Pharmaceutical foams with optimized microemulsion and propellant-free pump

E. Dauphin-Chanard; C. André; D. Hoste; D. Marchaud
Gattefossé, 36 chemin de Genas, CS 70070, 69804 Saint-Priest cedex, France, edauphin@gattefosse.com

INTRODUCTION

Even though the OTC market for topical treatments is dominated by conventional vehicles including lotions, creams, ointments and gels, a significant trend towards a more innovative topical dosage form is being observed. Foam is gaining more attention as it combines patient's desire for more appealing dosage forms, pharmaceutical companies potential for innovation and contributes to better patient adherence to the treatment.
Microemulsions are thermodynamically stable dispersions of oil and water phases with a surfactant/co-surfactant system. They differ from conventional emulsions by their physical properties: transparency, low viscosity, small particle size (< 200 nm). This criterion yields a large interfacial area, increasing drug release through the skin[1].
Propellant-free pump allows introduction of air in the liquid microemulsion, resulting in foam production[2].
Moreover the device is very simple to use and convenient for the patient.
This study aims to combine the benefits of using microemulsion and propellant-free device to obtain pharmaceutical foam. The challenge was to transform a low viscosity microemulsion into an easy to apply dosage form with the foam. A screening of surfactant, co-surfactant and oily vehicle was investigated using pseudo-ternary diagrams to determine the microemulsion areas providing foaming capacity[3].
Diclofenac sodium (Non Steroidal Anti-Inflammatory Drug) was studied as a model drug using the optimized O/W microemulsion system. The therapeutic target depends on the drug loading: at 1%, the treatment is used for osteoarthritis, joint/back pain, whereas at 3%, it is aimed for actinic keratosis. Both concentrations have been used to develop optimized formulations.

EXPERIMENTAL METHODS

Materials
Caprylocaproyl macrogol-8 glycerides (Labrasol®), polyglyceryl-3 dioleate (Plurol® Oleique CC 497), medium chain triglycerides (Labrafac™ lipophile WL 1349) were provided by Gattefossé (France).
Polysorbate 80 (Tween® 80) was supplied by BASF (Germany). Diclofenac Sodium (ARCH PharmaLABS Limited, India) was used as model drug. Propellant-free pump devices (50 ml, PET) were purchased from Packit (Germany).

Method
Evaluation of solubility of diclofenac sodium
The solubility of diclofenac sodium was determined at 25°C after two weeks in each individual excipient.
Drug concentration was determined by HPLC (Waters chromatograph Alliance 2695D model, coupled with a 2487 model UV detector at 281 nm).

Design of microemulsion zones in pseudo-ternary diagram
Pseudo-ternary phase diagrams were constructed by titration of homogenous liquid mixtures of oil, surfactant, and co-surfactant, with water at room temperature to determine the microemulsion areas. Diclofenac sodium was then added at 1 or 3% W/W to a selection of microemulsions.

Foamability evaluation of microemulsion
Liquid microemulsions were tested in a propellant-free pump for their capacity to generate foam. The visual assessment was done over time (instantly and after 3 minutes).

RESULTS AND DISCUSSION

Selection of surfactant

Solubility of diclofenac sodium
The solubility of diclofenac sodium was determined in individual surfactant, co-surfactant, oil and water (Table 1). Labrasol® is the best solubilizer of diclofenac sodium.

Table 1. Diclofenac sodium solubility after 2 weeks at 25°C.

Excipient	Function	Solubility at equilibrium (mg/mL)
Labrasol®	Surfactant	213.2
Tween® 80		103.7
Plurol® Oleique CC497	Co-Surfactant	159.5
Water		18.3
Labrafac™ Lipophile WL 1349	Oily Vehicle	0.5

Foamibility evaluation
Candidate surfactants were diluted at 10% into water and poured into propellant-free device. The pictures of the obtained foams at t0 (Figure 1) show that Labrasol® has better foaming capacity than Tween® 80.

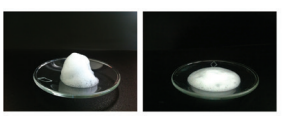

Figure 1. Foams obtained with Labrasol® (left) or Tween® 80 (right) at 10% in water.

Design of microemulsion zones in pseudo-ternary diagram

Figure 2 shows the microemulsion/emulsion zones obtained with Labrasol®/Plurol® Oleique CC497 (6/1), Labrafac™ Lipophile WL 1349 and water.

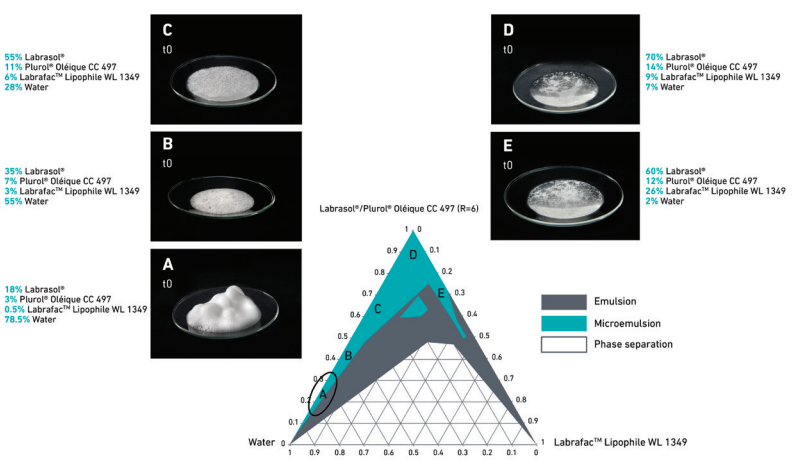

Figure 2. Microemulsion/emulsion zones.

Using the pseudo-ternary diagram, several microemulsions (A, B, C, D and E) have been evaluated for their foaming capacity. The optimal zone where microemulsion makes a foam is represented in Figure 2 (black circle). Microemulsions should contain 15-30% of surfactant/cosurfactant and minimum 70% of water to produce foams of good quality and 3 minutes persistency (Figure 3).

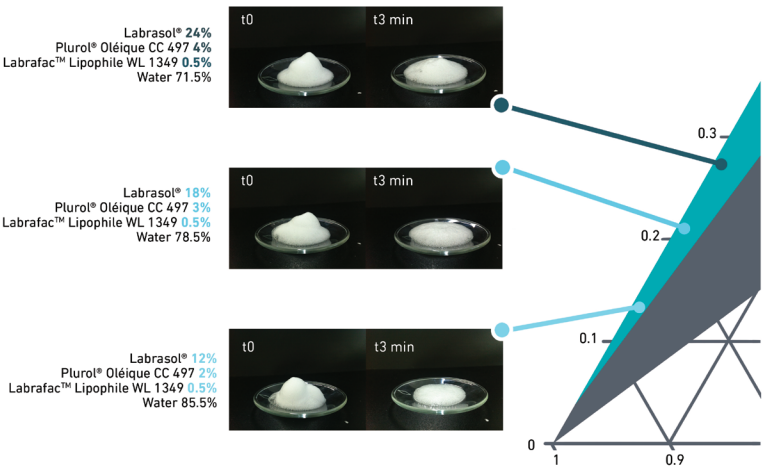

Figure 3. Foam obtained with optimal placebo microemulsion at t0 (left) and t3 min (right).

Diclofenac sodium was added to this microemulsion. The objective is to fully solubilise the drug and keep the foaming capacity and persistency.

At 1% of diclofenac sodium, the optimal formula is composed of:

Labrasol®	18.0%
Plurol® Oleique CC497	3.0%
Labrafac™ Lipophile WL 1349	0.5%
Water	78.5%

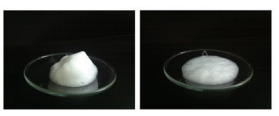

Figure 4. Foam obtained with 3% diclofenac sodium microemulsion at t0 (left) and t3 min (right).

To formulate 3% of drug, the formula is made of:

Labrasol®	24.0%
Plurol® Oleique CC497	4.0%
Labrafac™ Lipophile WL 1349	0.5%
Water	71.5%

In both cases, the incorporation of diclofenac sodium does not impact the foam capacity and persistency (Figure 4).

CONCLUSION

This study highlights the foaming capacity of Labrasol®. At 10% in water, it can create a foam when used in a propellant-free pump. Moreover its dual function as surfactant and as powerful solubilizer, enables the realization of foam containing 1% or 3% of diclofenac sodium.

This study underlines the potential of using microemulsion in propellant-free device to obtain foams. This enables to match efficacy, practicality and therapeutic adherence in skin drug delivery. As shown with diclofenac sodium, foaming microemulsion represent a promising topical dosage form.

REFERENCES

[1] Lu, G. W. and Gao, P. Emulsions and Microemulsions for Topical and Transdermal Drug Delivery. In Kulkarni, V. S., Handbook of Non-Invasive Drug Delivery Systems, p. 59-94. Boston: William Andrew Publishing (2010).
[2] Arzhavitina A. and Steckel H. Foams for pharmaceutical and cosmetic application. Int. J. Pharm.; 394: 1-17 (2010).
[3] Gattefossé, Lipid excipients for topical drug delivery, brochure (2010).