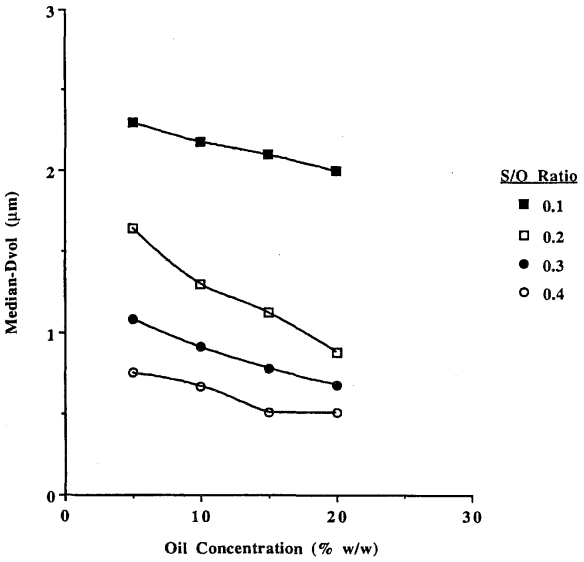

Figure 3—Effect of surfactant and oil concentrations on the particle size of soybean oil emulsions containing 50% w/w propylene glycol.

grams of this emulsion was added to 18 grams of the LVP solution to make a 1:10 dilution. The particle size was measured before dilution, immediately after dilution, and 1 hour, 6 hours and 24 hours after dilution. The LVPs used were Sterile Water for Injection (SWFI), 10% Mannitol Solution and 0.9% Sodium Chloride Injection. These solutions are commonly used in the preparation of intravenous admixtures.

Viscosity values of emulsions and of aqueous solutions corresponding in composition to the respective external phase of each emulsion were also determined. The viscosity measurements were made with a Brookfield Model DV II cone and plate viscometer at 25°C.

Results and Discussion

Effect of Increasing Surfactant Concentration (S/O ratio)

The effect of increasing surfactant concentration, with a corresponding increase in the S/O ratio, on the particle size reduction of emulsions containing 20% w/w oil is shown in Figure 1. The effect of 50% w/w polyhydroxy alcohol concentration on the particle size can also be noted in Figure 1. The effect of increasing S/O ratio on particle size at four concentrations of oil is given in Figure 2 for emulsions with GLY and in Figure 3 for emulsions with PG. It is evident that increasing the S/O ratio caused further decrease in particle size. Increasing the S/O ratio from 0.1 to 0.4 resulted in a four-fold decrease in the particle size. The particle size of emulsions with GLY decreased from about 2.1 μm to about 0.5 μm. The particle size reduction effect is similar, but more pronounced, for emulsions with PG.

It was found that particle size reduction to below 1 μm could be achieved by increasing the surfactant concentration above a critical surfactant concentration (CSC) for emulsions containing PG or GLY. The CSC required for emulsions with 50% w/w PG and 20% w/w oil was found to occur at a surfactant concentration at 0.2 S/O ratio. The CSC required for emulsions with 50% w/w PG and lower oil concentrations was at surfactant concentrations corresponding to 0.3 S/O ratio. On the other hand, the CSC was at 0.3 S/O ratio for all oil concentrations for emulsions with 50% w/w GLY. This indicates that PG acts as a more effective cosurfactant than GLY at the higher oil concentration.

Several theories on the reduction of particle size and formation of microemulsions due to the addition of cosurfactant have been proposed (9–14). Two of the predominant theories include reduction of interfacial tension (9–14) and solubilization of oil in surfactant micelles (15). The addition of polyhydroxy alcohols in the external phase can cause changes in the interfacial properties, since the surface tensions of both PG (40.1 dynes/cm) and GLY (63.4 dynes/cm) are considerably lower than that of water (72.8 dynes/cm) at 20°C. It is likely that the interfacial tensions of polyhydroxy alcohol solutions (that make up the external phase) and the oil will be significantly lower than between water and oil. Hence, it is likely that the predominant factor in the reduction of particle size is the lower interfacial tension. This mechanism is also supported by other studies reported for microemulsions. Prince (13) proposed that the formation of small droplets in microemulsions was in part due to a reduction in the interfacial tension of oil and water, in the presence of a cosurfactant. Ruckenstein and Chi (14) also explained the formation and stability of microemulsions using the surface tension

TABLE II
Particle Size Stability of Emulsions Containing Propylene Glycol After Dilution with Large Volume Parenteral Solutions

	Particle Size, Median-D_{vol} (μm) ± SD[a]					
	10% Mannitol		0.9% Sodium Chloride Injection		Sterile Water For Inj. (SWFI)	
Time	A	B	A	B	A	B
Before dilution	1.8 ± 1.3	0.6 ± 0.6	1.8 ± 1.3	0.6 ± 0.6	1.8 ± 1.3	0.6 ± 0.6
After dilution	1.2 ± 0.9	0.4 ± 0.4	1.6 ± 1.1	0.4 ± 0.4	1.4 ± 1.0	0.4 ± 0.5
After 1 hour	1.4 ± 1.2	0.4 ± 0.4	1.6 ± 1.0	0.4 ± 0.4	1.4 ± 1.0	0.4 ± 0.4
After 6 hours	1.5 ± 1.2	0.4 ± 0.3	1.6 ± 1.2	0.4 ± 0.4	1.4 ± 1.2	0.4 ± 0.4
After 24 hours	1.5 ± 1.3	0.4 ± 0.3	1.1 ± 0.7	0.4 ± 0.4	1.5 ± 1.1	0.4 ± 0.4

A: Emulsions containing S/O ratio of 0.1. B: Emulsions containing S/O ratio of 0.4. Emulsions contained 20% oil and 50% propylene glycol in the external phase.

[a] Standard Deviation. The particle size of three separate samples was measured for each emulsion.

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