GATTEFOSSÉ

Tefose® 63

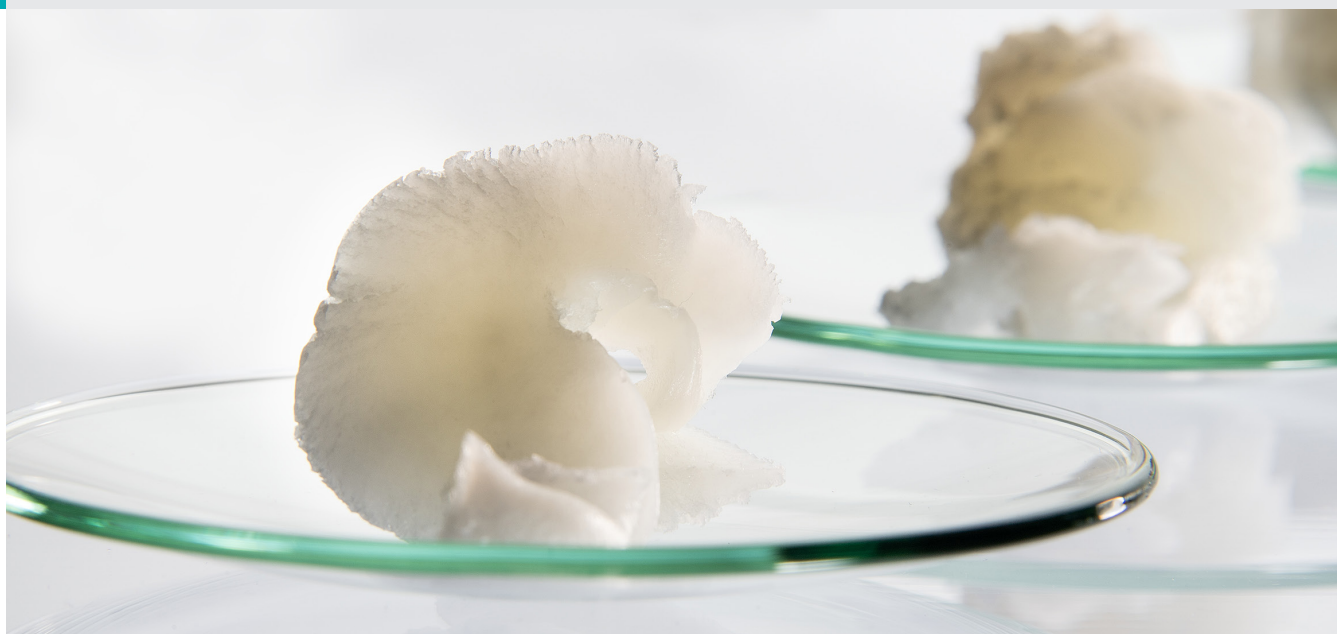
Oil-in-Water emulsifier for topical dosage forms

People make our name

ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **DSC:** Differential Scanning Calorimetry; **EDTA:** Ethylene Diamine Tetraacetic Acid; **FDA:** Food and Drug Administration; **HLB:** Hydrophilic Lipophilic Balance; **IID:** Inactive Ingredient Database; **OTC:** Over-the-counter; **O/W:** Oil-in-Water; **PEG:** PolyEthylene Glycol; **UNII:** Unique Ingredient Identifier; **USP NF:** US Pharmacopoeia National Formulary; **W/W:** Weight / Weight

Contents



Product description

A multi-component system

Tefose® 63 is a physical mixture of three compendial components: PEG-6 palmitostearate, ethylene glycol palmitostearate and PEG-32 palmitostearate. The exact quantity of each component has been carefully selected to obtain a self-emulsifying base (Figure 1).

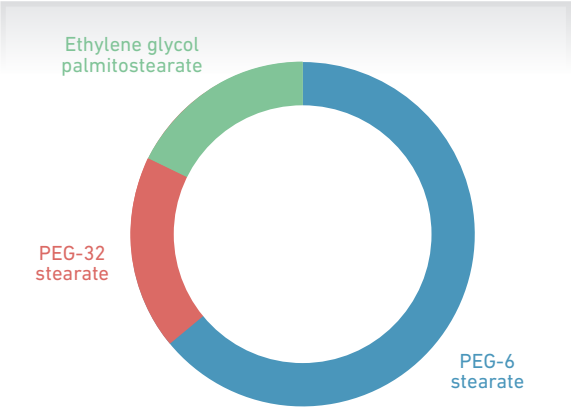


Figure 1: Composition of Tefose® 63

Table 1: Main physico-chemical properties

Drop point (Mettler, °C)	48.90 ± 0.53 (n=78)
HLB (calculated)	9.5
Solubility in ethanol 96°	Insoluble
Solubility in chloroform, methylene chloride	Soluble
Solubility in n-hexane	Insoluble
Solubility in mineral oil	Insoluble

Melt characteristics

Tefose® 63 has a wide melting range (Figure 2), from about 20 to 60°C, which implies:

- A temperature of 70-80°C is recommended to fully melt the excipient.
- At 20-25°C the excipient is not fully crystallized and contains a fraction in liquid state, therefore, it is a semi-solid supplied in block form.

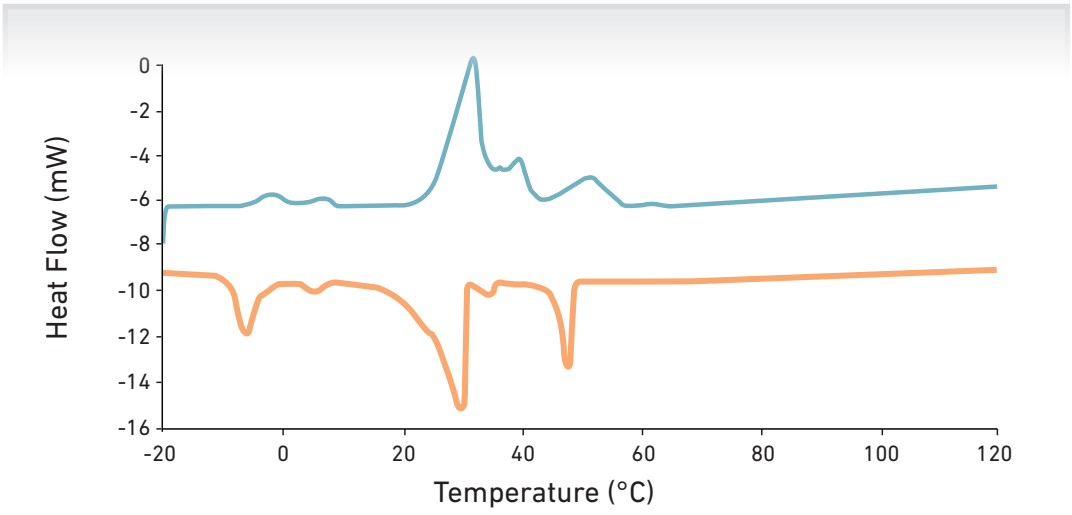


Figure 2: DSC thermogram of Tefose® 63

Product functionality

Tefose® 63 is a non-ionic oil-in-water emulsifier used in topical dosage forms. It contains all the components to easily obtain fine and homogenous emulsions with pleasant texture.

Traditionally emulsions are prepared using two surfactants; one with low HLB and one with high HLB. A series of emulsions using different ratios of these surfactants is prepared to determine the ratio at which the emulsion is stable (i.e. corresponding to the required HLB of the system).

With Tefose® 63 self-emulsifying base, formulation development and process are much simpler (Figure 3).

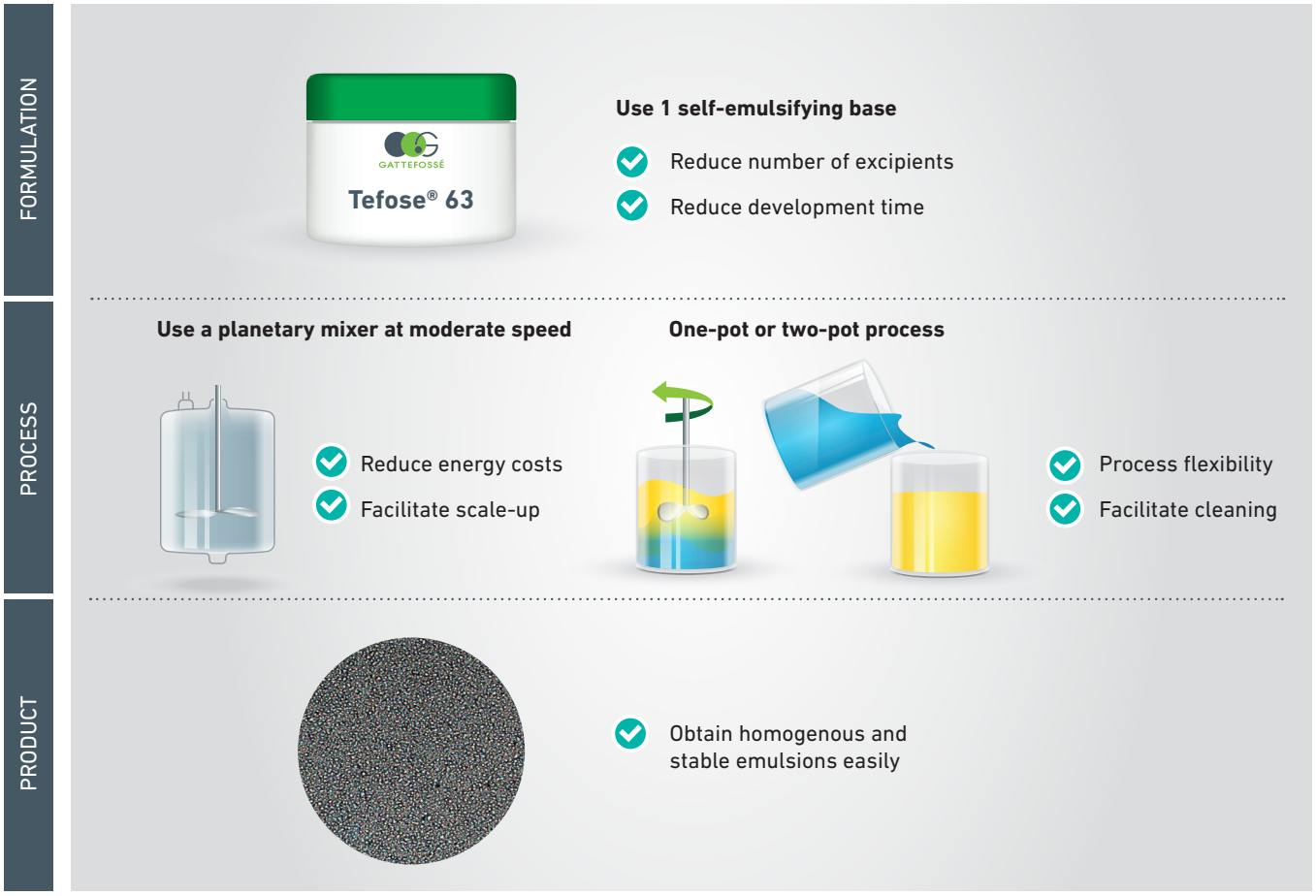


Figure 3: Formulation and process benefits of using Tefose® 63 self-emulsifying base

Handling and processing

Tips for correct product handling

Do:

- ✓ Entirely melt and mix Tefose® 63 before use
- ✓ Flush the container with nitrogen after use
- ✓ Store containers tightly sealed at room temperature

Don't:

- X Scrape the surface of Tefose® 63 for aliquoting
- X Heat the product in a water bath in an open beaker
- X Stir vigorously and incorporate air

Did you know?

Tefose® 63 is composed of several fractions with different densities and crystallization temperatures. After production, the molten excipient is hot filled in the container. During cooling and crystallization the product stratifies resulting in a non-homogenous composition in the container. Therefore, the entire product in the original container must be **fully melted at 70-80°C and homogenized before sampling and use.**

A detailed product handling sheet is available on request

Level of use

Tefose® 63 is used at 5 to 20% depending on the dosage form and target viscosity (Figure 4).

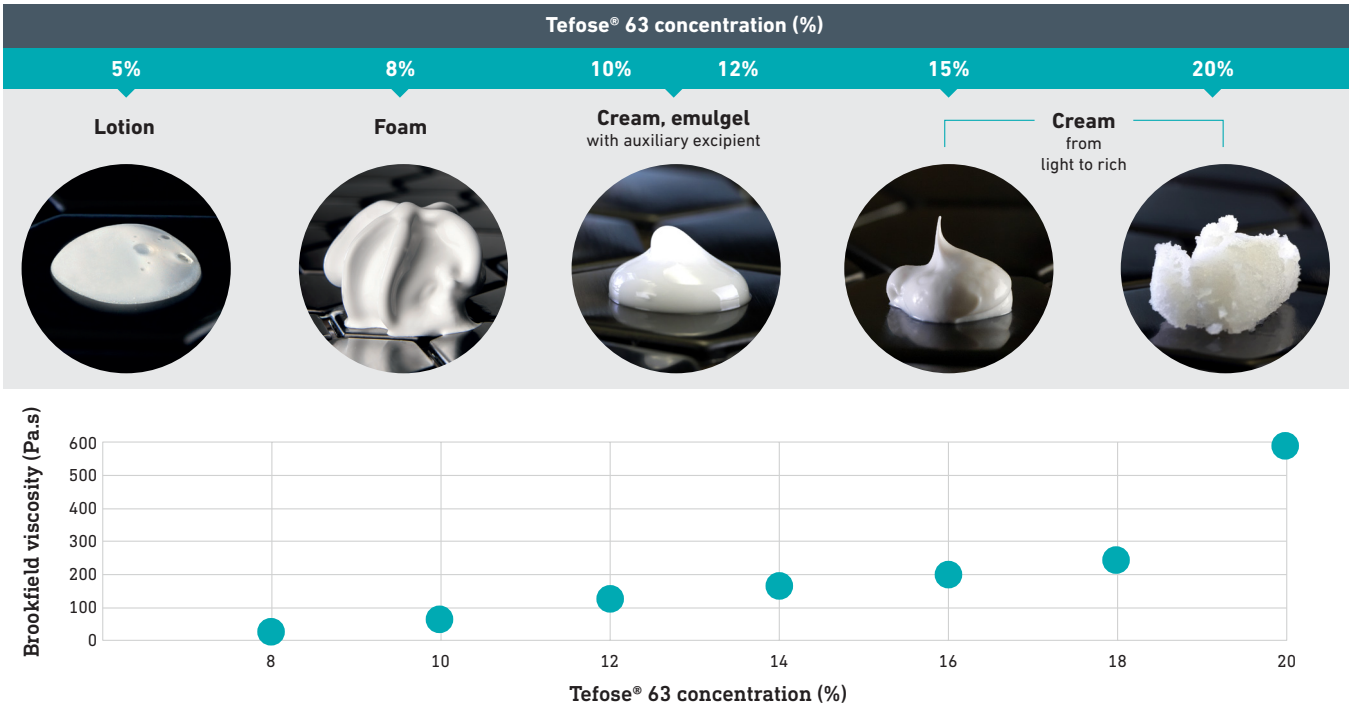


Figure 4: Viscosity of Tefose® 63 as a function of its concentration in water at 25°C

Process considerations

Fine and homogenous O/W emulsions are obtained with Tefose® 63, whatever the formulation process (Figure 5).

Classical "two-pot" process

In this process, aqueous and oily phases are prepared, heated separately; then combined and mixed.

- When water is poured in oil, a fine dispersion is quickly obtained. Note that a phase inversion occurs during the emulsification.
- When oil is poured in water, a longer dispersion time is required to get the fine emulsion.

Did you know?

Emulsions undergo a process called "Ostwald ripening" leading to an increase in viscosity during 2 - 4 days after production. Therefore, viscosity of the emulsion should be measured after this period. Note that a phase inversion process reduces the maturation time to 1 - 2 days.

"One-pot" process

In this process, all the ingredients of the emulsion are added at once and homogenized to obtain a fine emulsion.

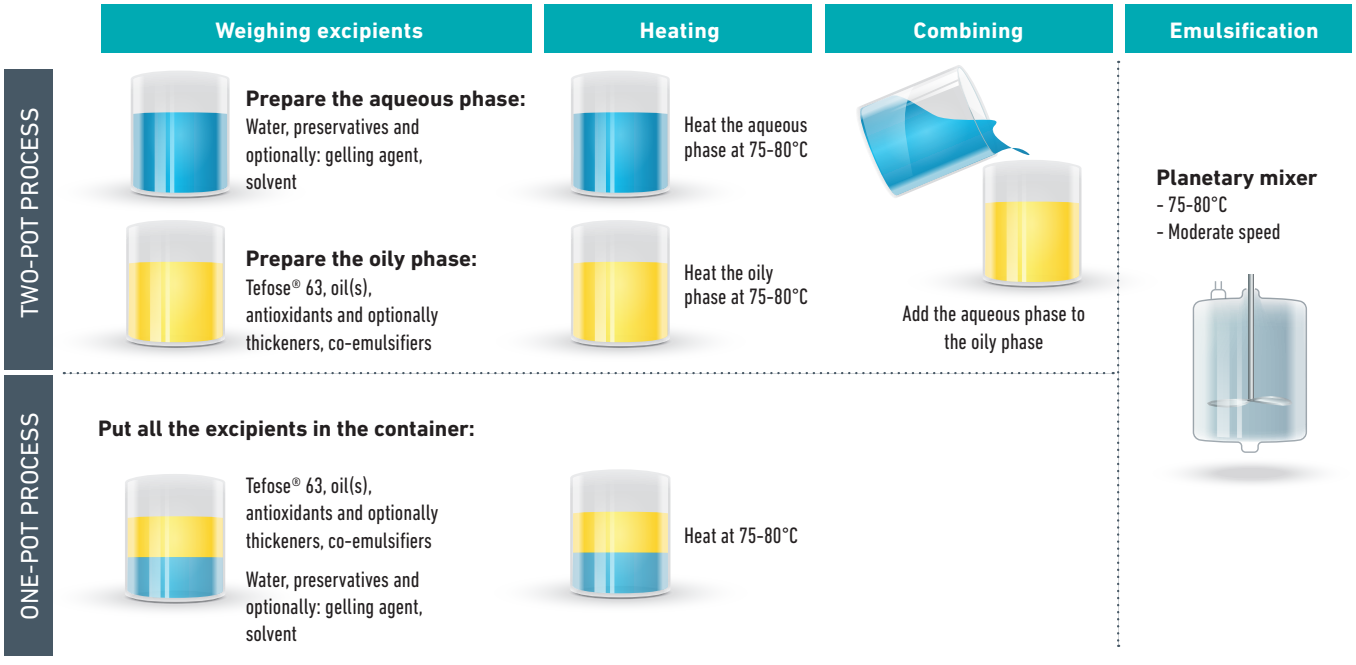


Figure 5: Tefose® 63 brings more process flexibility

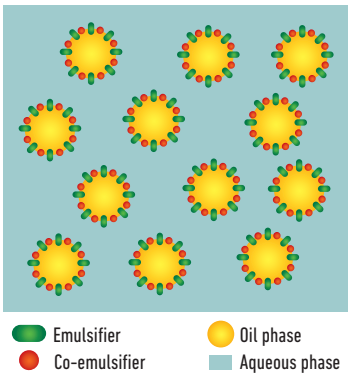
Did you know?

It is critical to ensure solid or semi-solid excipients are fully molten before use by heating at the correct temperature for an appropriate length of time.
In pilot or industrial production, the block of Tefose® 63 must be fully molten in the mixing vessel before using the planetary mixer to avoid potential damage to the axis.

Impact of auxiliary excipients

An emulsion consists of an oily phase, an aqueous phase and an emulsifier and is, by nature, an unstable thermodynamic system. To ensure shelf-life stability of final dosage forms it might be necessary to stabilize the system by acting on one or more of its components.

Using a co-emulsifier



Co-emulsifiers reinforce the action of the emulsifier at the interface between the aqueous and oily phases.

The ideal co-emulsifier for Tefose® 63 is Labrafil® M 1944 CS used at a ratio 2:1.

Labrafil® M 2130 CS can also be used at the same ratio however as a semi-solid co-emulsifier it will impart higher viscosity to the system (Figure 6).

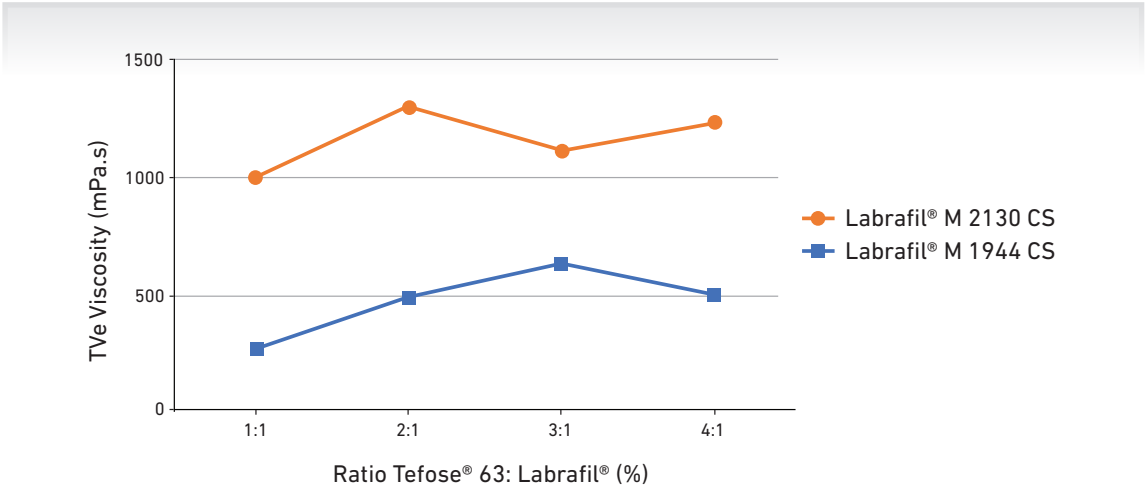
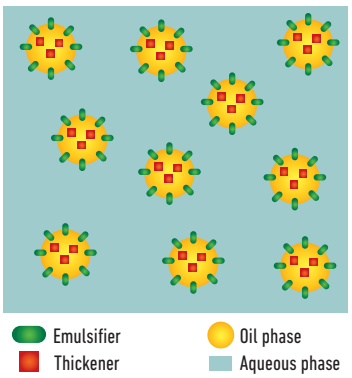
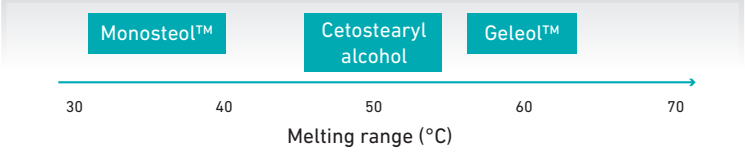


Figure 6: Effect of co-emulsifiers on emulsion viscosity (8% Tefose® 63, 8% mineral oil)

Adding a thickener to the oily phase



Increasing the viscosity of the oily phase reduces the risk of oil droplet coalescence. A high melting point lipophilic glyceride can be added to partially recrystallize in the oil droplets thereby increasing viscosity.



Monosteol™, cetostearyl alcohol and Geleol™ mono and diglycerides NF are common thickeners used in O/W emulsion at 2% (Figure 7).

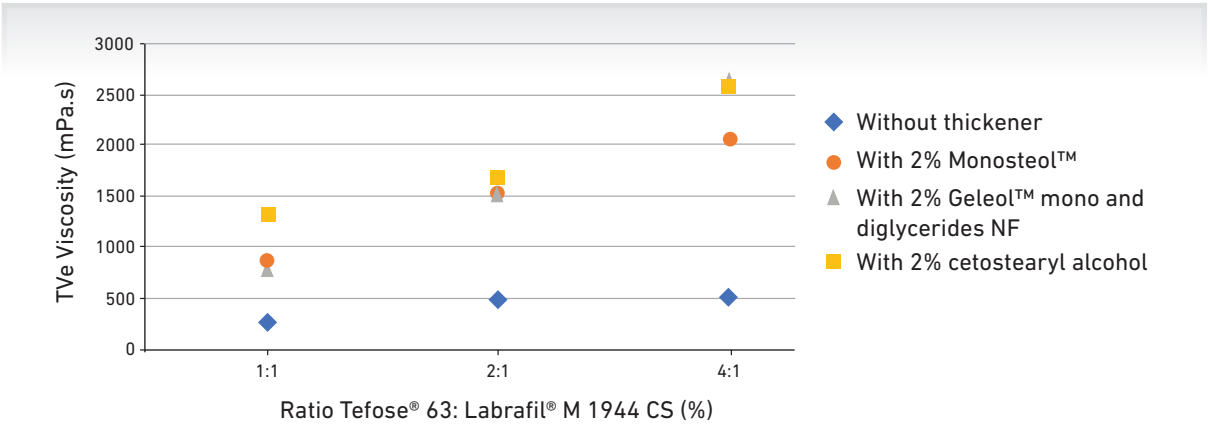
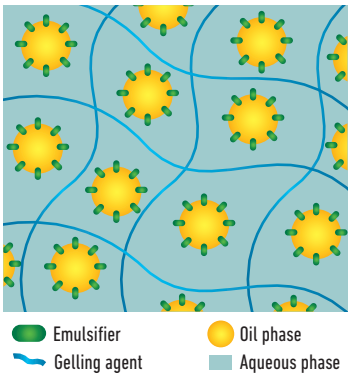


Figure 7: Effect of thickeners on emulsion viscosity (8% Tefose® 63, 8% mineral oil)

Adding a gelling agent in the aqueous phase



The use of a gelling agent in the aqueous phase increases viscosity dramatically (Figure 8). The polymer chains stiffen the aqueous phase preventing oil droplet movement.

Using a carbomer as gelling agent (e.g. Carbopol® 974 P) requires NaOH neutralization at the end of the process to stabilize the polymer network.

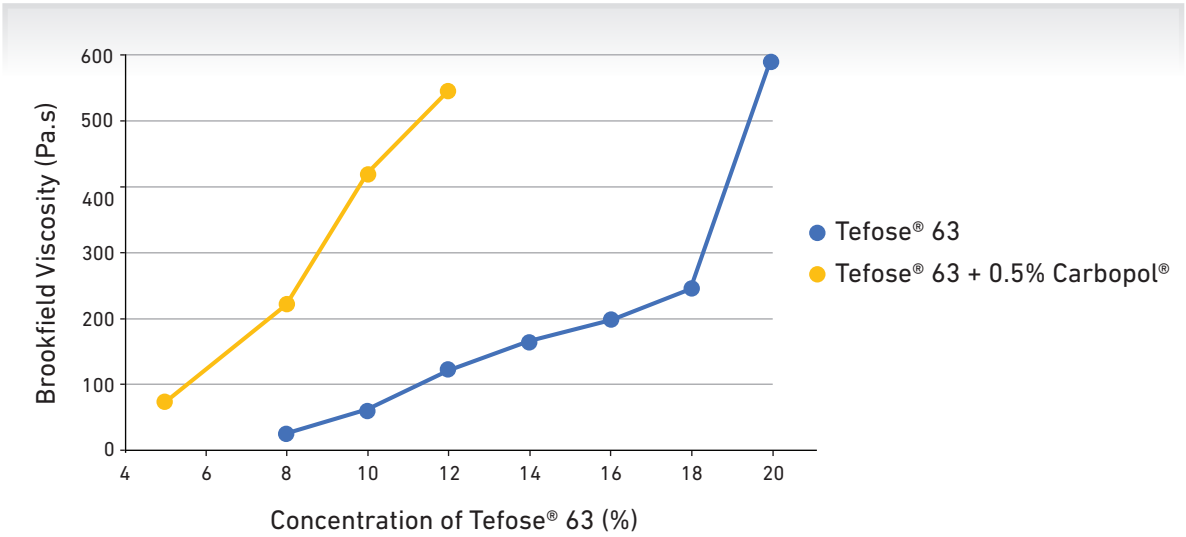


Figure 8: Effect of a gelling agent on emulsion viscosity (8% Tefose® 63, 8% mineral oil)

Case studies

#1: Antifungals for topical and vaginal application

Antifungals of the azole group are widely used as first-line treatments for topical and vaginal mycoses. Dosage forms range from light lotions to rich creams. Major worldwide market references use a mixture of PEG-stearates and ethylene glycol stearate i.e. Tefose® 63 as the emulsifying base.

Did you know?

Azoles are difficult to formulate APIs:

Highly reactive and sensitive to oxidation → an antioxidant is compulsory

Dispersed in the formulation (not fully solubilized) → an auxiliary agent is often necessary

Gattefossé has extensive know-how in developing and characterizing formulations for "azole" APIs. Formulations are developed to match the properties of approved market references and to provide tips to formulate antifungals in various dosage forms (Figure 9).

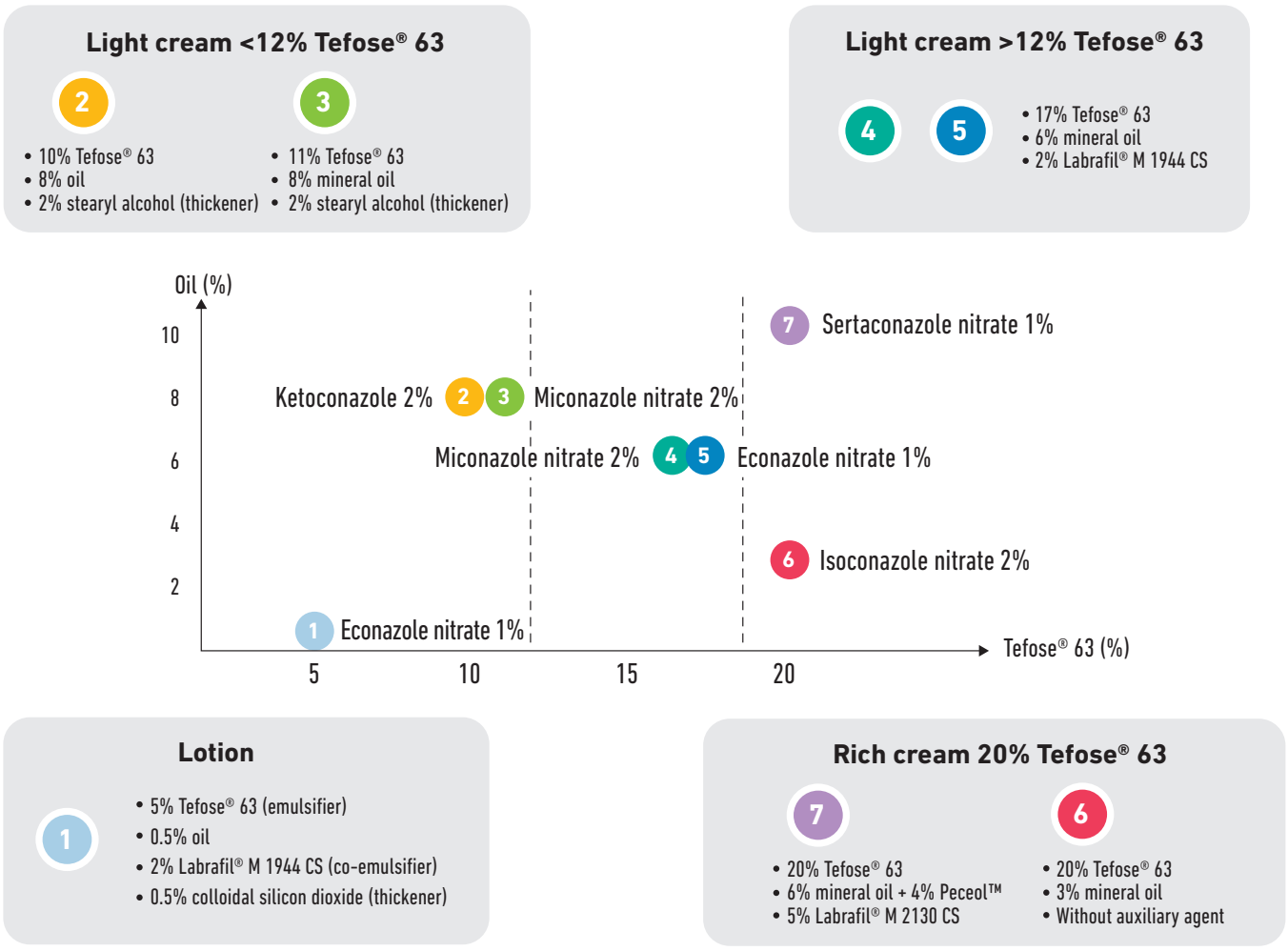


Figure 9: Generic prototypes of major antifungal market references using Tefose® 63

Gattefossé has developed generic formulation dossiers for popular antifungal actives comprising:

- ✓ Gattefossé formulation equivalent to originator
- ✓ Complete physico-chemical characterization
- ✓ Process parameters for lab scale manufacturing
- ✓ Stability data over 1 year

Generic dossiers for antifungal creams are available upon request

Did you know?

Tefose® 63 is a non-irritant emulsifier, suitable for topical and mucosal drug delivery that has been used safely for more than 50 years.

Precedence of use in topical dosage forms with the following antifungal APIs has been recorded:

- Azoles: isoconazole, clotrimazole, econazole nitrate, miconazole nitrate, sertaconazole
- Allylamines / benzylamines: terbinafine hydrochloride
- Hydroxypyridones: ciclopirox olamine
- Other group: tolnaftate.

In vaginal creams precedence of use is established with the following antifungal APIs:

- Azoles: clotrimazole, econazole nitrate, metronidazole, miconazole nitrate
- Allylamines / benzylamines: terbinafine hydrochloride.

#2: Designing dosage forms for patient preference

Anti-inflammatories are available in a variety of dosage forms, such as creams, gels, emulgels and foams. Emulgels and foams are reported to receive positive patient feedback due to their pleasant application and sensorial properties. Examples of emulgel and foam formulations are provided below as alternatives to marketed creams.

Emulgels: the softness of a cream, the strength of a gel

Multiple benefits are associated with emulgels, such as light texture, non-greasiness, non-tackiness, increased stability due to the gelling agent, effective skin delivery due to the dual system emulsion/ gel and suitability for hydrophilic and hydrophobic drugs.

	Excipient	Functionality	Quantity (% W/W)
A	Diclofenac diethylamine	API	1.0
	Transcutol® P	Solubilizer	6.0
	Propylene glycol	Solubilizer	6.0
	Benzyl alcohol	Preservative	1.0
B	Carbomer 980 NF	Gelling agent	0.5
	Water	Aqueous phase	81.7
C	Tefose® 63	O/W emulsifier	2.0
	Mineral oil	Oil	1.0
D	Triethanolamine (sol. 50%)	Neutralizing agent	0.8

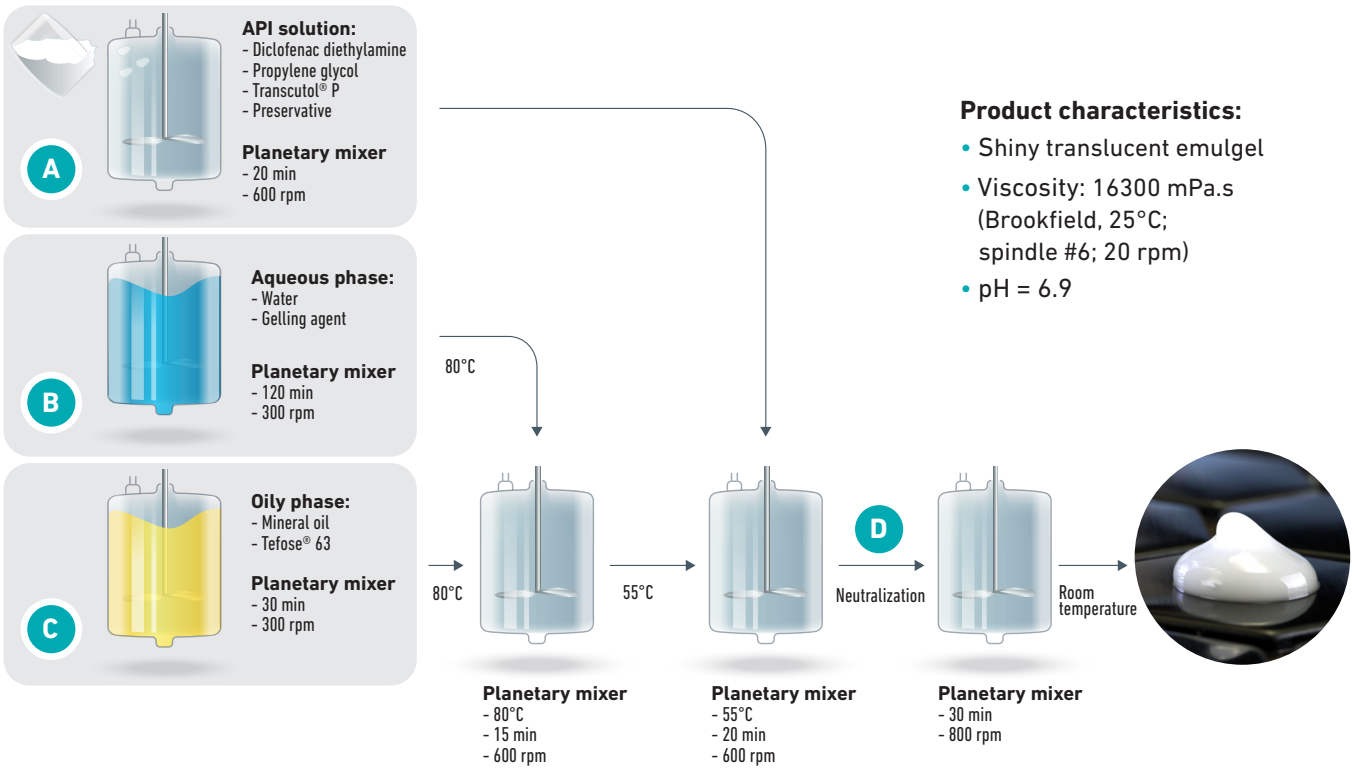


Figure 10: Emulgel process (lab scale)

Foams: high spreadability with limited residue on the skin

Pharmaceutical foams provide advantages to patients including pleasant application, texture and sensorial features. Gattefossé has developed prototype microemulsion formulations that can easily be converted in a foam with a propellant device.

	Excipient	Functionality	Quantity (% W/W)
A	Diclofenac sodium	API	1.0
	Transcutol® P	Solubilizer	5.0
	Propylene glycol	Solubilizer	5.0
B	Tefose® 63	O/W emulsifier	8.0
	Labrafil® M 1944 CS	Co-emulsifier	4.0
C	Benzyl alcohol	Preservative	1.0
	Water	Aqueous phase	76.0

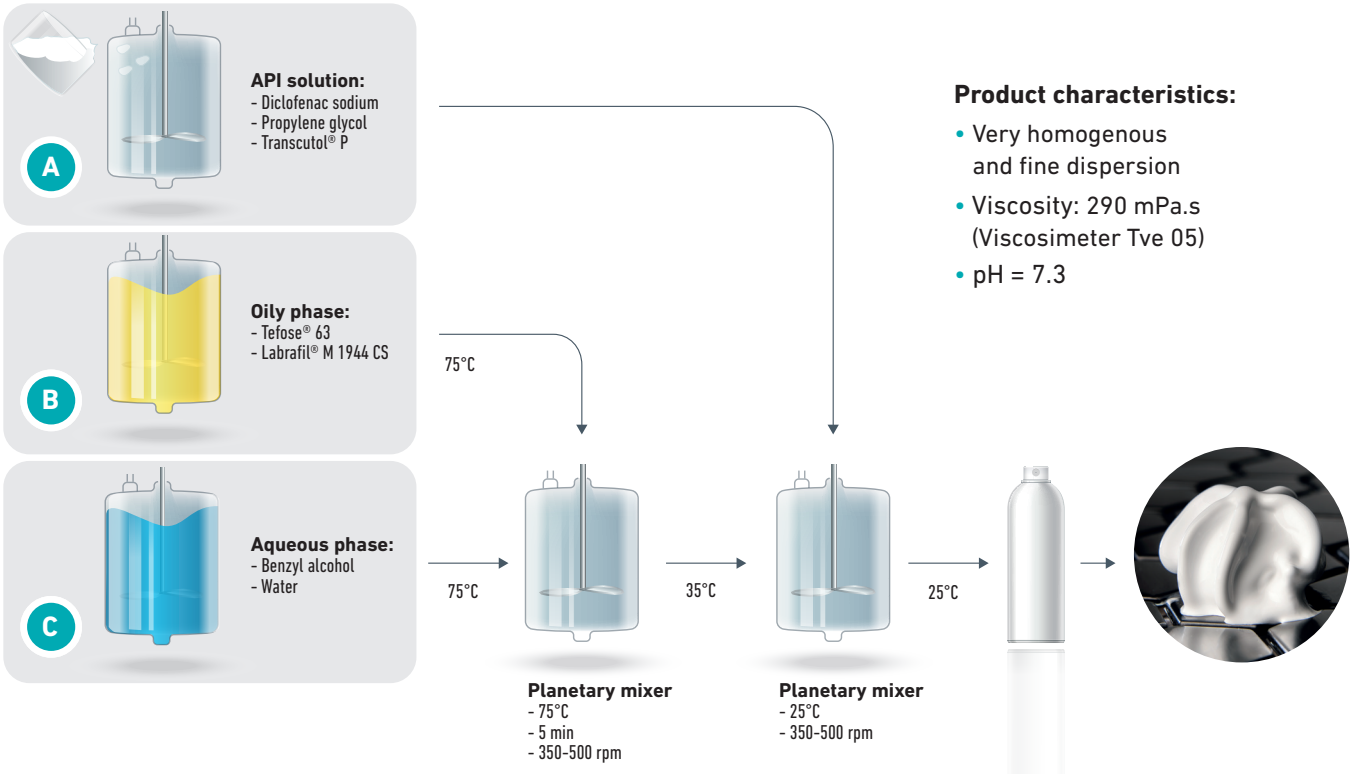


Figure 11: Foam process (lab scale)

The texture of the prototype foam was evaluated and compared to a marketed foam, gel and emulgel by a trained sensory panel. Foam benefits were highlighted: non-tacky, non-greasy after-feel, light texture, easy spreadability, softness during and after application and reduced film residue.

Download our publications on foams

#3: Tefose® 63: a versatile emulsifier

Several formulations are provided below with different APIs and dosage forms to illustrate the versatility of Tefose® 63. More prototype formulations are available upon request.

Anti-acne: lotion with adapalene

	Excipient	Functionality	Quantity (% W/W)
A	Tefose® 63	O/W emulsifier	4.00
	Labrafil® M 1944 CS	Co-emulsifier	1.00
	Stearyl alcohol	Thickener	0.50
	Mineral Oil	Oil	6.00
	Methylparaben	Preservative	0.05
	Propylparaben	Preservative	0.05
B	Carbopol 981	Gelling agent	0.15
	EDTA-2Na	Chelating agent	0.10
	Demineralized water	Aqueous phase	77.90
C	Propylene glycol	Solvent	5.00
	Transcutol® P	Solubilizer	5.00
	Adapalene	API	0.10
D	NaOH solution (10%)	Neutralizing agent	0.15

Product characteristics:

- Viscosity: 6700 mPa.s (Brookfield 25°C, spindle#5; 20 rpm)
- pH: 5.0 ± 0.5

- Prepare phase A: mix all ingredients and heat to 70°C
- Prepare phase B: mix all ingredients and heat to 70°C
- Prepare phase C: solubilize the API in propylene glycol and Transcutol® P
- Add phase A into phase B under continuous stirring
- Add phase C into the blend at about 55°C under continuous stirring
- Add phase D to adjust pH
- Cool down to room temperature while stirring

Corticosteroids: cream with halometasone

	Excipient	Functionality	Quantity (% W/W)
A	Tefose® 63	O/W emulsifier	10.00
	Stearyl alcohol	Thickener	3.00
	Mineral oil	Oil	12.00
	Ethylparaben	Preservative	0.10
B	EDTA-2Na	Chelating agent	0.10
	Demineralized water	Aqueous phase	71.75
C	Transcutol® P	Solubilizer	3.00
	Halometasone	API	0.05

Product characteristics:

- Viscosity: 20000 mPa.s (20°C; spindle #6; 20 rpm)
- pH: 3.6 ± 0.5

- Prepare phase A: mix all ingredients and heat to 80°C
- Prepare phase B: mix all ingredients and heat to 80°C
- Prepare phase C: dissolve the API in Transcutol® P
- Add phase A into phase B under continuous stirring
- Add phase C into the blend at about 55°C under continuous stirring
- Cool down to room temperature while stirring

Cicatrizant: cream with hyaluronic acid

	Excipient	Functionality	Quantity (% W/W)
A	Tefose® 63	O/W emulsifier	12.00
	Ovucire® WL 3264 pellets	Texture agent	5.00
	Sweet almond oil	Emollient, oil	5.00
B	Hyaluronic acid (sodium salt)	API	0.20
	Glycerin	Moisturizing agent	5.00
	Methyl paraben sodium salt	Preservative	0.05
	Sorbic acid	Preservative	0.10
	Demineralized water	Aqueous phase	72.65

Product characteristics:

- Viscosity: 5000 mPa.s (20°C; spindle #6; 20 rpm)
- pH: 4.5 ± 0.5
- Fine and homogenous dispersion

- Prepare phase A: mix all ingredients and heat to 80°C
- Prepare phase B: add the API, preservatives and glycerin to water then heat the aqueous phase to 80°C
- Add phase B to phase A under moderate stirring for 5 min at 80°C
- Cool down to room temperature while stirring

Anti-acne: emulgel with benzoyl peroxide

	Excipient	Functionality	Quantity (% W/W)
A	Propylene glycol	Solubilizer	4.0
	Transcutol® P	Solubilizer	10.0
	Benzoyl peroxide (sol. 75%)	API	6.7
B	Tefose® 63	O/W emulsifier	3.0
	Sweet almond oil	Oil	6.0
C	Carbopol 940NF	Gelling agent	0.5
	Benzyl alcohol	Preservative	1.0
	EDTA	Anti oxidant	0.1
	Demineralized water	Aqueous phase	67.7
D	NaOH (sol. 10%)	Neutralizing agent	1.0

Product characteristics:

- Viscosity: 2700 mPa.s (viscosimeter TVe-05 25°C)
- pH: 5.5 ± 0.5

- Prepare phase A: solubilize the API in propylene glycol and Transcutol® P
- Prepare phase B: add Tefose® 63 to sweet almond oil and heat the oily phase to 75°C
- Prepare phase C: add the preservative and antioxidant to water and disperse the gelling agent (1500 – 2000 rpm) and allow to hydrate. Then heat the aqueous phase to 75°C
- Pour the aqueous phase in the oily phase under moderate stirring (500 rpm) for 5 min at 75°C
- Cool down and add the API solution when the temperature reaches 45°C
- Neutralize with 10% NaOH solution
- Cool down to room temperature

Regulatory information and precedence of use

Tefose® 63 is a mixture of PEG-6 stearate (type I) NF and Ethylene glycol palmitostearate EP/NF/JPE and PEG-32 stearate (type I) NF (Table 2). Since it is a mixture of components, no direct use level is given in the US FDA Inactive Ingredient Database. However, IID values for chemical equivalents and for the most similar equivalents of the individual components are listed (Table 3). Tefose® 63 is a well-characterized, safe excipient with a long history of use in approved topical and vaginal medicines (Table 4).

Table 2: Tefose® 63 regulatory summary

USP NF Name	Mixture of Polyoxyl 6 Stearate Type I, Ethylene Glycol Stearates and Polyoxyl 32 Stearate Type I
EP Name	Mixture of Macrogol-6 stearate type I (pending), Ethylene glycol monopalmitostearate and Macrogol-32 stearate type I (pending)
UNII Code (FDA)	8LQC57C6B0 0324G66D0E 33GX5WQC0M
Other denomination	Pegoxol-7 stearate
Handbook of Pharmaceutical Excipients	Polyoxylethylene stearates
Drug master file	Canada MF 2016-201

Table 3: US FDA inactive ingredient database references

	Inactive Ingredient listed in FDA database	Route / Dosage form	Use level
Chemical equivalent	Pegoxol-7 stearate	Topical / Emulsion, cream	22% W/W
		Vaginal / Emulsion, cream	20%
	PEG 6-32 stearate/glycol stearate	Topical / Emulsion, cream	19.6% W/W
		Vaginal / Emulsion, cream	19.6%
Most similar chemical to PEG-6 stearate and PEG-32 stearate	Polyoxyl 6 and polyoxyl 32 palmitostearate	Topical / Emulsion, cream	20% W/W
		Topical / Lotion	2% W/W
	Polyoxyl stearate	Topical / Emulsion, cream	20% W/W
		Topical / Lotion	2% W/W
Most similar chemical to ethylene glycol stearate	Glycol stearate	Topical / Emulsion, cream	1% W/W

For more information please request our Regulatory Datasheet

Table 4: Examples of marketed topical dosage forms containing pegoxol-7 stearate

Active ingredient	Indication	Dosage form	Country
Acyclovir	Antiviral	Cream	Italy, Taiwan
Benzoyl peroxide	Antibacterial	Cream	Taiwan
Betamethasone 17-valerate Gentamycin sulfate	Antiinflammatory Antibiotic	Cream	Taiwan
Centella asiatica extract	Healing	Cream, Ointment	Taiwan, South Korea
Clobetasol propionate	Antifungal	Cream	Tunisia
Clotrimazole Betamethasone hydrochloride	Antifungal Antiinflammatory	Cream	Taiwan
Clotrimazole Hexamidine	Antifungal Antiseptic	Cream	Turkey
Colostrum Sodium hyaluronate	Hydrating agents	Cream	Worldwide
Crotamiton Hydrocortisone	Antifungal Antiinflammatory	Cream	Taiwan
Econazole	Antifungal	Cream	France
Econazole Triamcinolon Gentamycin	Antifungal Antiinflammatory Antibiotic	Cream	South Korea
Econazole nitrate	Antifungal	Cream, Lotion	France, Switzerland, USA
Econazole nitrate Triamcinolone acetonide	Antifungal Antiinflammatory	Cream	South Korea
Centella asiatica extract Hydrocortisone Neomycin sulfate	Healing Corticosteroid Antibiotic	Ointment	South Korea
Gentamycin sulfate	Antiinflammatory	Cream	Taiwan
Gentamycin sulfate Clotrimazole Betamethasone hydrochloride	Antibiotic Antifungal Antiinflammatory	Cream	Taiwan
Heparin sulfate	Anti-varicose	Cream	Italy
Hydrocortisone	Antiinflammatory	Cream	The Philippines
Hydrocortisone Miconazole nitrate	Antiinflammatory Antifungal	Cream	Spain
Isoconazole	Antifungal	Cream	France, Morocco, Taiwan
Miconazole	Antifungal	Cream	Germany
Miconazole nitrate	Antifungal	Cream	France, Italy, Spain, Egypt, USA
Nadifloxacin	Antibiotic	Cream	Taiwan
Oxymetazoline hydrochloride	Sympathomimetic	Cream	USA
Sertaconazole	Antifungal	Cream	France, Spain
Terbinafine hydrochloride	Antifungal	Cream	USA, Taiwan, Tunisia
Tolnaftate Chlorydrine HCl	Antibacterial Antifungal	Cream	Taiwan
Triamcinolon Econazole nitrate	Antiinflammatory Antifungal	Cream	Australia, Europe
Urea	Hydrating agent	Cream	South Korea

More than 50 years of safe use of Tefose® 63

Tefose® 63 is a safe non-irritant emulsifier that has been used for more than 50 years in vaginal and topical formulations, for acute and chronic diseases, for adult and paediatric populations, in OTC and prescription medicines. Some major market reference examples are given below to illustrate Tefose® 63 versatility of uses.

Pevaryl — 1975

A vaginal cream containing econazole nitrate formulated with Tefose® 63 and Labrafil® M 1944 CS.

The cream contains 1% econazole nitrate. The other ingredients are **Tefose® 63, Labrafil® M 1944 CS**, *mineral oil, butylated hydroxyanisole (E320), benzoic acid (E210), purified water.*

http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=61685323&typedoc=R#RcpListeExcipients

Pevisone — 1978

A cream for topical application containing econazole nitrate and triamcinolone as active ingredients and Tefose® 63 and Labrafil® M 1944 CS.

Each gram contains 10 mg econazole nitrate and 1 mg triamcinolone. List of Excipients: Benzoic acid, **PEG-6 (and) PEG-32 (and) glycol stearate, oleoyl macrogolglycerides**, *paraffin oil, butylated hydroxyanisole, disodium edetate, purified water.*

http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=66108628&typedoc=N

Pharmatex — 1997

A vaginal cream with benzalkonium chloride as local contraceptive and an emulsifier such as Tefose® 63.

The cream contains 1.2% benzalkonium chloride. List of Excipients: Anhydrous citric acid, **macrogol stearate and ethylene glycol (i.e. Tefose® 63)**, *sodium hydrogenophosphate, essential oil, purified water.*

http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=65147126&typedoc=N

Monazol — 1998

A cream for topical and vaginal application containing sertaconazole nitrate as active ingredient and Tefose® 63 and Labrafil® M 1944 CS.

Active Ingredient: Sertaconazole nitrate 2%. Other Ingredients: **Polyoxyethylene glycol stearate and ethylene glycol (Tefose® 63), lauric macroglycerides (Labrafil® M 2130 CS)**, *glycerol isostearate (isostearic peceol), light liquid paraffin, sorbic acid, methylparaben, purified water.*

http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=66910838&typedoc=R

Rhofade — 2017

This USA FDA approved cream is a prescription medicine for chronic treatment of persistent rosacea in adults.

Each gram of RHOFADE cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8 mg (0.88%) of oxymetazoline free base and the following inactive ingredients: sodium citrate dihydrate, citric acid anhydrous, disodium edetate dihydrate, butylated hydroxytoluene, anhydrous lanolin, medium chain triglycerides, diisopropyl adipate, oleyl alcohol, polyethylene glycol 300, **PEG-6 stearate, glycol stearate, PEG-32 stearate**, *cetostearyl alcohol, ceteareth-6, stearyl alcohol, ceteareth-25, methylparaben, propylparaben, phenoxyethanol, and purified water.*

https://www.rxlist.com/rhofade-drug.htm#indications

Xepi — 2019

A recent USA FDA, Canada and EMEA approved cream containing a quinolone antimicrobial indicated for the topical treatment of impetigo due to Staphylococcus aureus or Streptococcus pyogenes in adult and pediatric patients 2 months of age and older.

Each gram of cream contains 10 mg of ozenoxacin (1% w/w) and the following inactive ingredients: benzoic acid, octyldodecanol, peglicol 5 oleate, **pegoxol 7 stearate**, *propylene glycol, purified water, stearyl alcohol.*

https://www.xepicream.com

Technical support

Gattefossé range of excipients for topical drug delivery include solubilizers, emulsifiers and viscosity modifying agents. Emulsifiers are designed for challenging formulations and deliver excellent texture and sensorial properties. Solubilizers provide skin penetration enhancement and viscosity agents stabilize formulations. Our excipients are used in creams, emulgels, lotions, foams, microemulsions and gels. Gattefossé can provide technical support to help you with the selection of excipients for topical drug delivery.

Please contact your local Gattefossé representative

GATTEFOSSÉ

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www.gattefosse.com

Corporate Headquarters
36 chemin de Genas - CS 70070 - 69804 Saint-Priest Cedex - **France**
+(33) 4 72 22 98 00

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