Technical Information

Kollicream® Grades
Kollisolv® MCT 70

Linear alcohols and esters, medium-chain triglycerides:
Emollients for topical applications.

February 2019 | Supersedes issue dated June 2013 | Last change WF-No. 137282

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1. Introduction

While the products cover a wide range of application fields, e.g. oral dosage forms for lipophilic APIs, this technical information sheet is designed to provide an overview on our pharmaceutical-grade emollients for topical pharmaceutical applications. With the inherently low potential for irritation, our petrolatum-free emollients are designed to create mild formulations that are easy to apply even onto large areas, and leave a pleasant feeling on the skin. The products are based on vegetable resources, and manufactured under IPEC-PQG GMP conditions.

Trade name	Compendial name	Highlights for use as an Emollient
Kollicream® 3 C	Ph. Eur.: Cocoyl Caprylocaprate	Solubilizer/penetration enhancer for some topical APIs
Kollicream® CP 15	Ph. Eur.: Cetyl Palmitate 15	Replacement for *spermaceti (from whales)*; relatively high melting point makes it a viscosity building agent in semi-solid creams, lotions and oils.
Kollicream® DO	Ph. Eur.: Decyl Oleate	Enhancing skin-penetration of some APIs by disordering stratum corneum lipid domains with its branched C_{18} chain.
Kollicream® IPM	Ph. Eur.: Isopropyl Myristate USP/NF: Isopropyl Myristate	Skin penetration enhancer for lipophilic actives.
Kollicream® OA	Ph. Eur.: Oleyl Alcohol USP/NF: Oleyl Alcohol	Enhancing skin-penetration of some APIs by disordering stratum corneum lipid domains with its branched C_{18} chain.
Kollicream® OD	Ph. Eur.: Octyldodecanol USP/NF: Octyldodecanol	Medium spreading, non-ester emollient, therefore inherently stable towards hydrolysis. Rapid plasticizer for com-promised skin.
Kollisolv® MCT 70	Ph. Eur.: Triglycerides, Medium-Chain USP/NF: Medium-Chain Triglycerides	Versatile solubilizer for lipophilic drugs, skin protectant through moisture retention.

2. Technical properties

Description

Kollicream® grades are either comprised of esters of fatty acids (3 C, CP 15, DO, IPM), or of natural (OA), as well as naturally derived (OD) long-chain alcohols. Except for CP 15, which is provided in the form of waxy pellets, all other members of the Kollicream® family, as well as Kollisolv® MCT 70, are transparent, colorless liquids at room tempreature. The raw material base is coconut oil, and/or palm kernel oil.


Kollicream® 3 C


Kollicream® DO


Kollicream® OA


Kollicream® CP 15


Kollicream® IPM


Kollicream® OD


Kollisolv® MCT 70

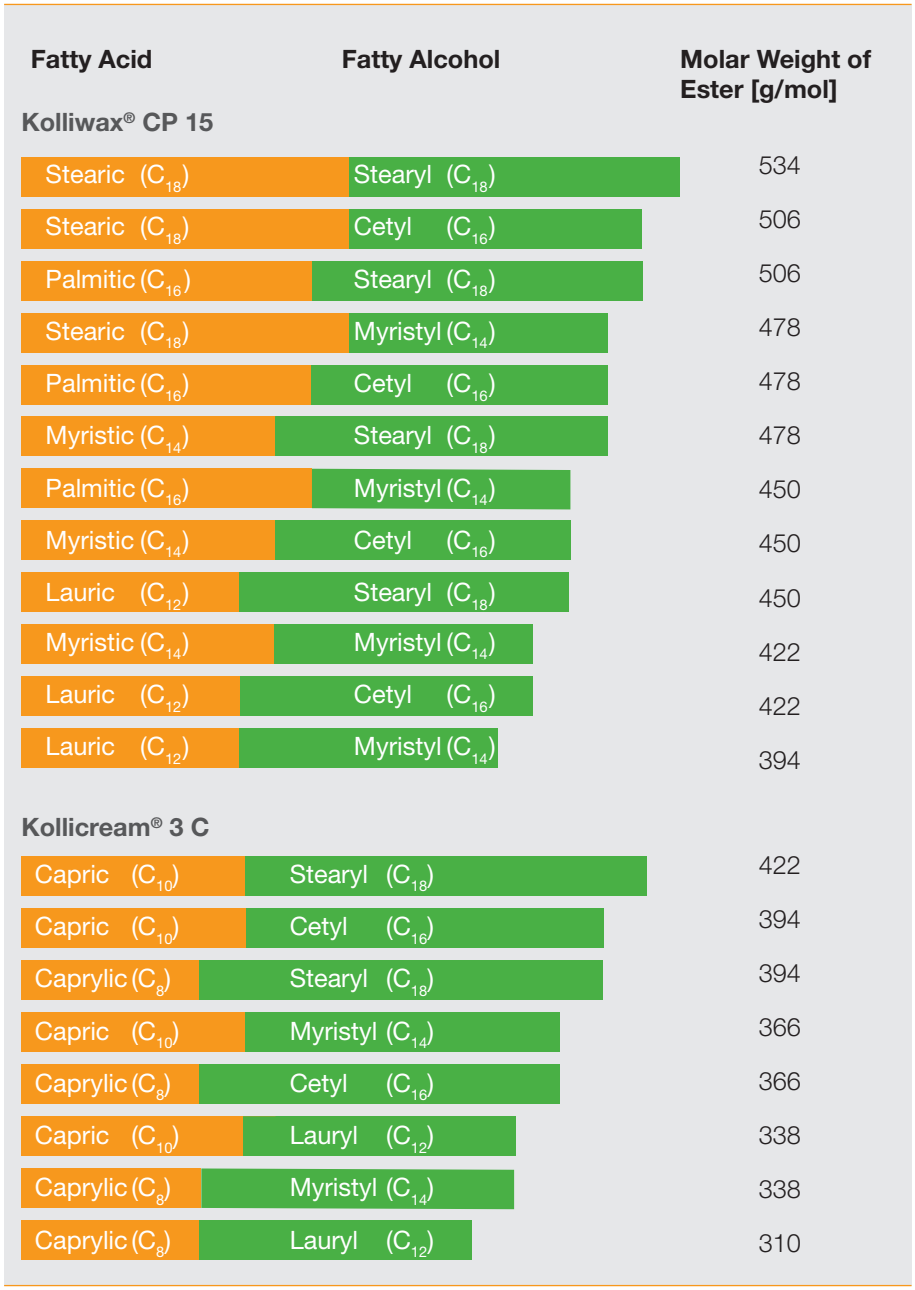


Figure 1: Overview on all esters contributing to the products Kollicream® CP 15 (top) and Kollicream® 3 C (bottom), ordered by molecular weight. The former name is derived from Cetyl Palmitate, the ester of palmitic acid and cetyl alcohol, which was historically made from Spermaceti, a waxy substance found in the head cavity of sperm whale. However, Kollicream® CP 15 is, as all our emollients, derived entirely from vegetable resources.
The name Cocoyl Caprylocaprate (Kollicream® 3 C) arises from coconut alcohol, a mixture of lauryl (C_{12}), and myristyl (C_{14}) alcohol, as well as caprylic (C_8) and capric (C_{10}) acid, which are among the most prevalent fatty acids in the triglycerides of coconut oil.

Brookfield Viscosities

The following graph summarizing the product viscositites is for guidance only: please refer to the individual specification sheets for detailed viscosity information. Brookfield viscosities were measured in a temperature-controlled glass vial of approx. 35 mm inner diameter at 100 rpm using a DV3T device with LV-73 spindle.

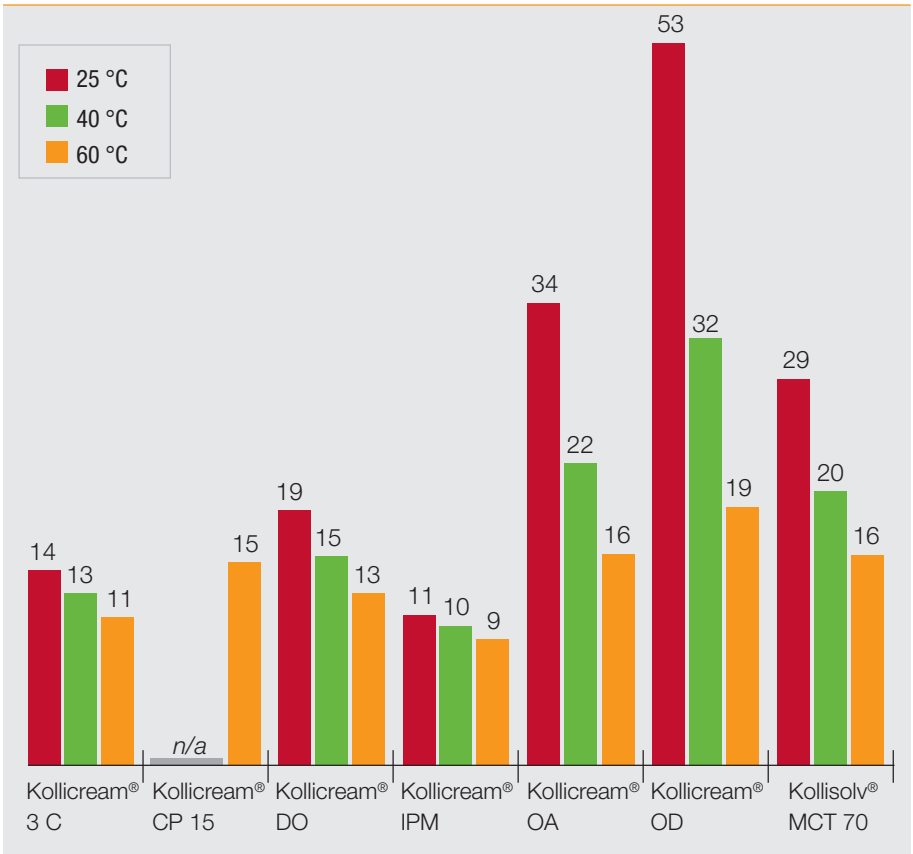
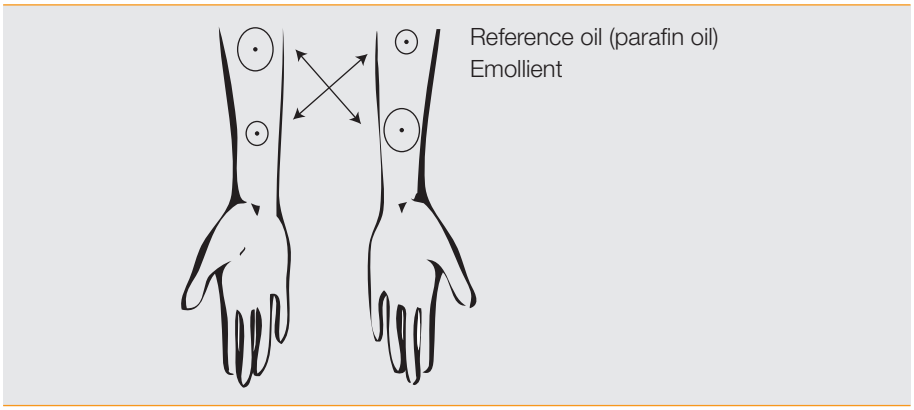


Figure 2: Brookfield Viscosities (values given in cP), measured at three different temperatures. Due to the relatively high melting point, Kollicream® CP 15 could not be measured at the first two temperatures.

Spreading

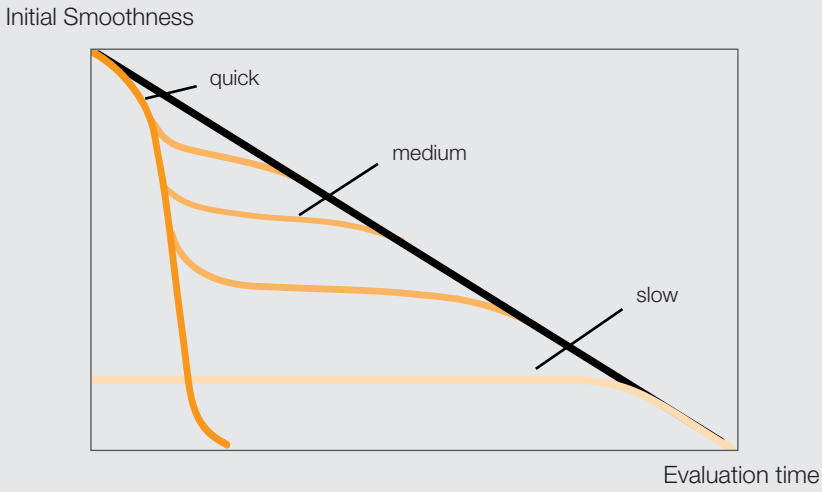
The spreading is defined as the surface area (in mm_2) of human skin of a test panelist, covered by 4 mg of emollient within 10 min in a room conditioned to 23 °C and 60% rel. humidity. Typically, four separate measurements are done with each panelist, whereby a reference oil with known spreading behavior is used Picture 1. In addition to this *in vivo* method, spreading can also be measured *in vitro*.



Picture 1: Test design to determine spreading of an emollient on human skin.

Emollient	Spreading value [mm²]	Emollience
Kollicream® 3 C	800	Medium
Kollicream® CP 15	n/a	Rich
Kollicream® DO	700	Medium
Kollicream® IPM	1200	Light
Kollicream® OA	700	Medium
Kollicream® OD	600	Medium
Kollisolv® MCT 70	550	Medium

The spreading value of an emollient has an important impact on the skin-feel of the resulting emulsion. Using a high amount of fast spreading emollients in your formulation will result in a smooth feeling on the skin perceived immediately upon application, but disappearing fast. In contrast, slow spreading emollients entail a rather subtle, but long-lasting smoothness. Combining emollients with different spreading behavior allows to tailor formulations towards the desired time profile of a smooth skin feel Picture 2.



Picture 2: Time profiles of emollients with different spreading behavior.

Water Permeability

The permeability/occlusivity of a film applied to the skin describes the ability to allow or prevent the passage of water, whereby a highly occlusive material (e.g. petrolatum) retains moisture by creating a barrier that prevents water from evaporating off the skin. Occlusivity is an important consideration for pharmaceutical formulations and the selection of emollients influences the permeability of an emulsion after spreading on the skin. Low permeability films can lead to hydration of the skin, increasing the flexibility of the stratum corneum.

Trade name	Water permeability
Kollicream® 3 C	medium
Kollicream® CP 15	low
Kollicream® DO	medium to low
Kollicream® IPM	high
Kollicream® OA	medium
Kollicream® OD	medium
Kollisolv® MCT 70	medium

Solubility Parameters

Using Formulating for Efficacy™ Software (Adaptive Cosmetic Technology Solutions Corp.), Hansen Solubility Parameters (HSP) were computed for the Kollicream® products, as well as for light mineral oil. With this set of three parameters, the three major forces that influence the behavior of solute in solvent are considered: polarity (δP), degree of hydrogen bonding (δH), as well as dispersive forces (δD). Solutes and solvents can be mapped in the three-dimensional space that is given by the three parameters. When the HSP of a solute is close to that of a solvent, it is very likely that the solute will have a high solubility in the solvent (Fig. 3).

Product	Hansen Parameters		
	δP	δH	δD
Kollicream® 3 C	2.1	3.4	16.3
Kollicream® DO	2.2	3	16.3
Kollicream® IPM	2.1	2.7	16
Kollicream® OD	3.8	9	16.1
Kollicream® OA	2.8	7.6	16.3
Light mineral oil	1.8	3.7	16.1
Kollicream® CP 15	1.4	2	16.1

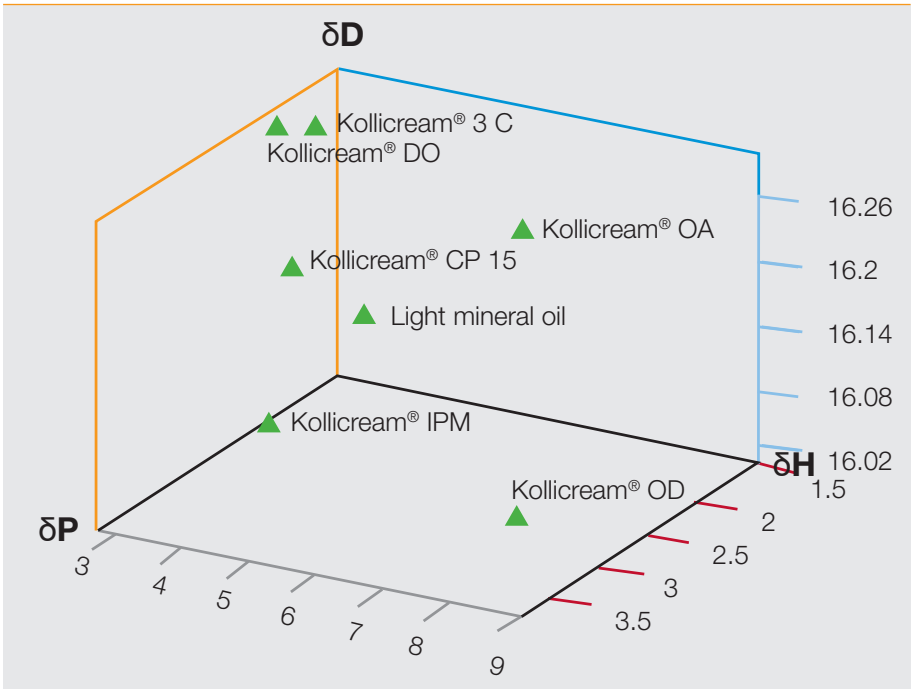


Figure 3: Hansen Parameters of some oils shown as a 3D plot.

3. Application

Skin Tolerance/Mildness

Clinical patch test studies on chronic contact dermatitis sufferers demonstrated that Kollicream® 3 C, OD, IPM and CP 15 are very mild.

Patch testing is considered to be the standard methodology for evaluating contact dermatitis. A list of standard allergens (70 substances) has been generated and recommended for standard diagnostic testing by the North American Contact Dermatitis Society. Dr. Joseph Fowler, and his team at Forefront Dermatology have been completing patch testing for over 15 years. Test subjects were patients who have presented with chronic dermatitis with an undetermined cause – these were highly sensitive patients. Finn Chambers were used to apply test substances to the backs of patients, per a globally standardized protocol. BASF Kollicream® products were applied at 35% in petrolatum. Patches were removed, and sites evaluated and scored after 48 – 72 hours. Study was concluded after 500 patients were treated. The following table lists the tested Kollicream® grades and the number of patients that showed no reaction at all to the application.

Test material (at 35%)	# of patients (out of 500) with no reaction
Kollicream® 3 C	500
Kollicream® IPM	500
Kollicream® OD	500
Kollicream® CP 15	500

Effects on API Penetration Through Skin

Studies on sodium ibuprofen in 96-well PAMPA system

Studies were conducted to determine the effect of the Kollicream® products and Kollisolv® MCT 70 on the permeation of Sodium Ibuprofen through a synthetic skin model membrane (Parallel Artificial Membrane Permeation Assay) in a 96 well format (in collaboration with Pion Inc., Billerica, MA, USA). Simple emulsions were prepared with the following composition: 45% w/w% water, 40 w/w% PEG 400 (Kollisolv® PEG 400), 2% Polysorbate 60 (Kolliphor® PS 60), 5 w/w% Na-Ibuprofen, and 8 w/w% of one of following; Kollicream® 3 C, Kollicream® OD, Kollicream® DO, Kollicream® IPM, Kollicream® OA or Kollisolv® MCT 70. (The control or “blank” in this study was the same composition but without any lipophile. Water content was increased to 53 w/w% to compensate.)

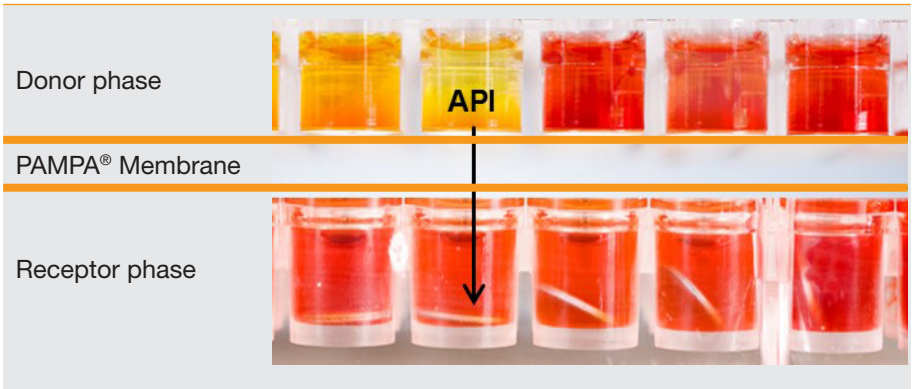


Figure 4: Cutout of the PAMPA setup for the measurement of API penetration through model membranes. The setup allows 96 parallel measurements.

The synthetic skin model membrane was sandwiched between an upper plate and a lower receiver plate. The lower wells were filled with phosphate buffered saline. The test emulsions were applied in the upper wells (6 – 12 replicates per sample). Both the test emulsions and the receptor solutions were stirred with small magnetic stirrers throughout the test period. The entire set-up was incubated at 37 °C for one hour and then the lower plate was removed and sodium ibuprofen concentration (µM) was measured in each well by means of a 96-well UV/VIS spectrophotometer.

The results of the emollient screening indicate that not all lipophilic fluids tested behave in the same way. While Kollicream® 3 C and OA, as well as Kollisolv® MCT 70 expressed the greatest impact on sodium ibuprofen permeation through the model membrane during the one-hour incubation period, emulsions with Kollicream® IPM, DO, as well as OD were not significantly different from the control experiment.

Test substance	[Na IBU] (µM) in receptor	Standard Deviation (+/-)	% increase in permeation vs control
Kollicream® OD	3602	785	0.3
Kollicream® DO	3890	810	8.4
Kollicream® IPM	4042	437	12.6
Kollicream® OA	4238	280	18.1
Kollisolv® MCT 70	4531	657	26.2
Kollicream® 3 C	4700	369	30.0
Control/Blank	3589	280	--

Studies of Clotrimazole permeation through Strat-M® membrane

Studies with 1% Clotrimazole creams were conducted to investigate the effect of different oil phase compositions on the skin permeation of the Clotrimazole. Creams were prepared as in the following table:

Ingredient	Description	Dosage [wt.-%]
Kollisolv® PG	Propylene glycol	8.0
Kolliwax® CSA 50	Cetostearyl alcohol	7.0
Variable	Lipophilic fluid (oil)	12.0
Kolliphor® CS 20	Polyoxyl 20 cetostearyl ether	3.0
Active Ingredient	Clotrimazole	1.0
Water	--	68.9
Euxyl 320	Phenoxyethanol	0.1

The lipophilic fluids (oils) subject to test were Kollicreams® 3 C, OD, IPM and mineral oil. Clotrimazole permeation through a skin model membrane (Strat-M®) was measured using Franz Cells: for each test, the cream was applied to the top surface of the membrane, in the donor compartment, at an "infinite dose" (≥ 200 µL). Samples were collected from the receptor phase at 0.5, 1, 2, 4, 6 and 8 hours, and analyzed for Clotrimazole concentration. The flux profile for each formulation is illustrated in the following chart.

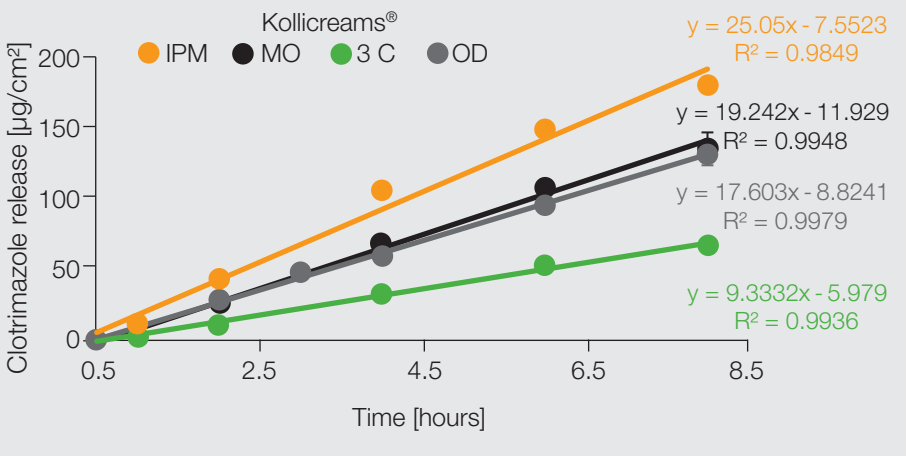


Figure 5: Time profiles of Clotrimazole permeation through a model membrane for different emollients: IPM = Kollicream® IPM, MO = Mineral Oil, 3 C = Kollicream® 3 C, OD = Kollicream® OD.

Note that the different lipophiles had differing influences on Clotrimazole flux rates. In this study the Kollicream® IPM-containing cream had the highest flux rate while the Kollicream® 3 C-containing cream had the lowest. The mineral oil and Kollicream® OD-containing creams had very similar flux rates. Clotrimazole is typically intended to prevent or treat fungal/yeast infections on mucosal membranes, so inhibition of permeation is desirable. In this case the Kollicream® 3 C-containing cream had the most desirable performance.

Example Formulations

The following cream formulations can all be prepared by the same basic procedure:

1. Blend all ingredients in phase A together and heat to 80 °C under stirring, until the blend is a clear liquid.
2. Blend all of the ingredients in phase B and heat to 80 °C under stirring, until homogeneous.
3. While strirring phase B vigorously (e.g. by means of a propeller mixer at 500 rpm), pour phase A into phase B and mix until a homogeneous emulsion forms (generally within a few minutes).
4. Transfer the mixture to a high-shear rotor-stator homogenizer and homogenize at approx. 5000 rpm for about ten minutes, making sure that the entire batch is homogenized.
5. Return the mixture to a propeller mixer and stir at 200 rpm whitout heating. After the mixtures has cooled to 45 °C, add the preservative. Continue mixing, until homogeneous.
6. Remove from mixer and fill to appropriate packaging, after the cream has cooled to 30 °C or below.

1. Cream Formulation with Kolliphor® PS 80

This composition yields a medium viscosity cream with a high loading (20 w/w%) of Kollicream® 3 C, emulsified by Kolliphor® PS 80. The high oil content will allow for solubilization of lipophilic APIs, smooth and pleasing sensory properties, and the benefits of a moisture barrier after application.

Phase	Ingredient	Name	Amount [%]
A	Kollicream® 3 C	Cocoyl caprylocaprate	20
	Kolliphor® PS 80	Polysorbate 80	3
	Kolliwax® GMS II	Glycerol monostearate 40-55 (type II)	3
	Kolliwax® CSA 70	Cetostearyl alcohol	5
B	Deionized water		68
	Preservative	Euxyl PE 9010	1

2. Rich Cream based on Kollisolv® MCT 70 and Kollicream® IPM

This formulation utilizes Kolliwax® CSA 70 and Kolliphor® PS 60 as consistency factor and emulsifier, respectively, to create a very stiff cream that offers a rich and cushioned feeling when rubbed into the skin. Kollicream® IPM is a fast spreading oil for topical semi-solid formulations and a penetration enhancer for some APIs.

Phase	Ingredient	Name	Amount [%]
A	Kolliwax® CSA 70	Cetostearyl alcohol	7.0
	Kolliwax® GMS II	Glycerol monostearate 40-55 (type II)	2.5
	Kolliphor® PS 60	Polysorbate 60	4.2
	Kollisolv® MCT 70	Medium chain triglycerides	11.5
	Kollicream® IPM	Isopropyl myristate	1.3
B	Deionized water		69.2
	Glycerol		3.3
C	Euxyl PE 9010	Phenoxyethanol	1.0

3. Cream based on Kollisolv® MCT 70

Kollisolv® MCT 70 can be a good solvent and carrier for lipophilic APIs, but exhibits rather slow spreading behavior due to its relatively high viscosity. Kollicream® IPM was added to reduce the overall viscosity of the oil phase and increase spreading after application.

Phase	Ingredient	Name	Amount [%]
A	Kolliwax® CSA 70	Cetostearyl alcohol	7.0
	Kolliwax® GMS II	Glycerol monostearate 40-55 (type II)	2.5
	Kolliphor® PS 60	Polysorbate 60	4.2
	Kollisolv® MCT 70	Medium chain triglycerides	11.5
	Kollicream® IPM	Isopropyl myristate	1.3
B	Deionized water		69.2
	Glycerol		3.3
C	Euxyl PE 9010	Phenoxyethanol	1.0

4. Cream with Kollicream® OD and Kolliphor® CS 20

Kollicream® OD is widely used in creams and lotions and can easily penetrate the skin and aid in the permeation of APIs, while remaining mild and non-irritating. It can also serve as a solvent for lipophilic APIs. It is emulsified by Kolliphor® CS 20, an unbranched linear alkyl PEG ether. Both are stable in a wide range of pH values. Creams prepared with Kollicream® OD and Kolliphor® CS 20 yield a medium viscosity, non-greasy formulation.

Phase	Ingredient	Name	Amount [%]
A	Kollicream® OD	Octyldodecanol	12.0
	Kolliphor® CS 20	Polyoxyl-20 cetostearyl ether	3.1
	Kolliwax® S	Stearic acid	0.1
	Kolliwax® CSA 50	Cetostearyl alcohol	7.5
	Kolliwax® GMS II	Glycerol monostearate 40-55 (type II)	0.5
B	Deionized water		75.8
C	Euxyl PE 9010		1.0

5. Gel Formulation: Emulgel

At concentrations above 15%, Poloxamers 188 and 407 can be used to make gels and viscous emulsions by both emulsifying and forming phases and networks via the hydrophobic and hydrophilic interactions driven by PPO and PEO segments of the polymer, respectively.

Kolliphor® P 407 helps emulsify the Kollicream® 3 C in this formulation, resulting in a translucent white gel with a cream-like structure visible underneath the microscope. Both Kolliphor® P 407 and Kollicream® 3 C have been shown to be very mild, *in vitro* and *in vivo*.

Phase	Ingredient	Name	Amount [%]
A	Ethanol 200 Proof		10
	Kollisolv® PEG 400	Polyethylene glycol 400	15
	Glycerol		5
B	Kolliphor® P 407	Poloxamer 407	18
	Deionized Water		42
C	Kollicream® 3 C	Cocoyl caprylocaprate	10

Preparation (Cold Process):

1. Keep mix of components listed under B refrigerated at 5 °C for 24 h, or until all Kolliphor® P 407 is dissolved.
2. Mix all C and A ingredients to phase A, stir slowly until Kolliphor® has gelled.

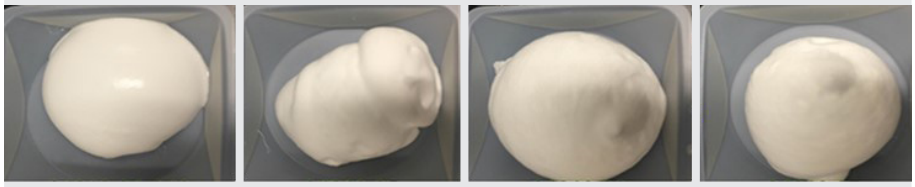
Preparation (Hot Process):

1. Prepare phase B by adding Kolliphor® to water preheated to 70 °C. Stir this mixture for at least 1 h to ensure proper dissolution of the poloxamer.
2. As solution B is cooling down to room temperature, add component mixtures A and C while stirring until a robust gel is formed.

6. Model Foam Formulation: General Aerosol Foams

Growing in popularity, topical foams can sometimes be preferred over a cream due to their pleasing sensory application. The four foam formulations below retain their shape upon application onto the skin, spreading easily and drying quickly.

Foams made with Kolliphor® CS 12 tend to demonstrate a higher viscosity and stiffness than foams formulated with Kolliphor® CS 20. Additionally, poloxamers such as Kolliphor® P 188 or Kolliphor® P 407 can be added to formulations as needed to create richer, creamier foams. This richness is aided by the use of an aerosol.



Picture 3: Macrostructures of aerosol foams.

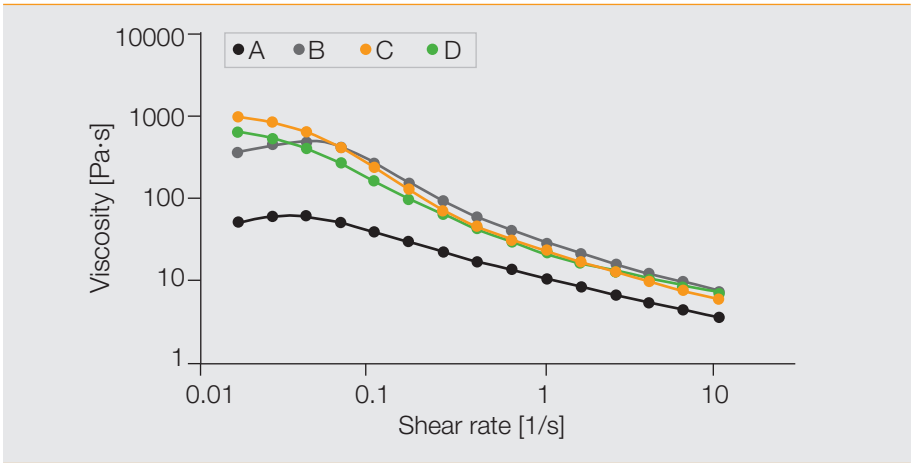


Figure 6: Viscosity profiles of aerosol foams.

Phase	Ingredient	Name	Amounts [%]			
			A	B	C	D
I	Kolliwax® CSA 50	Cetostearyl alcohol	3	3	3	3
	Kolliphor® CS 12	Macrogol cetostearyl ether 12	0	0	6	5
	Kolliphor® CS 20	Macrogol cetostearyl ether 20	5	6	0	0
	Kollicream® 3 C	Cocoyl caprylocaprate	3	3	3	3
	Kolliphor® P 188	Poloxamer 188	1	0	0	1
	Deionized Water		82	82	82	82
	A 46	Propane/Isobutane	6	6	6	6

Preparation:

1. Mix formulation ingredients in a beaker, using slight heat if necessary to ensure uniform distribution of the components.
2. Place the mixture in an aerosol container, charge with desired propellant.

4. Handling & Safety

Please refer to the individual material safety data sheet (MSDS) for instructions on safe and proper handling and disposal. Material safety data sheets are available on request and are sent with every consignment.

5. Product Specification

The current version of the product specification is available on BASF WorldAccount, or from your local BASF sales representatives.

6. Regulatory & Quality

Please refer to the individual document quality & regulatory product information (QRPI), available on BASF WorldAccount and from your local sales representative. The QRPI document covers all relevant information including retest periods and storage conditions.

7. PRD and Article numbers

PRD-No.*	Product name	Article numbers	Packaging
30554439	Kollicream® 3 C	50268489	800 kg Composite IBC (31HA1)
		50363006	175 kg Steel drum
		50259481	0.5 kg Plastic bottle**
30554443	Kollicream® CP 15	50253253	20 kg Plastic film bag
		50259485	0.5 kg Plastic bottle**
30554441	Kollicream® DO	50253252	175 kg Steel drum
		50259484	0.5 kg Plastic bottle**
30554463	Kollicream® IPM	50264409	850 kg Composite IBC (31HA1)
		50253267	175 kg Steel drum
		50259491	0.5 kg Plastic bottle**
30554462	Kollicream® OA	50253265	175 kg Steel drum
		50259490	0.5 kg Plastic bottle**
30554460	Kollicream® OD	50253259	175 kg Steel drum
		50259489	0.5 kg Plastic bottle**
30554489	Kollisolv® MCT 70	50253413	190 kg Steel drum
		50259496	0.5 kg Plastic bottle**

* BASF's commercial product number.

** Free non-GMP samples (0.5 kg) for testing purposes are available on request.

8. Publications

http://pharmaceutical.basf.com/en.html

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February 2019