Technical Information

March 2016
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WF-No. 131204

Kolliphor® PS grades – Polysorbates

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PRD-No., Article-No. and CAS.-No.

Tradename	PRD-No.	Article-No.	CAS.-No.
Kolliphor® PS 20	30554436	50253857	9005-64-5
Kolliphor® PS 60	30554490	50253808	9005-67-8
Kolliphor® PS 80	30554437	50253859	9005-65-6

Table 1: PRD, Article and CAS numbers of the Kolliphor® PS grades

Regulatory Status

In table 2 you can find all the monographs for the Kolliphor® PS grades

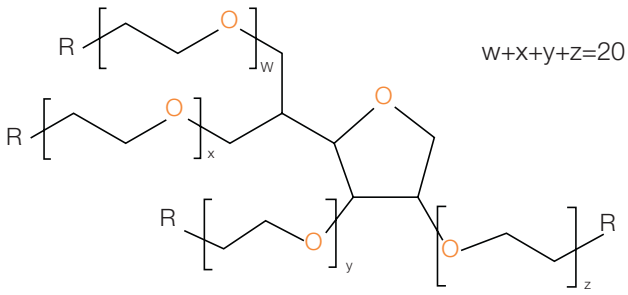
New Name	Monograph Tests
Kolliphor® PS 20	Ph. Eur. : Polysorbate 20 USP/NF : Polysorbate 20
Kolliphor® PS 60	Ph. Eur. : Polysorbate 60 USP/NF : Polysorbate 60 JPE : Polysorbate 60
Kolliphor® PS 80	Ph. Eur. : Polysorbate 80 USP/NF : Polysorbate 80

Table 3: Compendial names

Polysorbates

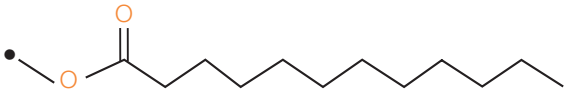
Polysorbates are non-ionic surfactants and emulsifiers for pharmaceutical application, derived from polyethoxylated sorbitan and fatty acids.

Chemical structure



Polysorbate 20

R=

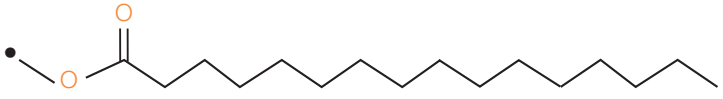


or

R= • — OH

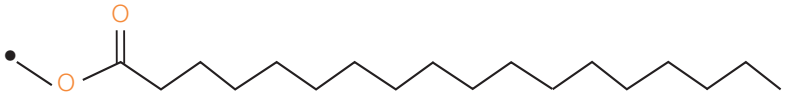
Polysorbate 60

R=



or

R=

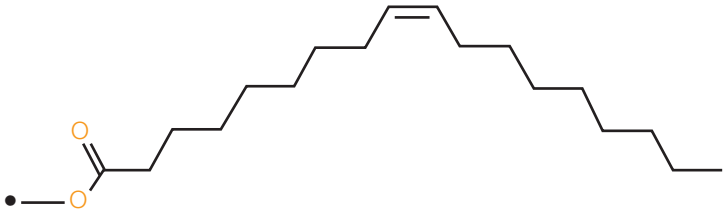


or

R= • — OH

Polysorbate 80

R=



or

R= • — OH

Chemical characterization

Typical property	Kolliphor® PS 20	Kolliphor® PS 60	Kolliphor® PS 80
Appearance	Oily, yellow or brownish-yellow, clear slightly opalescent liquid	Yellowish- brown gelatinous mass, clear liquid at temperatures above 25 °C	Oily, colorless or brownish-yellow, clear or slightly opalescent liquid
Composition of fatty acids	C 6, ≤ 1.0% C 8, C 10 ≤ 10.0% C 12, 40.0 to 60.0% C 14, 14.0 to 25.0% C 16, 7.0 to 15.0% C 18, ≤ 7.0% C 18:1 ≤ 11.0% C 18:2 ≤ 3.0%	C 18, 40.0 – 60.0% C 16 + C 18 ≥ 90.0%	C 14, ≤ 5.0% C 16, ≤ 16.0% C 16:1 ≤ 8.0% C 18, ≤ 6.0% C 18:1, ≥ 58.0% C 18:2, ≤ 18.0% C 18:3, ≤ 4.0%
Acid value	≤ 2.0	≤ 2.0	≤ 2.0
Hydroxyl value	96 – 108	81 – 96	65 – 80
Saponification value	40 – 50	45 – 55	45 – 55
Peroxide value	≤10.0	≤10.0	≤10.0
HLB*	16.7	14.9	15.0
CMC	0.0499	0.0167	0.015

Table 3: Typical chemical properties of Kolliphor® PS grades

** The HLB value of non-ionic emulsifiers is very much temperature dependent. Meaning the HLB decreases with elevated temperatures. This leads to a change in the behavior of the emulsifier, wich is then no longer hydrophilic but lipophilic. This is a result of the temperature sensitivity of the hydrogen bonds of the molecule. The polarity of the molecule can change strongly, as with the elevated temperature the lipophilic interactions are in favor and this can lead to a phase inversion of an emulsion.*

Furthermore, Kolliphor® PS 20, 60 and 80 meet the requirements of the above-mentioned monographs. The chemical characterization shown in Table 3 above is only for information purposes and should be interpreted as typical properties of Kolliphor® PS 20, 60 and 80.

Specifications

See separate documents: “Standard Specification” (not for regulatory purposes) available via BASF’s WorldAccount: https://worldaccount.basf.com (registered access).

Additional chemical characterization Differential scanning calorimetry (DSC)

Kolliphor® PS 20

Heating 2 K/min -70 °C → +80 °C	Cooling 20 K/min +80 °C → -70 °C	Heating 2 K/min -70 °C → +80 °C	TGA
Tg: -63 °C Tm: -47 °C -17 °C	Crystallization start: -17.0 °C Crystallization peak: -19.0 °C -36.2 °C	Tg: -61.0 °C Tm: -40.0 °C -16.6 °C -10.1 °C	Stable unil 140 °C

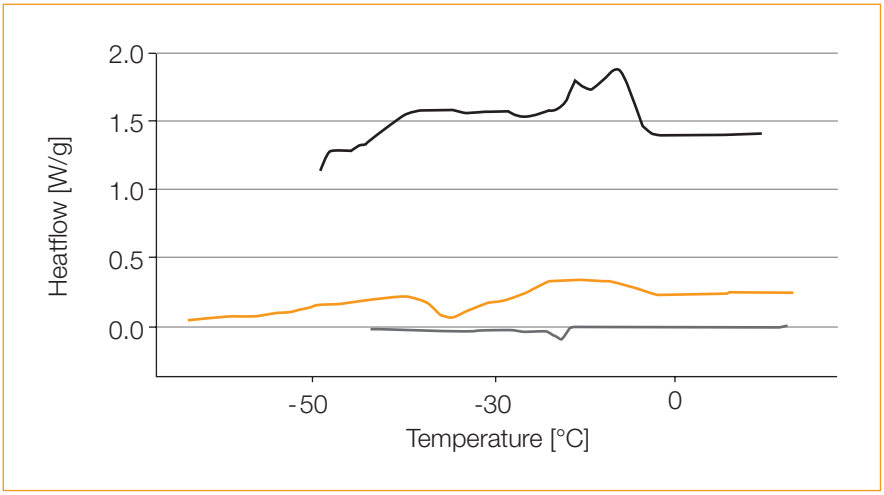


Figure 1: DSC of Kolliphor® PS 20

Kolliphor® PS 60

Heating 2 K/min -70 °C → +80 °C	Cooling 20 K/min +80 °C → -70 °C	Heating 2 K/min -70 °C → +80 °C	TGA
Tg: -59.0 °C Tm: -1.7 °C 18.0 °C 24.3 °C	Crystallization start: 29.0 °C Crystallization peak: 23.4 °C 4.1 °C -2.7 °C	Tg: -59.0 °C Tm: 6.0 °C 18.1 °C 24.3 °C	Stable unil 140 °C

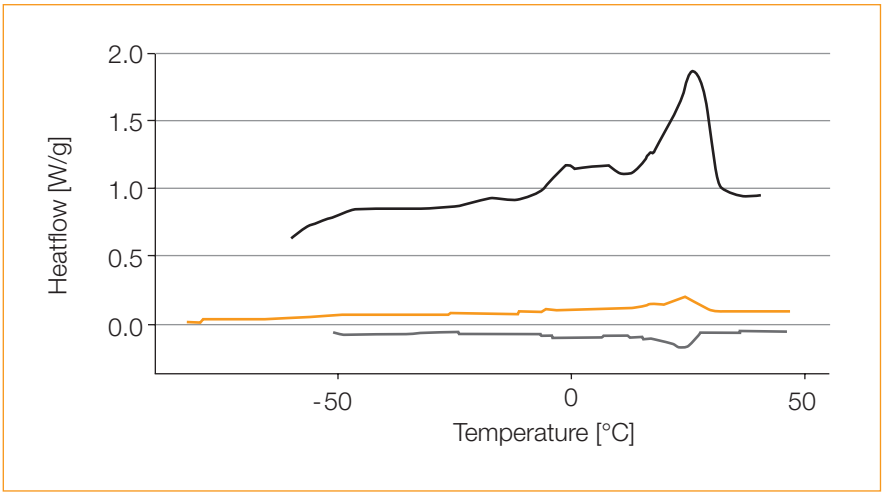


Figure 2: DSC of Kolliphor® PS 60

Kolliphor® PS 80

Heating 2 K/min -70 °C → +80 °C	Cooling 20 K/min +80 °C → -70 °C	Heating 2 K/min -70 °C → +80 °C	TGA
Tg: -66.0 °C Tm: -14.5 °C	Crystallization start: -31.0 °C Crystallization peak: -36.8 °C	Tg: -65.0 °C Tm: -14.2 °C	Stable unil 168 °C

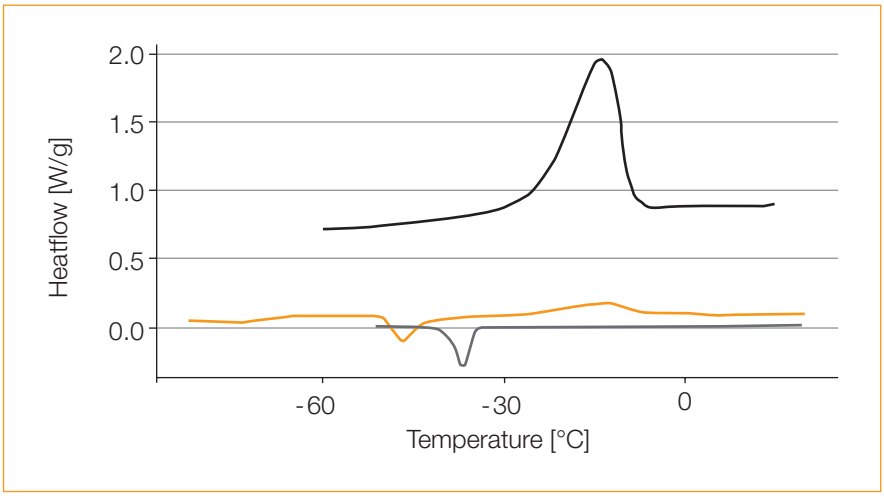


Figure 3: DSC of Kolliphor® PS 80

Typical physical properties

Solubility in water

Kolliphor® PS 20	Kolliphor® PS 60	Kolliphor® PS 80
Miscible in all parts	Up to 5 %	Miscible in all parts

Application

Polysorbates are mainly used as solubilizers, emulsifiers or suspension stabilizers for pharmaceutical applications.

Depending on the HLB value and the miscibility in water of the product, they either act more as a solubilizer or emulsifier. Products like Kolliphor® PS 20 and Kolliphor® PS 80 are more suitable for use as a solubilizer of poorly water soluble drug substances in either liquid or solid oral dosage forms.

Kolliphor® PS 60 is more likely to be used as an emulsifier in topical applications like cream and lotions.

Overview of applications of Kolliphor® PS grades

Product	*Ph. Eur.*	W/O Emulsifier	O/W Emulsifier	Solubilizer	Suspension stabilizer	Oral solid dosage forms	Semi-solid dosage forms	Cold processing	Skin penetration enhancer	Liquid dosage forms	Broad ph rage
Kolliphor® PS 20	Polysorbate 20			×	×				×	×	×
Kolliphor® PS 60	Polysorbate 60		×			×	×	×		×	×
Kolliphor® PS 80	Polysorbate 80			×	×	×	×		×	×	×

Application as solubilizer for liquid or solid oral dosage forms

Performance of different Polysorbate grades based on model APIs

Pharmaceutical scientists increasingly face the challenge of formulating poorly water soluble active pharmaceutical ingredients (API). This trend is likely to increase, as new APIs in pharmaceutical research become more and more lipophilic and complex molecules. A high-throughput screening robot was established at BASF SE to reduce development time and formalize early solubilizer screening activities. The aim of this study is to screen the solubilizing performance of three Polysorbate grades based on model APIs with different physico-chemical profiles. The solubilizer concentration with max. 20% exceeds the typical usage levels in standard pharmaceutical liquid or solid formulations in order to assess a potential saturation effect.

The selected model APIs differ in molecular weight, estimated logP values, estimated water solubility and melting point. Table 4 shows an overview of these attributes for all selected model compounds.

	Molecular Weight*	**logP***	**Water solubility***	**Tm**
	g/mol		mg/mL	°C
Carbamazepin	236.27	2.1	1.52×10^{-1}	201 – 206
Cinnarizin	368.514	5.19	1.72×10^{-3}	117 – 120
Danazol	337.455	3,62	7.07×10^{-4}	224 – 227
Fenofibrate	360.831	4.86	1.76×10^{-2}	80.5
Ketoconazol	531.431	4.3	9.31×10^{-3}	146
Piroxicam	331.346	2.2	1.43×10^{-1}	198 – 200

Table 4: Overview of physico-chemical properties of the selected model APIs

Figure 4 shows the enhancement of the saturation solubility of Kolliphor® PS 60 by using only 1 and 5% of the solubilizer stock solution.

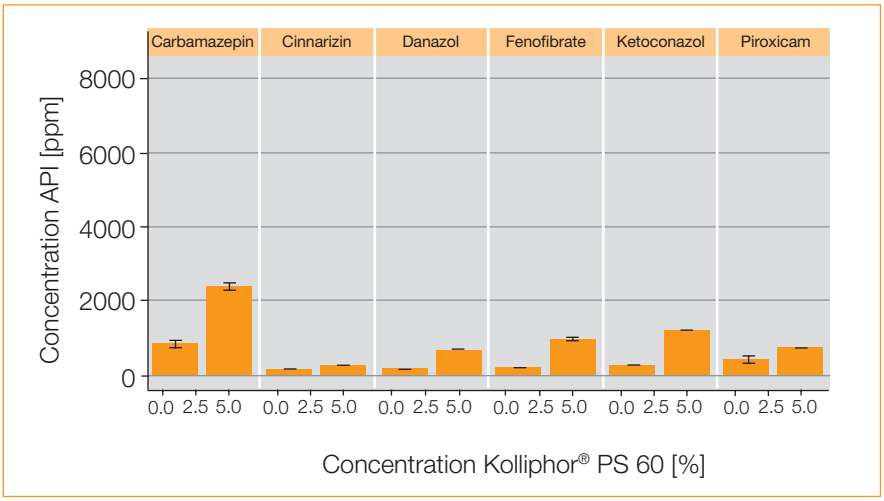


Figure 4: Solubility enhancement of model APIs by using Kolliphor® PS 60 (Polysorbate 60)

Both Kolliphor® PS 20 and PS 80 form clear solutions in water at concentration levels ranging from 1 – 20%. Therefore, these substances are adequate for the evaluation of a potential saturation effect by solubilizer concentration. The results of figure 4 and 5 support this and show, that the solubility enhancement of all substances increase with solubilizer concentration.

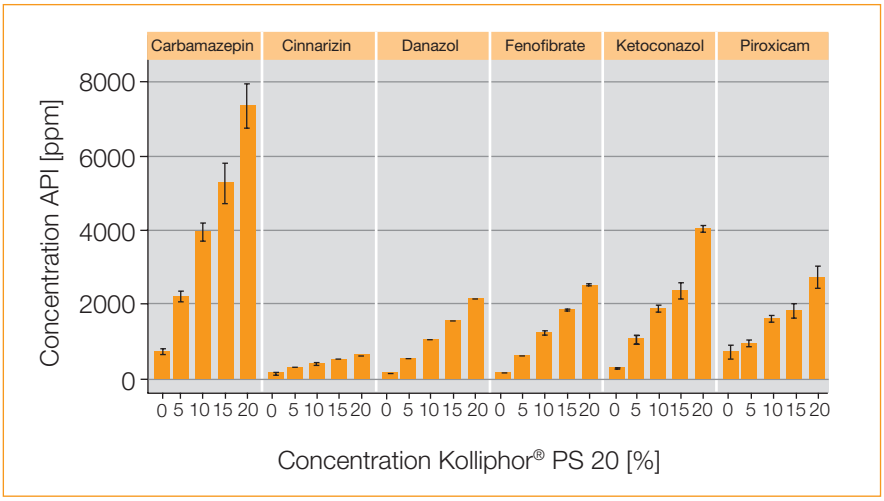


Figure 5: Solubility enhancement of model APIs by using Kolliphor® PS 20 (Polysorbate 20)

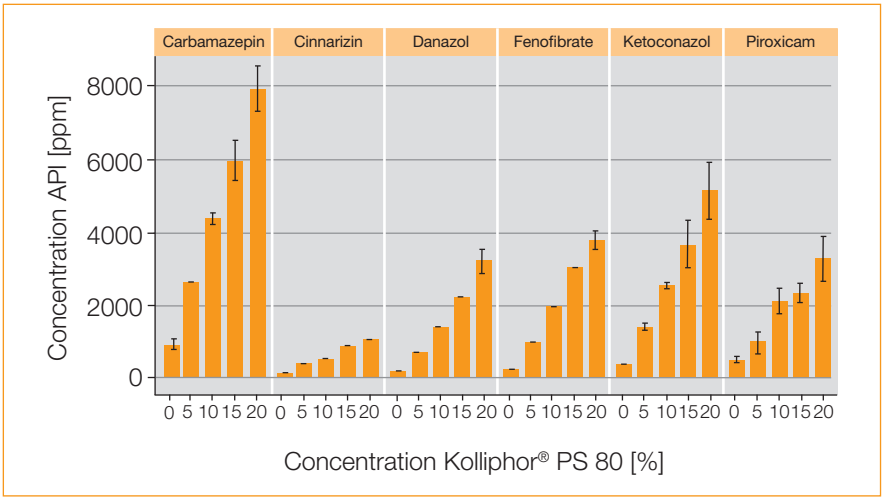


Figure 6: Solubility enhancement of model APIs by using Kolliphor® PS 80 (Polysorbate 80)

<u>Conclusion:</u>

Overall, Kolliphor® PS 80 shows the best improvement in the saturation solubility of all three excipients regardless of the physico-chemical attributes of the model API. For most of the APIs, the solubility enhancement is linear to the usage concentration of the solubilizer and dependent on the alkyl chain. This is the case even at high concentrations of about 20%.

Kolliphor® PS 60 shows a limitation with regards to its ability to form clear solutions at higher concentrations. This may explain the preference of Kolliphor® PS 60 to be used in emulsion type systems.

Kolliphor® PS 20 and Kolliphor® PS 80 for Hot melt extrusion (HME):

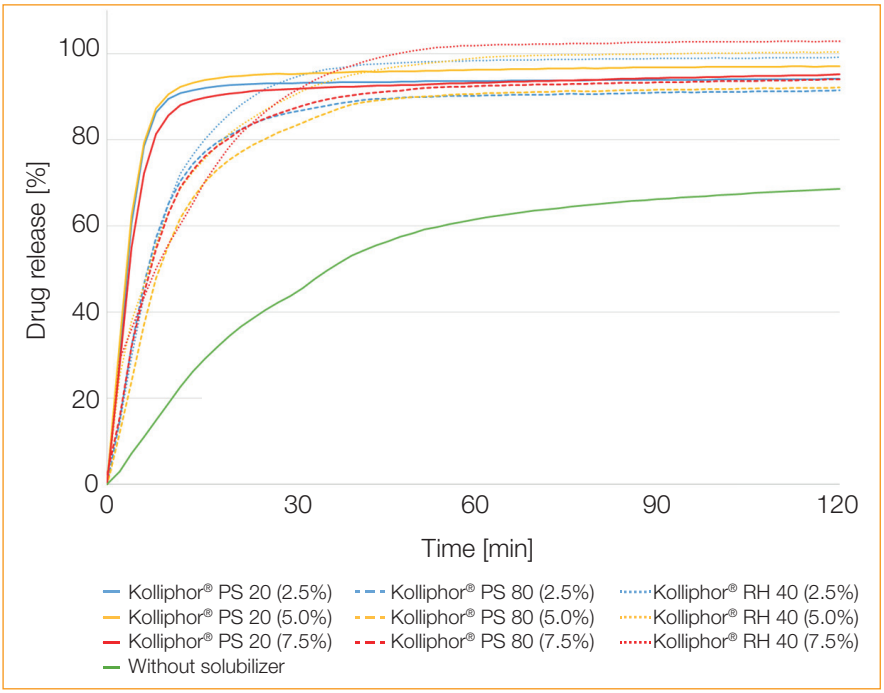
Formulation

- API: Ritonavir
- Polymer: Kollidon® VA 64
- Solubilizer: Kolliphor® PS 20/Kolliphor® PS 80/ Kolliphor® RH 40

API	Polymer	Solubilizer
30.0%	70.0%	–
30.0%	67.5%	2.5%
30.0%	65.0%	5.0%
30.0%	62.5%	7.5%

Process

- 16 mm Twin Screw Extruder PTW Thermo Fisher
- Throughput: 1 kg/h
- Screw speed: 200 rpm
- Extrusion temperature: 135 °C
- Pelletezing: 1.5 mm
- Dissolution: 0.8 M HCL pH = 1.2 (2 h)



Conclusion:

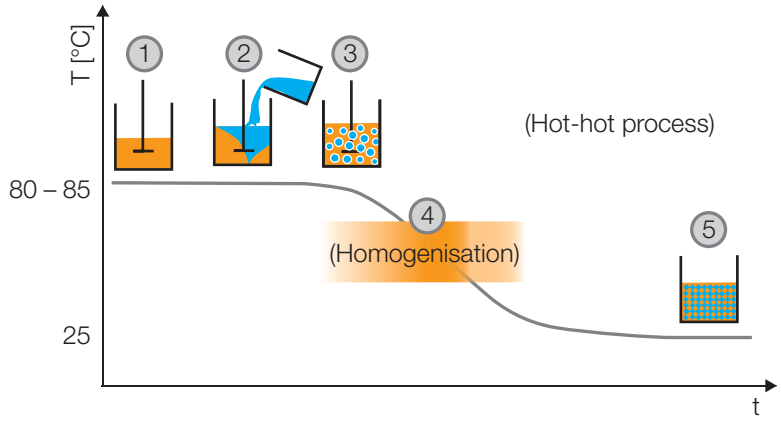
Kolliphor® PS 20 is the best solubilizer in study. All Kolliphor® PS grades are easy to handle in HME applications. No significant difference can be observed in handling compared to other semi-solid solubilizer such as Kolliphor® RH 40. Enhancement of concentration of solubilizer shows no influence on drug dissolution.

Semi-solid/Topical Application

A topical formulation is a complex mixture of ingredients with varying functionality. The majority of such products are stabilized emulsions of an emollient in water. The formulation needs to deliver both water-soluble actives and oil-soluble ingredients to the stratum corneum and preferentially control the penetration of these substances to the epidermis and dermis. The formulation typically needs a shelf life of more than 24 months. The physical stability of the system is maintained primarily by the viscosity-building effect of the emulsifiers and consistency factors. Finally, the formulation also needs to be aesthetically and acceptable in order to meet patient demands.

The choice of emulsifiers for specific applications depends on the desired properties of the formulation (e.g. stability, viscosity, skin feel and API), or on the desired processing technology (e.g. PIT, Hot or cold processing).

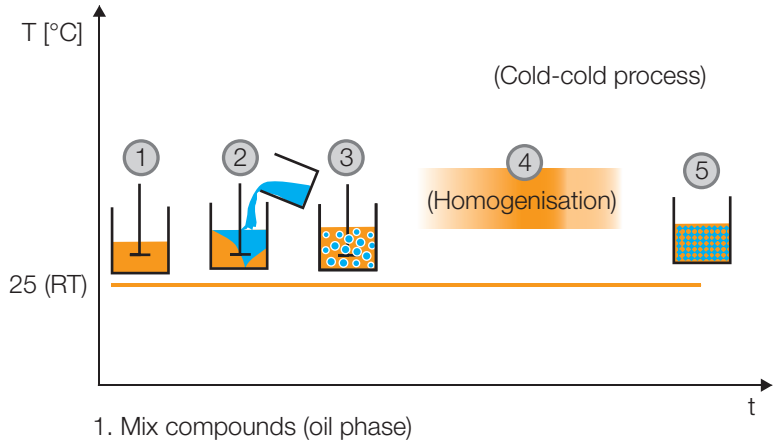
Formulation procedure:



1. Mix compounds (oil phase)
2. Add water phase very slowly while stirring
3. Allow to cool while stirring (approx. 50 – 60 °C)
4. If necessary homogenisation (e.g. Ultra Turrax)
5. Finished emulsion

Besides the well-known emulsifying process with two hot phases there is also the possibility to formulate an emulsion at room temperature. The processing of O/W emulsions at room temperature has several significant benefits. For example, it is no longer necessary to heat the water and oil phase to 70 – 80 °C. This saves considerable amounts of energy and reduces the production time as the cooling step is eliminated. Another very important advantage is that heat-sensitive APIs can be added to the emulsions at any point.

Kolliphor® PS 60 is very suitable for this kind of application.



1. Mix compounds (oil phase)
2. Add water phase very slowly while stirring
3. Stirring
4. If necessary homogenisation (e.g. Ultra Turrax)
5. Finished emulsion

Semi-solid Formulation examples (Hot-hot processing)

Phase	Ingredients	Chemical name	Wt%							
A	Kollicream® OD	Octyldodecanol	20	20	20	20	0	0	0	0
	Kollisolv® MCT 70	Triglycerides Medium-chain	0	0	0	0	20	20	20	20
	Kolliwax® CA	Cetyl Alcohol	3	0	0	0	3	0	0	0
	Kolliwax® S	Stearic Acid	0	3	0	0	0	3	0	0
	Kolliwax® SA	Stearyl Alcohol	0	0	3	0	0	0	3	0
	Kolliwax® MA	Myristyl Alcohol	0	0	0	3	0	0	0	3
	Kolliwax® GMS II	Glyceryl Monostearate 40-55 (typ II)	1.25	1.25	1.25	1.25	2.08	2.08	2.08	2.08
	Kolliphor® PS 60	Polysorbate 60	3.75	3.75	3.75	3.75	2.92	2.92	2.92	2.92
B	Deionized Water		69.8	69.8	69.8	69.8	69.8	69.8	69.8	69.8
	Carbopol ETD 2020 Polymer	Acrylates/C_{10-30} Alkyl Acrylate Crosspolymer	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
C	Triethanolamine		1	1	1	1	1	1	1	1
D	Germaben		1	1	1	1	1	1	1	1

HLB can be lowered by mixing with Kolliwax® GMS II to achieve stable and aesthetically acceptable cream or lotion emulsions with Kollicream® IPM.

Phase	Ingredients	Chemical name	Wt%	
A	Kollicream® IPM	Isopropylmyristate	20	20
	Kolliwax® GMS II	Glyceryl Monostearate 40-55 (typ II)	1.45	1.45
	Kolliphor® PS 60	Polysorbate 60	3.55	0
	Kolliphor® PS 80	Polysorbate 80	0	3.55
B	Deionized Water		72.8	72.8
	Carbopol ETD 2020 Polymer	Acrylates/C_{10-30} Alkyl Acrylate Crosspolymer	0.2	0.2
C	Triethanolamine		1	1
D	Germaben II	Propylene Glycol (and) Diazolidinyl Urea (and) Methylparaben (and) Propylparaben	1	1

Kollicream® 3C has demonstrated excellent mildness in clinical studies. Kolliphor® PS 60 or PS 80 can be used to make very stable, aesthetically acceptable, emulsion creams with Kollicream® 3C.

Phase	Ingredients	Chemical name	Wt%	
A	Kollicream® 3C	Cocoyl Caprylocaprate	20	20
	Kolliwax® GMS II	Glyceryl Monostearate 40-55 (typ II)	2.5	2.5
	Kolliphor® PS 60	Polysorbate 60	2.5	0
	Kolliphor® PS 80	Polysorbate 80	0	2.5
B	Deionized Water		72.8	72.8
	Carbopol ETD 2020 Polymer	Acrylates/C_{10-30} Alkyl Acrylate Crosspolymer	0.2	0.2
C	Triethanolamine		1	1
D	Germaben II	Propylene Glycol (and) Diazolidinyl Urea (and) Methylparaben (and) Propylparaben	1	1

The following processing steps apply in all of the above formulations:

Procedure:

1. Phase A was weighed in a clean beaker and heated until the waxes melted.
2. In another beaker, water was heated to 80 °C and sprinkled with carbopol while stirring.
3. Phase A was added into phase B with stirring and then neutralized with TEA.
4. The mixture was homogenized for about 2 minutes.
5. Mixture was allowed to cool under mild shear. Germaben II (Phase D) was added during cooling mixing step.

IIG listing

http://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm

Skin Tolerance

All Kolliphor® PS types have a good skin tolerance.

Raw material origin

All Kolliphor® PS grades are based on vegetable and synthetic raw materials.

Toxicology

The toxicological abstracts are available on request.
Individual reports can be shared under secrecy agreement.

Stability and storage

In originally sealed containers all Kolliphor® PS types can be stored for at least 18 months. It is important that they are protected from moisture and stored at less than 30 °C.

Handling and Disposal

Please refer to the individual Material Safety Data Sheet (MSDS) for instructions on safe and proper handling and disposal.

Note

March 2016