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RESEARCH PAPER

Scale-Up of an Oil/Water Cream Containing 40% Diethylene Glycol Monoethyl Ether

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ABSTRACT

The purpose of this study was to scale up an oil/water (o/w) cream formulation containing 40% diethylene glycol monoethyl ether (DGME), developed via 300-g laboratory batches in a 2^{5-2} fractional factorial design, to 7-kg batch sizes in a Brogli-10 homogenizer. The o/w cream was manufactured via a standard phase-inversion process in the Brogli-10 homogenizer. Partitioning studies of DGME were conducted in test tubes at ambient temperature and after 24 hr at 70°C in a convection oven. Phase height was measured by vernier calipers. Microscopy studies of excipients with and without treatment with water or a DGME/water mixture were conducted with a Nikon microscope after equilibration at 35°C for 24 hr. During creation of the 7-kg pilot-scale batches, congealed material was observed between the sweep agitation blade and the discharge port, where the Brogli-10 homogenizer is not temperature jacketed. Factors that increased the amount of congealed material were higher temperatures during primary emulsification and longer cooling times. Partitioning studies revealed that DGME resides in the aqueous external phase of this formulation. Microscopy studies revealed that DGME in the external phase of this cream has a profound impact on the solubility of certain solid, waxy excipients (e.g., cetyl alcohol and polyoxyethylene-2-stearyl ether) at 35°C. From this study, it appears that DGME resides in the external phase of the o/w cream. During manufacturing, it is hypothesized that the presence of DGME in the external phase alters the solubility of certain solid, waxy excipients in the formula such that they no longer primarily reside in the internal oil phase. On cooling, these materials

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precipitate or congeal in the external phase. The fractional factorial experimental design at the 300-g laboratory scale did not predict the issues encountered during scale-up. Differences between laboratory scale and pilot plant scale that explain why this phenomenon was not seen during laboratory scale are differences in cooling times, nonjacketed or ''cold spots'' in the Brogli-10 homogenizer, and a low proportion of congealed material in relation to the total batch size (<1.5%).
Key Words: *Cream; Diethylene glycol monoethyl ether; Scale up; Semisolids; Topicals; Transcutol.*

INTRODUCTION

Diethylene glycol monoethyl ether (DGME; marketed as Transcutol® by Gattefosse) has been shown to enhance the penetration of pharmacologically active agents and to increase the solubility of these same agents (1). DGME is described as a hygroscopic liquid, freely miscible with polar and nonpolar solvents. DGME is nontoxic and nonirritating (2). DGME was proven to be an effective vehicle for topical delivery of ivermectin, a broad-spectrum antiparasitic agent, through bovine skin. This study showed that DGME is capable of forming cutaneous depots and could have application in the development and optimization of topical/transdermal products (3). An anhydrous, semisolid cream using 25% DGME was developed for a novel thymidylate synthase inhibitor for the treatment of psoriasis. Again, the incorporation of DGME increased solubility and increased permeation (4).

Although DGME has been studied and used in a variety of formulations, including colloidal silicon dioxide gels (5,6), carbomer gels (7), and an anhydrous, semisolid cream (4), there is no documentation of the study of DGME in oil/water (o/w) creams. The purpose of this study was to scale up an o/w cream formulation containing 40% DGME, developed via 300-g laboratory batches in a 2^{5-2} fractional factorial design, to 7-kg batch sizes in a Brogli-10 homogenizer.

EXPERIMENTAL METHODS AND MATERIALS

Materials

All materials were used as received from the vendors. Table 1 gives the formulation manufactured in 7-kg batch sizes in the Brogli-10 homogenizer.

Manufacturing Equipment

The 7-kg pilot plant batches were manufactured in a Brogli-10 homogenizer with a Brogli TT-250 heater and Brogli Multi-Homo-Recorder.

Manufacturing Process

The manufacturing process for all batches was the same and followed a standard phase-inversion process. The steps occurred in the following sequence:

1. The polyoxyethylene-21-stearyl ether (Brij® 721) and polyoxyethylene-2-stearyl ether (Brij 72) were melted by placing the containers of both materials in a water bath heated on a hot plate.
2. Once the Brij 721 and Brij 72 were melted, they were placed in the bowl of the Brogli-10 homogenizer.
3. Next, light mineral oil USP, stearyl alcohol USP, and cetyl alcohol NF were added to the bowl of the Brogli-10 homogenizer.
4. The bowl of the Brogli-10 homogenizer was raised, and agitation was started at 30 rpm (low speed). The chilled processed water and heater were turned on, and the jacket temperature was set to approximately 65°C–70°C.
5. Purified water USP was heated in a suitable container to 65°C–70°C.
6. In a separate suitable container, DGME was added. In the case of the active batches, the drug substance was added to DGME, covered, and mixed with propeller agitation to form a suspension.
7. When materials in the bowl reached the proper conditions and were clear, the heated water was slowly added to the bowl through the liquid addition port.
8. Agitation was increased to 60 rpm (high speed), and agitation continued for 5–10 min.
9. The cold water for the vacuum pump was turned on.
10. The agitation speed was decreased to 30 rpm after the materials were mixed for 10–15 min.
11. A vacuum was pulled on the Brogli-10 homogenizer.
12. A vacuum close to 15 inches Hg was achieved by slowly closing the valve to the air filter outlet.

Table 1

Cream Formula

Ingredient	% w/w	Batch Quantity (g)
Drug substance	5.27	368.9
Diethylene glycol monoethyl ether (Transcutol)	40.0	2800.0
Purified water, USP/EP	31.78	2224.6
Light mineral oil, USP	8.0	560.0
Stearyl alcohol, USP	5.5	385.0
Polyoxyethylene-21-stearyl ether (Brij 721)	3.65	255.5
Cetyl alcohol, NF	3.5	245.0
Polyoxyethylene-2-stearyl ether (Brij 72)	2.3	161.0
Total	100.0	7000.0

13. Once a vacuum was pulled, a gap setting of 2 was used, and the material was homogenized at 6000 rpm (high speed) for 3–5 min. A temperature of 65°C–70°C was maintained.
14. An agitation speed of 30 rpm was continued, and the homogenizer speed was decreased to 3000 rpm while cooling the bulk cream to 50°C–55°C.
15. At 50°C–55°C, DGME (or DGME/drug substance for active batches) was slowly added to the Brogli-10 homogenizer through the liquid addition port.
16. Conditions outlined in step 14 were maintained.
17. The product was cooled to 40°C–45°C.
18. The homogenizer was stopped.
19. Continue slow agitation while cooling to 30°C–35°C.
20. The finished bulk product was discharged by releasing the vacuum, connecting the compressed air, applying positive pressure, and opening the discharge chute at the bottom of the bowl.
21. The agitation was stopped, and the compressed air line was disconnected.

Partitioning Studies

Partitioning studies of DGME were conducted in test tubes at ambient temperature and after 24 hr at 70°C in a convection oven. Phase height was measured by vernier calipers. Initially, light mineral oil and water were added to the test tubes. This mixture was vortexed for approximately 1 min, allowed to settle, and then each phase height was measured with vernier calipers. Next, DGME was added to the test tubes containing light mineral oil and water. The ratio of light mineral oil to DGME to water was the same as given in Table 1. This mixture was vortexed for approximately 1 min. After allowing the mixture to settle, the height of each phase was measured with vernier calipers. Finally, these test tubes were capped and placed in a 70°C convection oven for 24 hr. After 24 hr, the test tubes were quickly removed from the oven, and the phase heights were measured with vernier calipers. To aid in the interpretation of these data, test tubes containing only light mineral oil, DGME, and water separately were placed in the 70°C convection oven for 24 hr to assess thermal expansion of the individual components.

Microscopy Studies

A duplicate set of microscope slides were prepared containing stearyl alcohol, cetyl alcohol, polyoxyethylene 21 stearyl ether, and polyoxyethylene 2 stearyl ether separately. Photomicrographs of these slides were taken and used as controls. One set of these slides was treated by placing 2 drops of water on each slide and placing the slides in a 35°C convection oven for 24 hr. The second set of slides was treated by placing 2 drops of a DGME/water mixture in proportion to their quantities in Table 1 on each slide and placing the slides in a 35°C convection oven for 24 hr. After 24 hr, the slides were removed from the oven, allowed to cool, and then photomicrographed. All microscopy studies were conducted with a Nikon Optiphot-Pol microscope. Additional equipment attached to the microscope consisted of a Sony CCD/RGB color video camera, Sony Trinitron video monitor, and Sony color video printer.

RESULTS AND DISCUSSION

During the first placebo (lot 8888) and active (lot 8890) 7-kg pilot-scale batches, congealed material was observed between the sweep agitation blade and the dis-

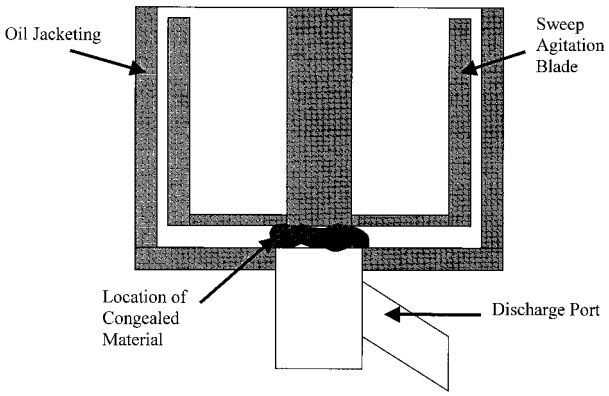

Figure 1. Location of congealed material in Brogli-10 homogenizer.

charge port, where the Brogli-10 homogenizer is not temperature jacketed (see Fig. 1). The initial theory was that possibly not all the solid, waxy materials in the oil phase had melted before incorporation of the aqueous phase ingredients. Therefore, during the last active batch (lot 8910), careful attention was paid to ensure that all oil phase solids had melted. In addition, a higher primary emulsion temperature was used to help ensure melting of all ingredients. However, the results were similar to those of the first two batches. Table 2 reveals that the congealed material and bulk cream were not homogeneous with respect to the active ingredient. Also, the higher primary emulsion temperature used during the last active batch actually resulted in more congealed material being present. Therefore, inadequate melting of oil phase ingredients was not the cause of this phenomenon.

Since the ingredients used in this cream were standard excipients (with the exception of DGME), the likely cause of this phenomenon seemed to be the effect of DGME on the physical properties of the cream. Partitioning studies were conducted to understand where DGME would reside in the cream. Since DGME is promoted as being both oil and water miscible, initial theories were that this ingredient may be moving between the internal and external phases of the cream, causing congealing of ingredients to occur. Table 3 shows the results of partitioning studies done at ambient temperature. These results indicate DGME resides in the aqueous phase. To ensure this did not change at temperatures even beyond those experienced during processing, these same samples were placed in a 70°C convection oven for 24 hr and measurements were repeated. Results showed no change in the preference for the aqueous phase outside the normal thermal expansion of the individual ingredients. Therefore, movement of DGME between the internal and external phases of the cream during cooling was not the cause of the congealed material.

Table 3

Partitioning Study Results

Trial	Δ in Oil Phase (mm)	Δ in Water Phase (mm)
1	−1.06	+33.22
2	−0.99	+34.14
3	−0.19	+33.37
Average	−0.75	+33.58

The next theory was to explore the possibility of the effect of DGME on the solubility of the solid, waxy ingredients in the formula such that they no longer clearly resided in either the internal or external phase of the cream. Since DGME resides in the external phase, its effective concentration in this phase is approximately 55%. Therefore, the external phase really is not an ‘‘aqueous’’ environment, and since it functions as a cosolvent, this could alter the affinity of the solid ingredients for this phase. To test this theory, simple microscopy studies were undertaken to see if the DGME/water external phase would solubilize the solid, waxy excipients used in the formula. Results of this study are given in Fig. 2.

In Fig. 2, stearyl alcohol showed little or no effect of treatment with either water alone or water with DGME. Polyoxyethylene-21-stearyl ether did show a significant

Table 2

Observations in 7-kg Scale-Up Batches

Lot	Amount Congealed (g)	Congealed Assay (%)	Bulk Assay (%)	Primary Emulsion Temperature (°C)
8888 (placebo)	40.9	N/A	N/A	65–70
8890	71.0	70–80	102–105	65–70
8910	107.6	50	107–110	70–75

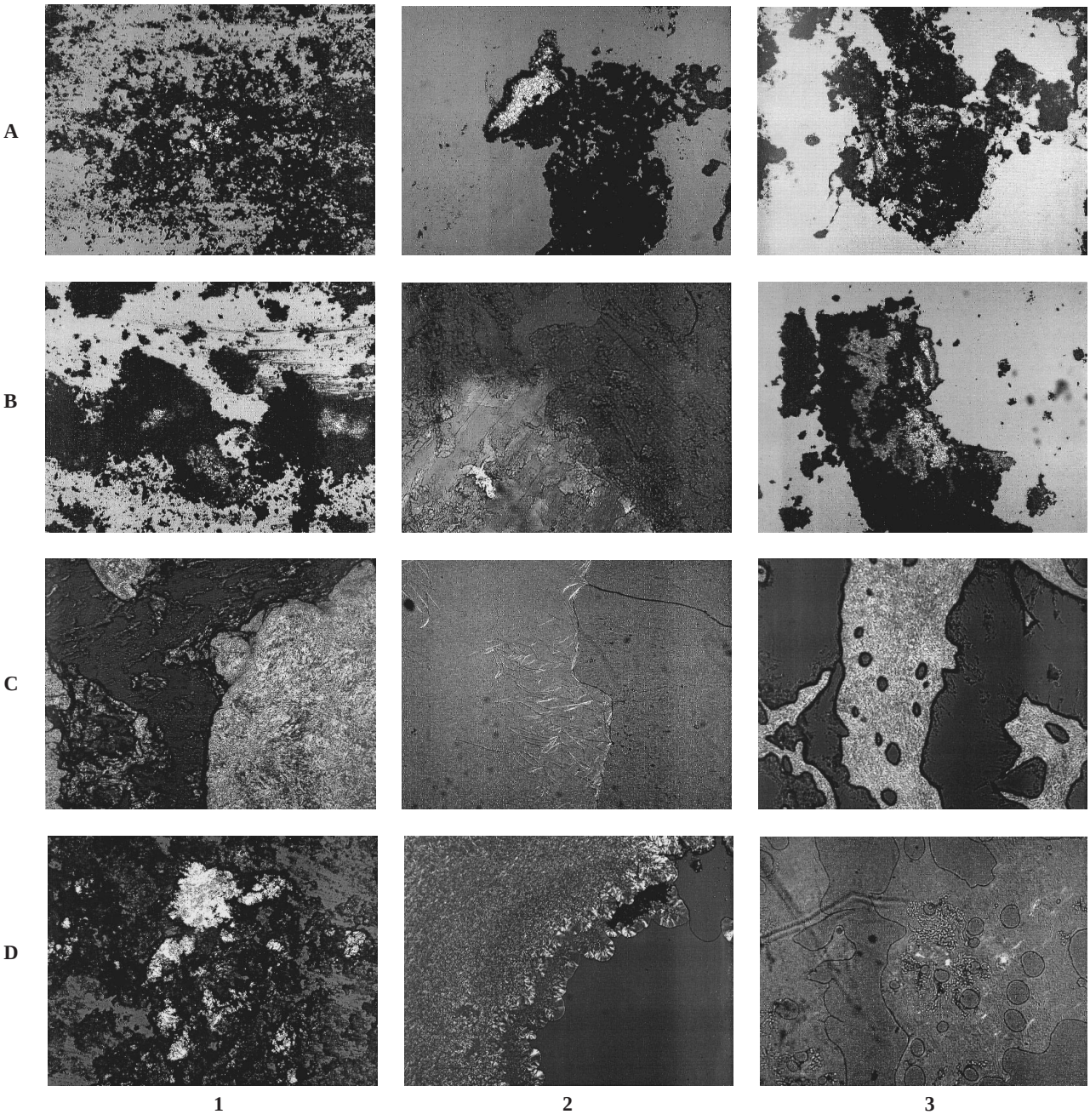

Figure 2. Microscopy study results (10×). A = stearyl alcohol; B = cetyl alcohol; C = polyoxyethylene-2-stearyl ether (Brij 72); D = polyoxyethylene-21-stearyl ether (Brij 721); 1 = no treatment; 2 = DGME/water; 3 = water, 35°C for 24 hr.

water solubilization effect. However, this is to be expected since it has an HLB (hydrophile-lipophile balance) value of 15.5 (8). What is interesting is that polyoxyethylene-21-stearyl ether showed little or no solubility in the DGME/water treatment. This may indicate that it will have a tendency to precipitate or congeal out in this particular aqueous phase. The two ingredients showing the largest difference in treatment with DGME/water versus water alone were cetyl alcohol and polyoxyethylene-2-stearyl ether. Cetyl alcohol is described as wa-

ter insoluble (9, pp. 99–103). Polyoxyethylene-2-stearyl ether has an HLB value of 4.9, indicating a preference for the oil phase (9, pp. 367–370). Figure 2 clearly shows that both excipients dissolve in the DGME/water treatment that mimics what it experienced during manufacturing. In water, neither cetyl alcohol nor polyoxyethylene-2-stearyl ether show any indication of solubilization. Therefore, it appears likely that the presence of DGME in the external aqueous phase had a profound impact on the solubilities of certain solid, waxy excipients used as emulsifiers and auxiliary emulsifiers. After the addition of DGME during manufacturing, the temperature was slightly elevated (55°C). The data indicate that cetyl alcohol and polyoxyethylene-2-stearyl ether have some affinity for the aqueous phase. This movement of materials (see Fig. 3) likely disrupted the stability of the emulsion. On cooling to ambient temperature, these excipients no longer had as much affinity for the aqueous phase and therefore precipitated or congealed out. This, coupled with the fact that polyoxyethylene-21-stearyl ether may have precipitated or congealed out of solution on the addition of the aqueous phase, supports the possibility for congealed material to be found during these batches.

There are a number of reasons why this phenomenon was not observed during the 300-g laboratory-scale batches. First, the cooling times for the different batch sizes were significantly different. Cooling times for the 300-g laboratory-scale batches were approximately 5 min. Cooling times for the 7-kg batches were approximately 60 min. Having the cream spend more time at an elevated temperature allows more time and opportunity for the excipients to move from one phase to another. A second reason could be that laboratory-scale batches were made in small stainless steel beakers that have no ''cold spots'' or areas where the homogenizer or spatula could not reach. In contrast, the Brogli-10 homogenizer has a cold spot or nonjacketed spot in the kettle where the discharge port is located. This spot is also inaccessible to the sweep agitation blades and homogenizer. Therefore, the cold spot in the kettle allows for precipitation of the solid, waxy materials in a location that cannot easily be reincorporated with the rest of the bulk cream. The third explanation for not seeing this phenomenon during laboratory-scale batches is simply that the proportion of congealed material to the batch size would make it extremely difficult to detect. Congealed material present in the 7-kg batch sizes represented less than 1.5% of the material present. For a 300-g laboratory-scale batch, this would mean less than 4.5 g of congealed material would be present. This would be extremely difficult to detect.

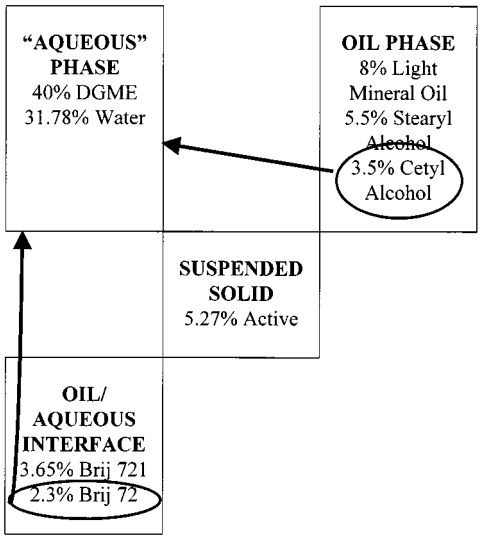

Figure 3. Movement of materials during emulsification.

CONCLUSIONS

DGME resides in the external phase of the o/w cream studied. During emulsification, it is hypothesized that the presence of DGME in the external phase alters the solubility of certain solid, waxy excipients in the formula such that they no longer primarily reside in the internal oil phase. On cooling, these materials precipitate or congeal in the external phase. The fractional factorial experimental design at the 300-g laboratory scale did not predict the issues encountered during scale-up. Differences between laboratory scale and pilot plant scale that explain why this phenomenon was not seen during laboratory scale are differences in cooling times, nonjacketed or cold spots in the Brogli-10 homogenizer, and the proportion of congealed material being very small in relation to the total batch size (<1.5%).

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REFERENCES

1. C.-M. Chiang and G. W. Cleary, W., Skin permeation enhancer compositions, CA Pat. 2012875 (1990); U.S. Pat. 327,321 (1989).

2. Gattefosse Company, *Product Information, Transcutol Product Profile*, Gattefosse Co.
3. M. Yazdanian and E. Chen, The effect of diethylene glycol monoethyl ether as a vehicle for topical delivery of ivermectin, Vet. Res. Commun., 19, 309–319 (1995).
4. L. Pavliv, K. Freeborn, T. Wilke, C.-C. Chiang, B. Shetty, and P. Tyle, Topical formulation development of a novel thymidylate synthase inhibitor for the treatment of psoriasis, Int. J. Pharm., 105, 227–233 (1994).
5. R. Panchagnula and W. A. Ritschel, Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol as a cosolvent: in-vitro, ex-vivo and in-vivo rat studies, J. Pharm. Pharmacol., 43(9), 609 (1991).
6. A. N. Shaaya, C. Kraus, D. H. Bauman, and W. A. Ritschel, Pharmacokinetics and bioavailability of papaverine HCl after intravenous, intracorporeal and penis topical administration in beagle dogs, Meth. Find Exp. Clin. Pharmacol., 14(5), 373–378 (1992).
7. W. A. Ritschel and A. S. Hussian, In vitro skin permeation of griseofulvin in rat and human skin from an ointment dosage form, Arzneim-Forsch., 38(11), 1630–1632 (1988).
8. M. Ash and I. Ash (compilers), *Handbook of Industrial Surfactants*, Gower, Hants, England, 1993, p. 84.
9. A. Wade and P. J. Weller (Eds.), *Handbook of Pharmaceutical Excipients*, 2nd ed., American Pharmaceutical Association, Washington, DC, 1994.