Guidelines to formulate OTC drugs in topical emulsions with improved sensorial properties

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PURPOSE

The main objective of a dermal formulation is to carry the active pharmaceutical molecule (API) across the skin barrier and to the site of action. But it should also display statisfying sensorial properties to drive patient compliance and product differentiation.

It is therefore important to provide formulators with guidelines to facilitate the selection of the right emulsifier to formulate their drug, ie. one which provides excellent emulsification and drug delivery properties in addition to having good textural properties and delivering a pleasurable sensorial aspect when applied on the skin.

MATERIALS

1. Gattefossé excipients

Trade name	Description	Functionnality
Apifil®	PEG-8 beeswax	O/W emulsifier
Gelot™ 64	Glycerol monostearate (and) PEG-75 palmitostearate	
Sedefos™ 75	Tricetearеth-4 phosphate (and) Ethylene glycol palmitostearate (and) Diethylene glycol palmitostearate	
Tefose® 63	PEG-6 palmitostearate (and) Ethylene glycol palmitostearate (and) PEG-32 palmitostearate	
Plurol® Diisostearique	Triglycerol diisostearate	W/O emulsifier
Emulcire™ 61 WL 2659	Cetyl alcohol (and) Ceteth-20 (and) Steareth-20	Co-emulsifier
Labrafil® M 1944 CS	Linoleoyl macrogol-6 glycerides	Oily phase
Labrafac™ Lipophile WL 1349	Triglycerides medium-chain	
Transcutol® P	Highly purified Diethylene glycol monoethyl ether	Hydrophilic solvent

2. Other materials

Mineral oil (supplied by Aiglon) and sweet almond oil (Cooper) were used as oily phases. Glycerine (Peter Cremer GmbH) was used as hydrophilic solvent and cetyl alcohol (Cognis) as texture agent. Carbomer (Lubrizol) was selected as gelling agent, sodium hydroxide (Merck) as its neutralizing agent. Preservatives used are methylparaben sodium salt (Quarrechim), methylparaben (Univar), propylparaben (Nipa) and sorbic acid (Chimidis). Stabilizers used are sodium chloride (Univar) and magnesium sulfate (Merck).

The OTC drug used is **sodium diclofenac** (supplied by Sigma Aldrich).

METHODS

1. Emulsification process

Emulsions are made by either a classic process or by a 'one-pot' process.

The classic process:

- Hot process: Weigh separately aqueous and oily phases and heat to 70-80°C. Pour aqueous phase into the oily phase under moderate stirring (350 rpm). Cool emulsion down to room temperature under stirring.
- Cold process: Weigh separately aqueous and oily phases and combine under faster stirring (3000 rpm) at room temperature.

The one-pot process:

Weigh aqueous and oily phases in the same container and heat to 70-80°C, under gentle stirring. Following emulsification, cool down to room temperature using a cold water bath under stirring.

2. Characterization of the emulsion (24 hours after production)

The different characterizations done on emulsions are:

- Macroscopic evaluation of the aspect, colour and consistency of the emulsion
- Microscopical assessment of the structure of the emulsion under a stereomicroscope
- pH evaluation using a pHmeter (only if the emulsion displays an aqueous external phase)
- Rheological evaluation of the emulsion (using a viscometer Tve-05 at 200 rpm at 25°C)
- Sensorial profile (obtained through Gattefossé panel of experts).

Stability studies are performed according to ICH conditions.

3. Drug solubility screening in excipients

The solubility/affinity screening method of the OTC drug in the excipients is adapted from the technique of "Solubility Analysis by Phases" adopted by the USP 24 and the OECD.

- Weigh 0.1 g of drug into a 15 ml screw capped clear glass flask and add 8.9 g the selected excipient (final concentration 1%)
- Put flask in a sonication bath (bath temperature set at 30°C for liquid excipients and 55°C for semi-solid excipients)
- Sonicate mixtures for 15 minutes at 35 kHz, then examin. If the drug is completely solubilised, solubilisation time is recorded as 15 minutes. If it is not solubilised, 15 more minutes are added. Repeat procedure until sonication time reaches 90 minutes.

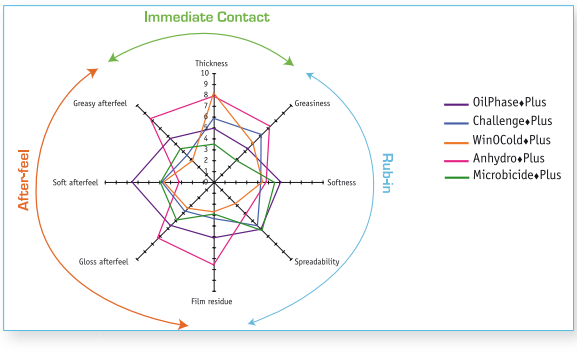
GATTEFOSSÉ 'DERMACARE' PLACEBO FORMULATIONS

Gattefossé has developed a 'Dermacare' kit to demonstrate the physico-chemical and the sensorial properties of five emulsifiers: Apifil®, Gelot™ 64, Plurol® Diisostearique, Sedefos™ 75 and Tefose® 63. This kit comprises 7 placebo creams selected for their enhanced sensorial properties (determined by sensorial analysis and mapping). Both the formulations and their evaluation are reported in the Dermacare brochure, available on request.

A brief presentation of five of them is done hereafter.

	OilPhase◆Plus	Challenge◆Plus	WinOCold◆Plus	Anhydro◆Plus	Microbicide◆Plus
Process	Classic (hot)	Classic (hot)	Classic (cold)	One pot	Classic (hot)
Emulsifier	Apifil®	Gelot™ 64	Plurol® Diisostearique	Sedefos™ 75	Tefose® 63
Stability (40°C)	9 months	6 months	3 months	6 months	12 months

The sensorial properties of the placebo Dermacare formulations are reported in the spider diagram below.



GUIDELINES FOR FORMULATING OTC DRUGS

The initial approach for selecting the right emulsifier for the drug is by drug solubility screening.
Two questions have then to be answered:

- How much solubilizer (either hydrophilic or lipophilic) is required to solubilize the drug?
- Which emulsifier can emulsify that amount of solubilizer?

Gattefossé has determined the maximum of lipophilic or hydrophilic phases that each emulsifier is able to disperse. This evaluation was done for emulsifier concentrations corresponding to those of the Dermacare placebo formulations. The results are presented in the following tables.

1. Matching emulsifiers with lipophilic phases

Max amount of excipient to be associated with:	Medium Chain Triglyceride	Mineral oil	Sweet Almond oil	Labrafil®
Apifil®	30%	40%	30%	30%
Gelot™ 64	12%	30%	20%	12%
Tefose® 63	18%	18%	18%	10%
Sedefos™ 75	25%	40%	25%	25%
Plurol® Diisostearique	< 4%	30%	< 4%	< 4%

2. Matching emulsifiers with hydrophilic phases

Max amount of excipient to be associated with:	Glycerine	Propylene glycol	Ethanol	Transcutol® P	PEG 300
Apifil®	15%	20%	10%	30%	< 10%
Gelot™ 64	20%	20%	10%	10%	< 5%
Tefose® 63	5%	< 30%	10%	10%	5%
Sedefos™ 75	Complete substitution	20%	10%	10%	< 20%
Plurol® Diisostearique	25%	< 3%	5%	10%	< 5%

3. Formulating OTC drugs

The solubility of **sodium diclofenac** is screened in the different excipients. The results obtained are listed hereafter.

Solubility screening of 1% sodium diclofenac at 55°C	
Apifil®	NS
Gelot™ 64	S (15 min)
Sedefos™ 75	S (60 min)
Tefose® 63	S (15 min)
Emulcire™ 61 WL 2659	S (15 min)

Solubility screening of 1% sodium diclofenac at 30°C			
Plurol® Diisostearique	S (90 min)	Glycerine	S (45 min)
Labrafil® M 1944 CS	S (90 min)	Ethanol	S (15 min)
Labrafac™ Lipophile WL 1349	NS	PEG 300	S (30 min)
Sweet almond oil	NS	Transcutol® P	S (30 min)
Mineral oil	NS	Propylene glycol	S (15 min)

S: soluble (amount of sonication time required to obtain solubilisation) - NS: non soluble after 90 minutes' sonication

Our aim is formulate an anti-inflammatory emulsion loaded with 1% sodium diclofenac. This emulsion should display good spreadability properties.

Combining the solubility results obtained for the drug in the excipients and the capacity of each emulsifier to emulsify them, one can select possible emulsifers to formulate this drug. An evaluation of the sensorial properties that each emulsifier can give to the final emulsion enables to select the most convenient emulsifier, both to solubilise the drug and to give the final emulsion the required sensorial properties. **Challenge◆Plus** (using Gelot™ 64) is selected as start-off formulation, as described in the following table.

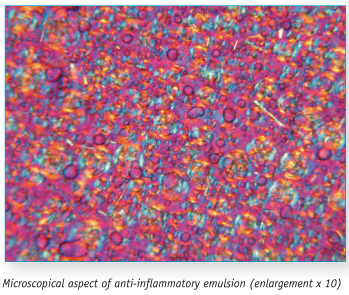
Anti-inflammatory emulsion

	Ingredients	Functionality	%W/W
Phase I	**Gelot™ 64**	**Emulsifier**	**3.00**
	Emulcire™ 61 WL 2659	**Emulsifier**	**3.00**
	Cetyl alcohol	Texture agent	3.00
	Labrafil® M 1944 CS	**Oily phase**	**2.00**
	Mineral oil	Oily phase	10.00
Phase II	Demineralized water	Aqueous phase	67.85
	Sorbic acid	Preservative	0.10
	Methyl paraben sodium salt	Preservative	0.05
Phase III	**Transcutol® P**	**Cosolvent**	**10.00**
	Sodium diclofenac	Drug	1.00

The emulsion's characteristics are listed in the table below:

Anti-inflammatory emulsion

Process	Classic (hot) with incorporation of phase III at 35°C
Macroscopic	Supple, compact white cream
Microscopic evaluation	Homogeneous and fine structure, presence of liquid crystals Droplet size ranging 10 to 40 µm
pH	7.44
Viscosity (mPa.s)	4776



Microscopical aspect of anti-inflammatory emulsion (enlargement x 10)

No particles can be seen. Stability study is on going.

CONCLUSION

Understanding the sensorial properties of emulsifiers now enables the selection of emulsifiers as well as the optimization of formulations based both on the solubility results of the drug in different excipients and on the 'sensorial' objectives of the formulation.