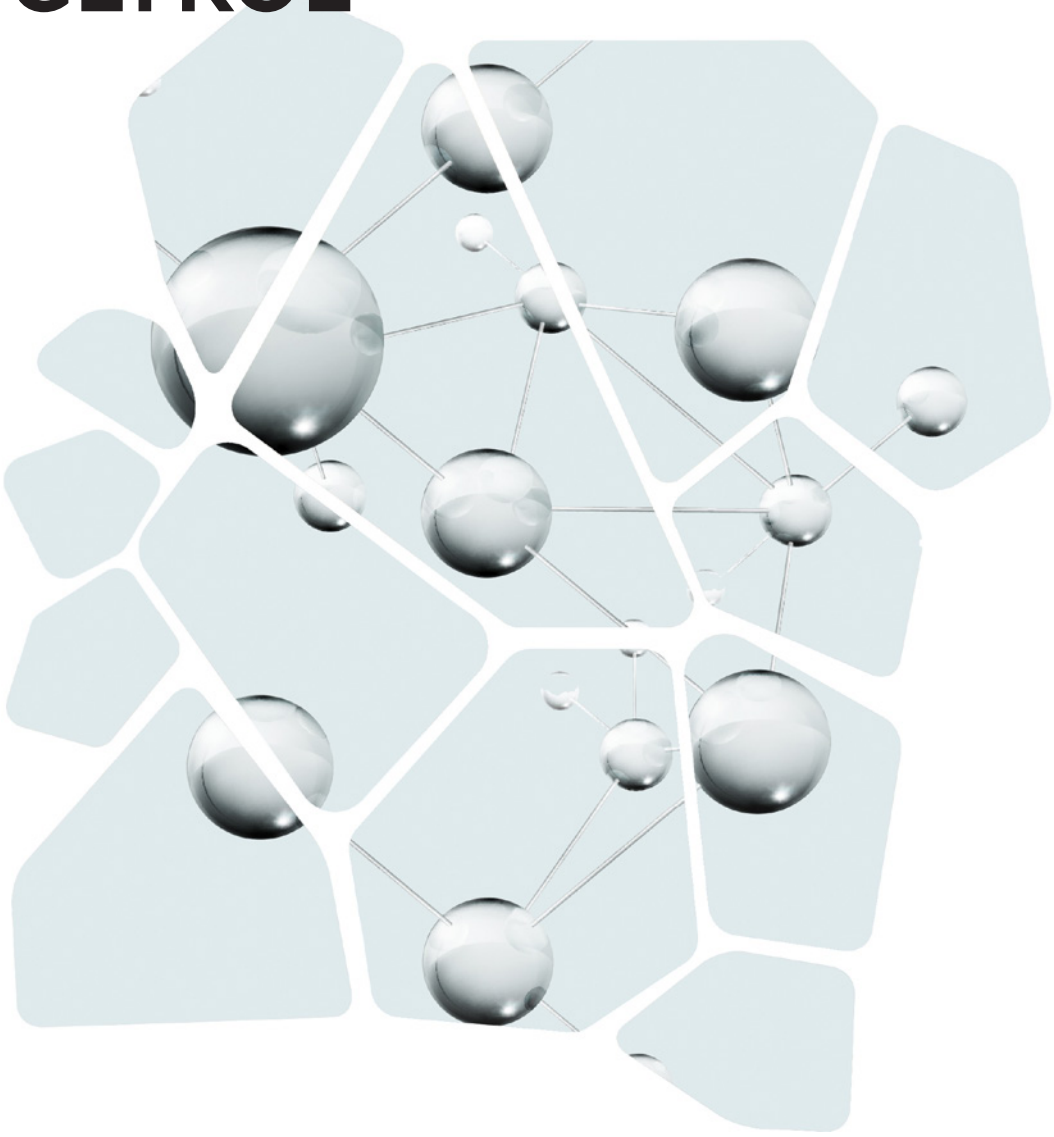
CLARIANT

Your universally applicable Polymer **POLYGLYKOL**



what is precious to you?

Your universally applicable Polymer
Polyglykol

Contents

This brochure provides comprehensive information on polyethylene glycols (PEG), their chemical and physical properties and the most important fields of application in the pharmaceutical and cosmetic industry.

Clariant trade names

CLARIANT TRADE NAMES FOR POLYETHYELENE GLYCOL / MACROGOLS / PEG

Clariant uses the name Polyglykol as a trade name for polyethylene glycols. After the word Polyglykol the number indicates the mean molecular weight of the polymer.

For liquid / waxy Polyglykols no additional descriptor is used, with the exception of Polyglykol 200 USP. The capital letters USP indicate that this special grade of Polyglykol 200 complies with the requirements for mono and diethylene glycol of the USP/NF.

For solid types the capital letter following the molecular weight number indicates the physical form of the material:
S (German Schuppen = flakes),
P (powder, milled), PF (powder fine, milled) or
PS (powder, spray dried).

Bulk quantities of melt can be delivered in heated road tankers under the code FL.

AVAILABLE TYPES

Polyglykol 200 USP
Polyglykol 300
Polyglykol 400
Polyglykol 600
Polyglykol 1000
Polyglykol 1500 S / FL
Polyglykol 2000 S
Polyglykol 3000 S / P
Polyglykol 3350 S / P / PS / PSN / PSB
Polyglykol 4000 S / P / PF / PS
Polyglykol 6000 S / P / PF
Polyglykol 8000 S / P / PF
Polyglykol 10000 S / P
Polyglykol 12000 S
Polyglykol 20000 S / P
Polyglykol 35000 S
Lanogen® 1500

Lanogen® 1500 is an ointment base according to the Japanese Pharmacopoeia, containing Polyglykol 300 and 1500 in a ratio of 1:1.

® = registered trademark of Clariant

Manufacture and Nomenclature

MANUFACTURE

Polyethylene glycols, also called macrogols in the European pharmaceutical industry, are manufactured by polymerization of ethylene oxide (EO) with either water, mono ethylene glycol or diethylene glycol as starting material, under alkaline catalysis (1, 2). After the desired molecular weight is reached (usually checked by viscosity measurements as in-process control) the reaction is terminated by neutralizing the catalyst with acid. Normally lactic acid is used, but also acetic acid or others can also be used. The result is a very simple chemical structure: HO-[CH2-CH2-O]n-H, where (n) is the number of EO-units.

MODIFICATION

X-ray structural analysis has shown that PEG chain may possess two different types of microstructure. The shorter chains, with a degree of polymerization not exceeding 10, are said to have a zigzag structure, while longer chains form a so-called meandering structure. The oxygen forms ether bridges at regular intervals in both types of chain which are responsible for many of the properties of PEG (3-5).

An even more accurate examination of the structure (6, 7) shows that PEG chain in the crystalline state is spiral shaped. The microstructure of PEG molecular chains is important in relation to the behaviour of PEG towards various solvents and also to the formation of addition compounds which link with the "residual valencies" of the ether oxygen atoms.

NOMENCLATURE

Although technically these products should be called polyethylene oxides, for products with mean molecular weights of 200 to 35000, the term polyethylene glycols is normally used to indicate the significant influence of the hydroxyl end groups on the chemical and physical properties of these molecules. Only products made by polymerization of ethylene oxide in solvents, with molecular weights up to several millions, are called polyethylene oxides.

As an abbreviation for polyglycols, the term "PEG" is used, in combination with a numerical value. Within the pharmaceutical industry, the number indicates the mean molecular weight, whereas in the cosmetic industry the number refers to the number (n) of EO-units in the molecule (8). Since the molecular weight of ethylene oxide is 44, the average molecular weight values of PEG are given as round values of n*44.

Unfortunately, the various pharmacopoeias use different nomenclature for some PEG molecular weights. The table lists in additional to the European, US and Japanese monographs, also the nomenclature of the British Pharmacopoeia II from 1993. Even though this monograph is no longer valid, the nomenclature is still often used today.

DIFFERENT NOMENCLATURES FOR PEG

MEAN MOLECULAR WEIGHT	**CLARIANT POLYGLYKOL**	**NOMENCLATURE PH. EUR. 7th EDITION** (9)	**NOMENCLATURE USP36-NF31** (10)	**NOMENCLATURE JAPANESE PH. 16**	**NOMENCLATURE BRITISH PH. II** (12)
1500	1500	1500	1450 / 1500	–	1540
3000	3000	3000	3000	4000	–
3335	3335	3335	3335	4000	4000
4000	4000	4000	4000	–	–
6000	6000	6000	6000	–	–
8000	8000	8000	8000	6000	–
ointment base 300:1500=1:1	Lanogen ® 1500	–	–	1500	–

Technical data*

POLYGLYKOL	INCI PEG -	PRODUCT DESCRIPTION AT 20°C	HAZEN COLOUR 25% A.I.IN WATER (EN 1557)	MOLECULAR MASS G / MOL	OH VALUE MG KOH / G (DIN 55240)	SOLIDIFICATION POINT (PH.EUR.) °C	VISCOSITY AT 20°C M PA · S (DIN 51562)
200 USP	4	clear, viscous	max. 30	190 - 210	534 - 591	abt. - 50	60 - 67
300	6	hygroscopic	max. 15	285 - 315	356 - 394	–15 - –10	88 - 96
400	8	liquids	max. 15	380 - 420	267 - 295	4 - 8	112 - 124
600	12	liquid or wax	max. 15	570 -630	178 - 197	17 - 22	50% 17 - 18
1000	20	soft wax	max. 30	950 - 1050	107 - 118	35 - 40	50% 24 - 28
1500	32	white waxy	max. 30	1400 - 1600	70 - 80	44 - 48	50% 36 - 42
2000	40	flakes	max. 30	1800 - 2200	51 - 62	48 - 52	50% 50 - 58
3000	60	white waxy	max. 30	2700 - 3300	34 - 42	53 - 56	50% 75 - 95
3350	75	flakes	max. 30	3050 - 3685	30 - 37	53 - 57	50% 85 - 105
4000	90	or powder	max. 30	3700 - 4400	25 - 30	53 - 58	50% 114-142
6000	150		max. 30	5600 - 6600	17 - 20	55 - 60	50% 210 - 262
8000	180		max. 30	7300 - 9000	12 - 16	55 - 61	50% 290 - 450
10000	220	pale, hard	max. 30	9000 - 11250	10 - 12	55 - 62	50% 550 - 750
12000	240	waxy flakes	max. 30	10500 - 15000	7.5 - 11.0	> 57	50% 1100 - 1400
20000	new 450 (old 350)	or powder	max. 30	16000 - 25000	4.5 - 7.0	57 - 64	50% 2700 - 3500
35000	800	pale, hard waxy flakes	max. 30	approx. 35000	–	> 57	50% 11000 - 14000
Lanogen® 1500	6 (and) 32	PEG ointment mixture 1500:300 = 1:1	max. 15	470 - 530	212 - 239	37 - 41	50% 18 - 25

* No delivery specification

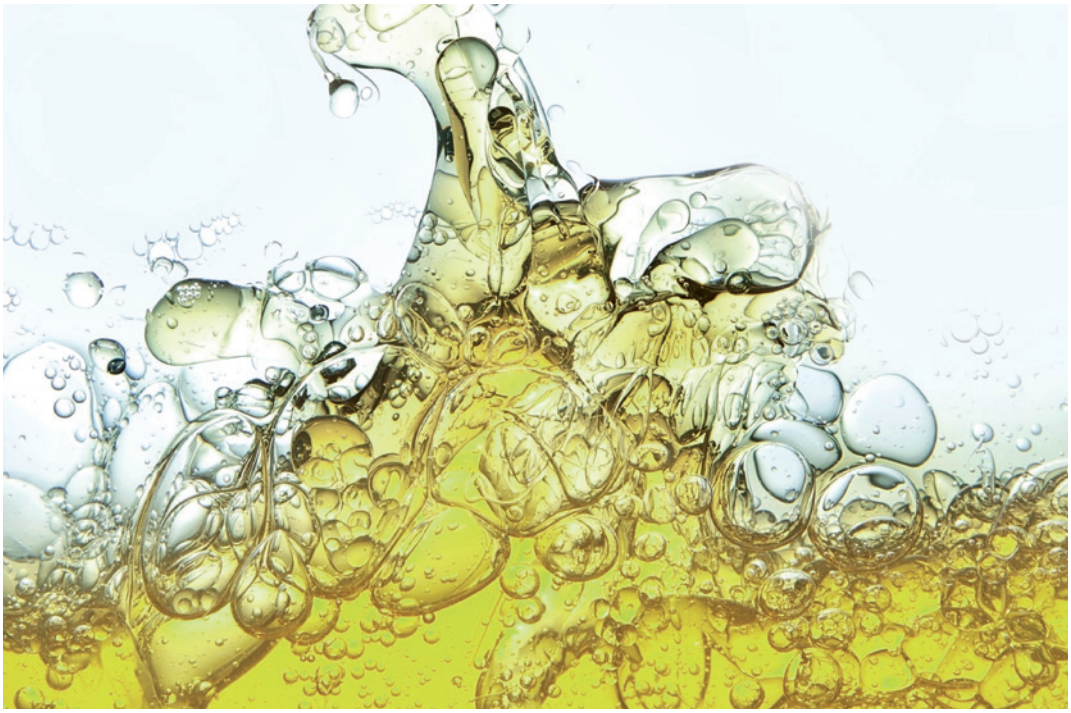
VISCOSITY AT 98.8°C = 270°F MM2 / S (USP-NF)	**PH 5% AQUEOUS SOLUTION** (DIN EN 1262)	**STABILIZER (BHA)** PPM	**WATER CONTENT % M/M** (DIN 51777)	**DENSITY AT 20°C G/CM 3 (+ 0.001)** (DIN 51757)	**VAPOUR PRESSURE AT 20°C HPA**	**SOLUBILITY IN WATER AT 20°C** % M / M
3.9 - 4.8	5.0 - 7.5	—	max. 1	1.124	< 0.1	∞
5.4 - 6.4	5.0 - 7.0	—	max. 1	1.125	< 0.1	∞
6.8 - 8.0	5.0 - 7.0	—	max. 1	1.126	< 0.01	∞
9.9 - 11.3	5.0 - 7.5	—	max. 1	1.126	< 0.01	∞
16 - 19	5.0 - 7.5	—	max. 1	solidified melt 1.126	< 0.001	75
26 - 32	5.0 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	62
38 - 49	5.0 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	58
67 - 93	5.0 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	56
76 - 110	5.0 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	56
110 - 158	5.0 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	55
250 - 390	5.0 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	54
470 - 900	5.0 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	54
–	5.0 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	53
–	5.0 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	53
–	4.5 - 7.5	100 - 200	max. 1	solidified melt 1.20	< 0.001	52
–	5.0 - 7.0	100 - 200	max. 1	solidified melt 1.20	< 0.001	50
–	5.0 - 7.0	—	max. 1	solidified melt 1.20	< 0.001	> 70

Properties

Polyethylene glycols with a mean molecular weight up to 400 are non-volatile liquids at room temperature. PEG 600 shows a melting range of about 17 to 22°C, so it may be liquid at room temperature but pasty at lower ambient temperatures, while PEG with 1000 to 2000 mean molecular weight are pasty materials with a low melting range. Above a molecular weight of 3000, the polyethylene glycols are solids and are available not only in flaked form but also as powder. Polyglykols up to a molecular weight of 35000 are commercially available. The hardness of Polyglykols increases with increasing molecular weight, however the melting range goes up to a maximum value of about 60°C.

The most important property of all PEG is their solubility in water, making them ideally suited for use in countless different applications. Liquid PEG up to PEG 600 are miscible with water in any ratio. But even solid PEG grades have excellent solubility in water. Although it falls slightly with increasing molar mass, even 50% (w/w) of a PEG 35000 can be dissolved. The solubility and viscosity of the solutions is not affected by the presence of electrolytes, since PEG are nonionic substances. PEG are quite soluble in hard water or in other aqueous solutions of various salts.

Some physical and chemical properties are described in more detail in the following chapters.



SURFACE TENSION

The surface tension of the liquid PEG 200 to 600 is about 47 mN/m at room temperature. There is only a slight difference in the surface tension of liquid and solid PEG in aqueous solutions; a 10% solution of PEG 400 has a value of 64 mN/m, while a 10% solution of PEG 4000 has a value of about 60 mN/m at 20°C.

PEG possess no characteristic surfaceactive properties and can therefore not be included in the class surfactants. Nevertheless, they frequently prove to be useful dispersing agents or solubilizers. It is not possible to give an HLB value for PEG.

LATENT HEAT OF FUSION

The latent heat of fusion of the solid PEG is 167-196 kJ/kg, depending to some extent on the degree of crystallinity.

SPECIFIC HEAT

The specific heat (heat capacity) of the liquid PEG at room temperature is about 2.1 kJ/kg K. With rising temperature it increases steadily and at 120°C reaches about 2.5 kJ/kg K.

THERMAL CONDUCTIVITY

For liquid PEG grades the thermal conductivity at room temperature is 0.23 W/m K. (Water: 0.6 W/m K).

COEFFICIENT OF THERMAL EXPANSION

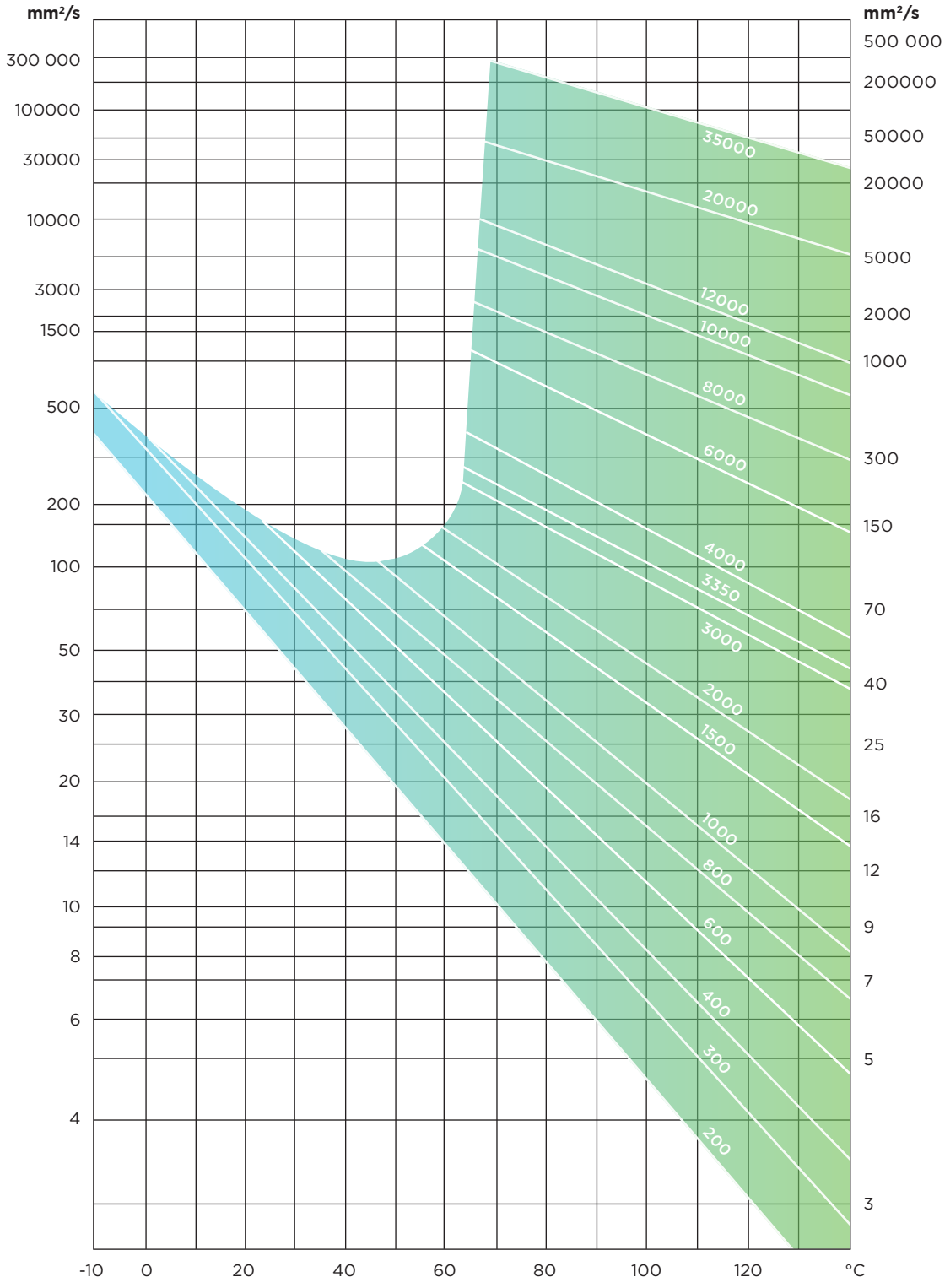
The coefficient of volumetric thermal ex pansion of liquid PEG at 20°C is about 0.00073 K^{-1} and increases linearly up to 0.00080 K^{-1} at 160°C.

VISCOSITY

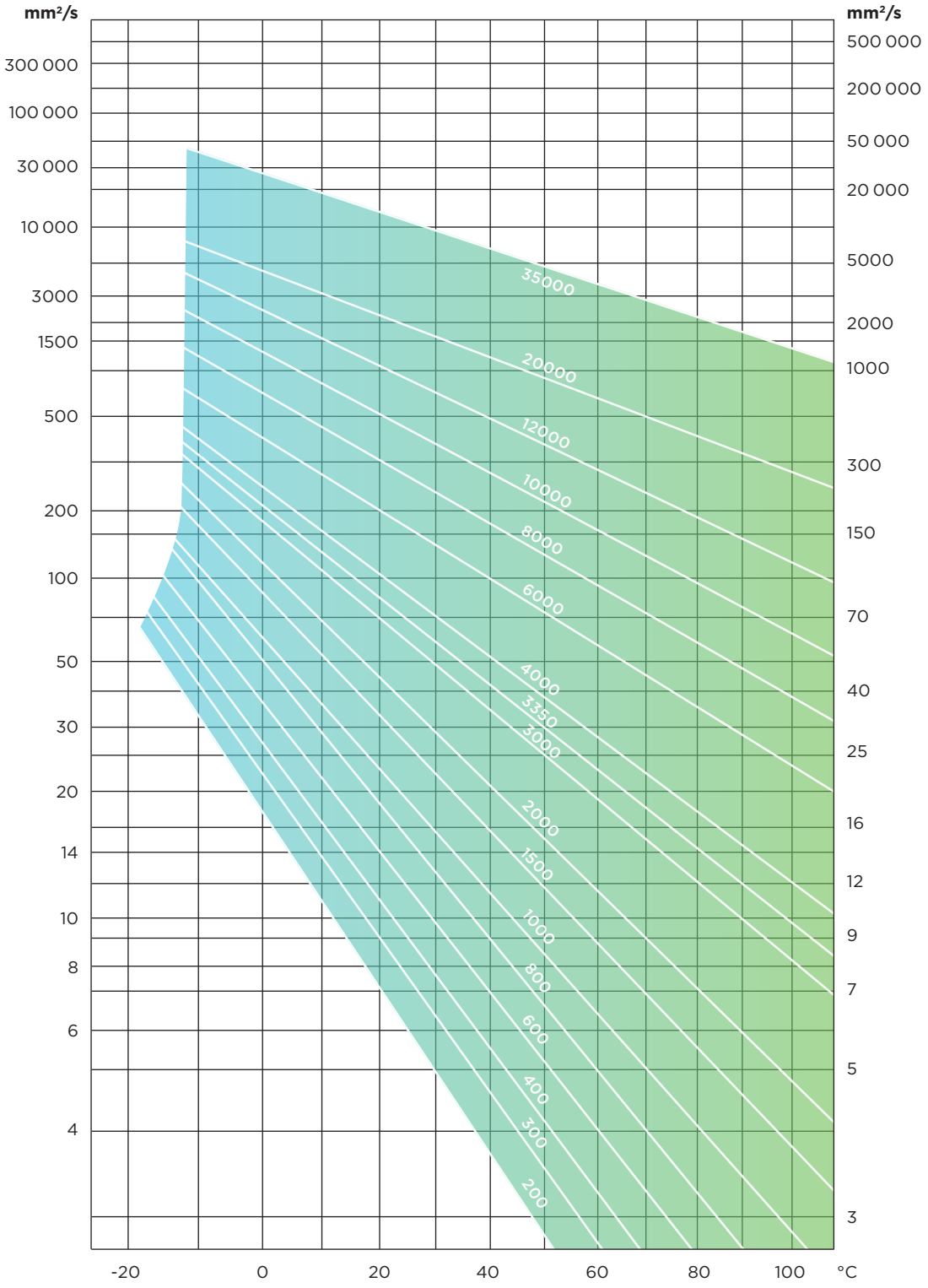
The dynamic viscosity (mPa · s) can be converted into kinematic viscosity (mm2/s) and vice versa according to the following formula, taking the density into account:

$$mm^2/s = \frac{mPa \cdot s}{density}$$

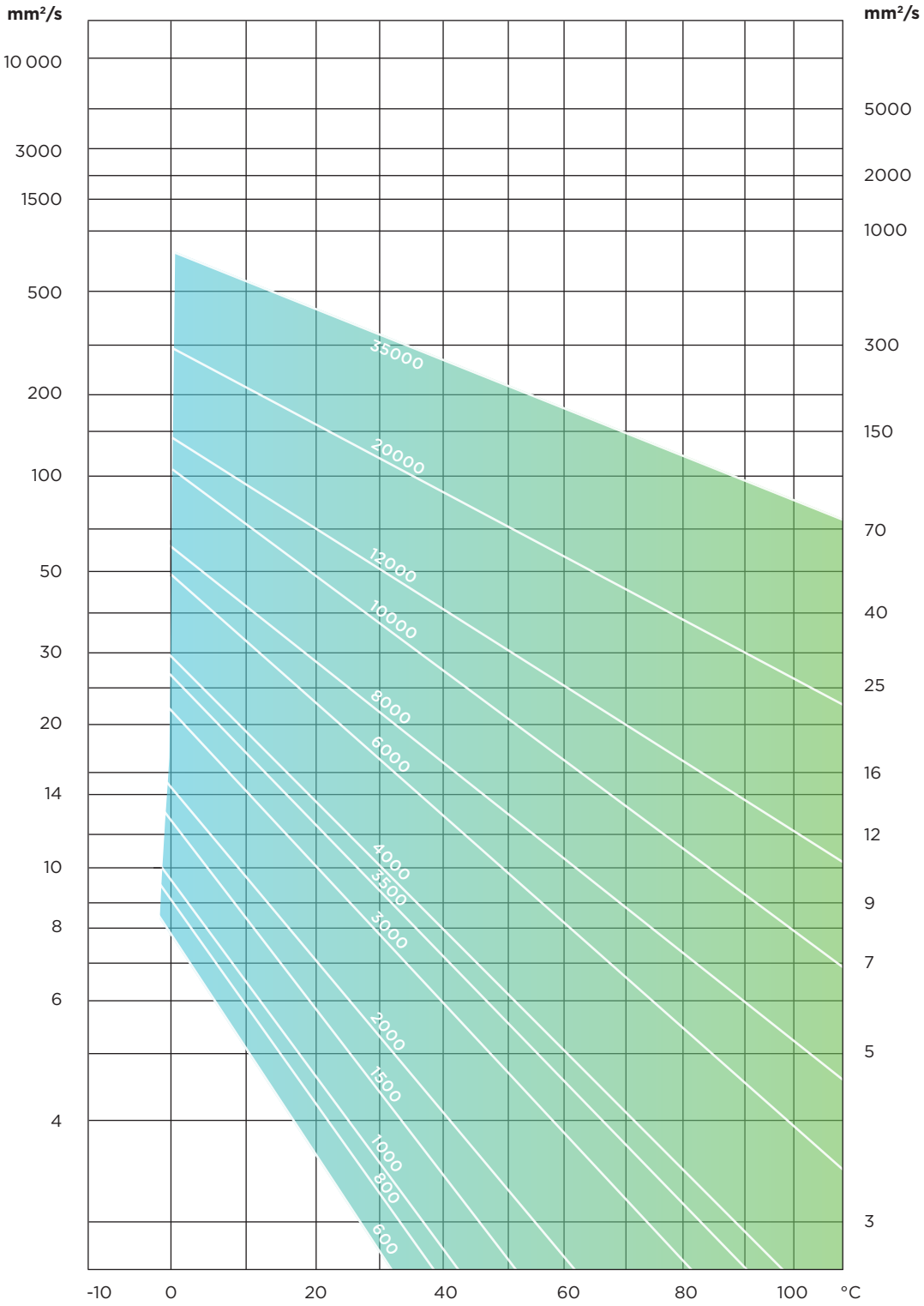
Viscosity of PEG 200 - 35000 as a function of temperature



PEG 200 - 35000, viscosity of 50% aqueous solution as a function of temperature



PEG 600 - 35000, viscosity of 25% aqueous solution as a function of temperature



SOLUBILITY IN WATER

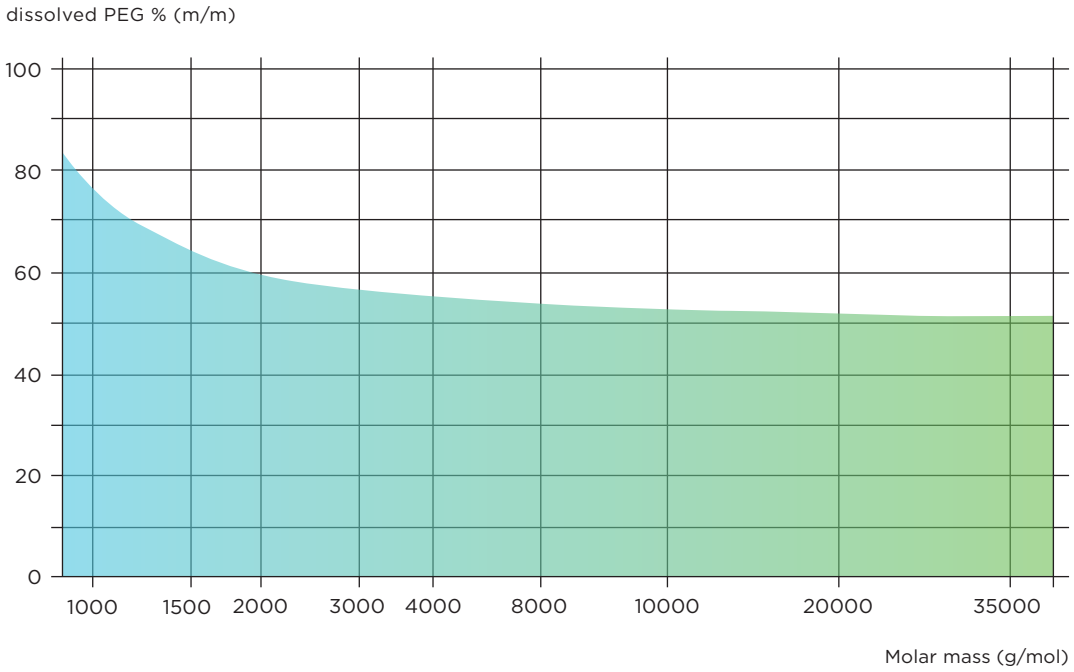
When liquid PEG are mixed with water, a volume contraction takes place. When equal parts by weight PEG 400 and water are mixed together, this contraction amounts to about 2.5%.

At the same time a marked heat effect occurs. The temperature rise taking place when equal parts by weight PEG and water are mixed is about 12°C for PEG 200 and about 14°C for PEG 600.

Even solid PEG grades have excellent solubility in water. For example, 75 parts by weight of PEG 1000 can be dissolved at room temperature in only 25 parts by weight water. Although the solubility in water falls slightly with increasing molar mass, it does not fall below 50% even in the case of PEG 35000. The dissolving process can be greatly accelerated by heating about the melting point.

PEG exhibit nonionic behaviour in aqueous solution. They are not sensitive to electrolytes and are therefore also compatible with hard water.

Solubility in water of PEG 1000 - 35000 at room temperature



WATER CONTENT

When our PEG are despatched, the water content is usually not more than 0.5%. Some pharmacopoeias permit a maximum water content of 2%.

If necessary, the water content can be reduced to 0.1% in drying oven at 105°C; with fresh or well regenerated molecular sieves (pore size 3-4 Å) it can be reduced to 0.05%.

NON-VOLATILITY AND THERMAL STABILITY

PEG are non-volatile, a factor of considerable importance in connection with their use as plasticizers and humectants.

If a certain weight loss is established despite the non-volatility of PEG when maintained at a constant temperature of 150°C and above (e.g. when used as heating bath liquids), this is due not to evaporation but to loss of volatile products of decomposition.

The breakdown products of PEG may vary, depending on the ingress of air; apart from water, carbon dioxide and aldehydes, simple alcohols, acids and glycol esters are formed.

Troublesome fumes from decomposition products have not been known to have an adverse effect on health.

Since the lower PEG grades are hygroscopic, moisture may be reabsorbed in the case of fairly long down times.

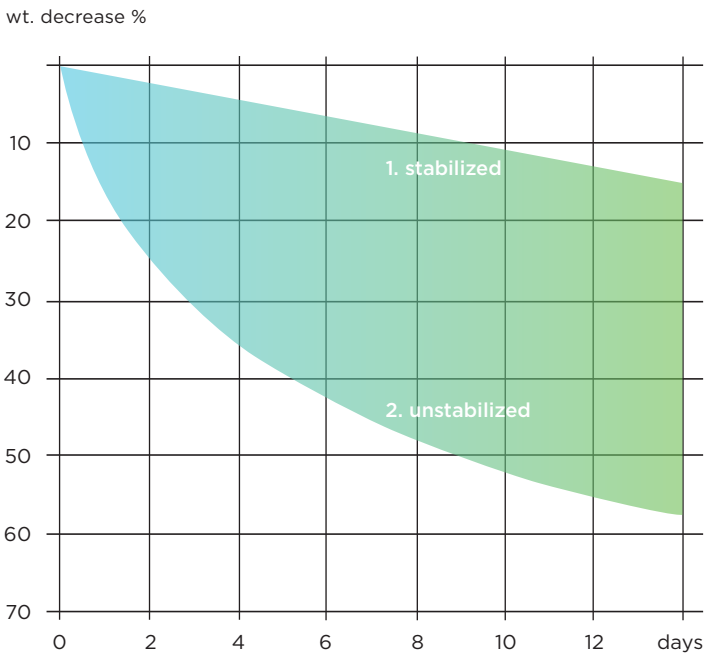
At temperatures above 100°C it is essential to add a suitable antioxidant to PEG. The type an quality of antioxidant is governed by the requirements imposed on PEG. Thus, not only the temperature and dwell time but also the physiological properties of the antioxidant and its solubility or insolubility in water must be taken into consideration. Where exposure to high thermal stress is involved, up to 3% antioxidant should be added.

The following substances have proved effective as antioxidants:

1. trimethyl dihydroquinoline polymer
2. diphenylamine derivatives
3. phenothiazine
4. phenyl-alpha-naphtylamine
5. 4,4'-methylene-bis.2,6-di-tert.-butylphenol
6. butylated hydroxyanisole (BHA)
7. methoxy phenole (hydroxyanisole)

As the following figure shows, oxidative decomposition can be slowed down considerably by the addition of antioxidants even at high temperatures (200°C). The bath was stabilized with 3% of one of the inhibitors numbered 1 to 4 in turn. No major differences were observed between the individual substances.

Thermal stability of PEG at 200°C



The pure thermal degradation without presence of oxygen can hardly be influenced with antioxidants.

Curve 1 applies to the following stabilizers (3% addition):
- trimethyl dihydroquinoline polymer
- diphenylamine-styrene adduct
- phenothiazine
- phenyl-alpha-naphtylamine

The phenolic stabilizers numbered 5-7 in the list are effective only at lower temperatures – up to about 150°C - but have two advantages: they cause less discoloration and some of them are water-soluble. The ingress of air should be excluded if possible or the bath should be blanketed with an inert gas atmos phere (nitrogen, carbon dioxide, etc.). This applies particularly to temperatures between 200 and about 220°C. Hot PEG attack iron and steel only slightly, but as a precaution when liquid PEG are used, a certain margin of alkalinity should be created by the addition of about 0.3% hydrated borax or triethanolamine. Other materials should be tested to establish their resistance to corrosion by PEG.

HYGROSCOPICITY

The liquid PEG grades are hygroscopic, although not to the same extent as for example diethylene glycol or glycerol. The ability to absorb water decreases with increasing molar mass.

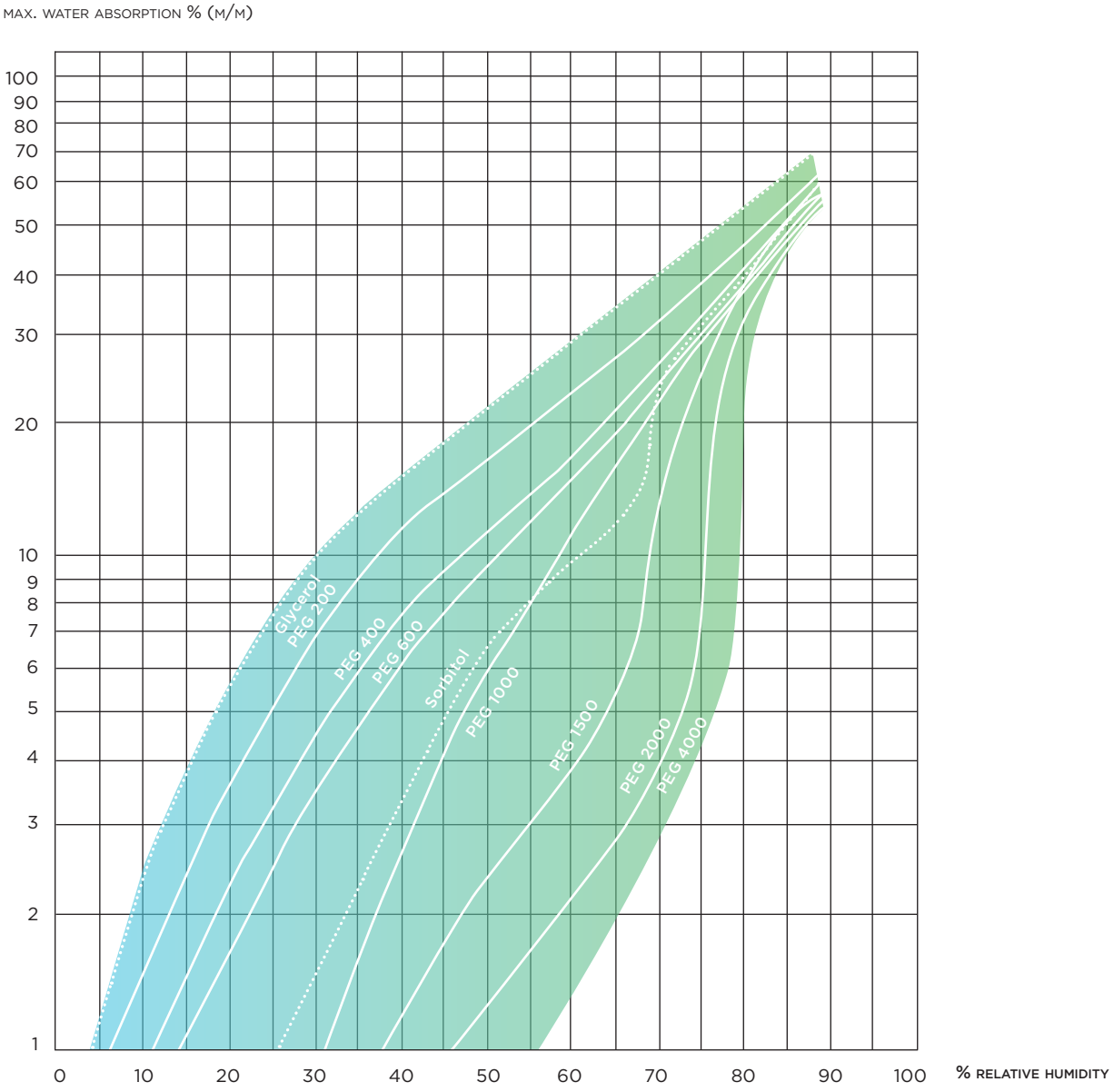
A rule of thumb is: With a relative humidity of about 50% PEG 200 has about ¾ of the hygroscopicity of glycerol. PEG 400 has about half, PEG 600 a third and PEG 1000 only a quarter. PEG 2000 and higher grades are no longer hygroscopic.

PEG take moisture from the air until an equilibrium is reached. By plotting the water content of the substance in the equilibrium state as a function of the relative humidity, absorption isotherm is obtained.

The moisture absorption of lower glycols such as monoethylene glycol, diethylene glycol or 1,2-ropylene glycol corresponds roughly to that of glycerol.

An adaptable moderate hygroscopicity may be advantageous for a conditioning agent because products treated with it are less sensitive to climatic changes and have better storage stability.

Sorption isotherms (23 ± 1°C) for PEG 200 - 4000, glycerol and sorbitol



SOLUBILITY PROPERTIES

The excellent solubility characteristics of PEG are of great importance in relation to their applications. Two advantages are especially significant:
Firstly, the ability of PEG to dissolve many substances and, secondly, their good solubility in numerous solvents.

In the preparation of aqueous solutions PEG sometimes act as specific solubilizers. The dissolving power and the solubility of PEG decrease as the molar mass increases. Both properties are improved by heating. Here is a list of solvents in which the liquid PEG are very readily miscible and in which the solid PEG dissolve:

Alcohols	*e.g. ethanol, isopropanol, benzyl alcohol*
Esters	*e.g. methyl acetate, utyl acetate*
Glycol ethers	*e.g. methyl glycol, butyl glycol and their acetates*
Ketones	*e.g. acetone, cyclohexanone*
Chlorinated	*e.g. ethylene chloride, hydrocarbons, chloroform*
Benzene	*e.g. benzene, xylene hydrocarbons*

PEG are insoluble in aliphatic hydrocarbons.

COMPATIBILITY

PEG have good compatibility with cetyl alcohol, glycerol, stearic acid, polyvinyl pyrrolidone, casein, vegetable albumin, dextrin, starch, chlorinated starch and various resins, e.g. colophony. Some ethereal oils are absorbed extremely well by liquid and molten PEG.

SUBSTANCES SOLUBLE IN PEG

Substances that dissolve at room temperature in PEG 400 are soluble to roughly the same extent in molten PEG 4000 (60-70°C). The following values indicate the approximate percentage of PEG 4000 in the solutions saturated at room temperature:

	% (m/m)		% (m/m)
Aniline	*30*	*Methanol*	*20*
Benzene	*10*	*Methylene chloride*	*53*
Carbon tetrachloride	*10*	*Pyridine*	*40*
Chloroform	*47*	*Trichlorethylene*	*25*
1,4-Dioxane	*10*	*Water*	*55*
Ethanol 60%	*50*	*White spirit*	*i.*
Ethylene chloride	*46*	*Xylenol*	*50*
Formamide	*30*		

The solubility of PEG increases sharply with rising temperature, as the following example shows:

PEG 20000 is soluble in pure ethanol as follows	
at 20°C	*0.1%*
at 32°C	*1%*
at 34°C about	*20%*

This means that a PEG that is insoluble at room temperature can be brought into solution by moderate heating.

It is worth noting that solid PEG are completely insoluble in liquid PEG at room temperature.

SOLUBILITY OF VARIOUS SUBSTANCES IN PEG 400 AT ROOM TEMPERATURE

A	
Acetanilide	16%
Acetic anhydride	∞
Acetone	∞
Acrylic acid	∞
Acrylonitrile	∞
Allyl alcohol	∞
Ammonia (25%)	∞
Amyl acetate	∞
Amyl alcohol	∞
Aniline	∞
Antipyrine	10%
Azulene (guaia azulene)	10%
B	
Beeswax	i.
Benzaldehyde	∞
Benzene	∞
Benzocaine	50%
Benzoic acid	10%
Benzyl alcohol	∞
Borax cryst.	0.3%
Bromobenzene	∞
n- Butanol	∞
Butyl acetate	∞
Butylamine	∞
Butyl diglycol	∞
Butyl glycol	∞
Butyl glycolate	∞
C	
Calcium chloride • 2 H_2O	*20%
Camphor	10%
Carbon disulphide	10%
Carbon tetrachloride	∞
Carnauba wax	i.
Casein	i.
Castor oil	1%
Ceresin wax	i.
Cetyl alcohol	sl.c.s.
Cetyl stearyl alcohol	sl.c.s.
Chloral hydrate	50%
Chloramine T	10%
Chlorobenzene	∞
Chloroform	∞
Chlorothymol	50%
Chlorparaffi n 56 and 70	∞
Citric acid	25%
Cobalt (III) chloride • 6 H_2O	*50%
Coconut fatty amine	10%
Colophony	50%
Copper (III) chloride • 2 H_2O	∞
Cresol	20%
Cyclohexane	i.
Cyclohexanol	∞
Cyclohexanone	∞
D	
Diacetone alcohol	∞
Dibutyl phthalate	∞
ß,ß-Dichloroethyl ether	∞
Di-(2-ethylhexyl) phthalate	i.
Cyclohexanone	∞
Diethanolamine	∞
Diethylene glycol	∞
Diethylene glycol dimethyl ether	∞
Diisopropyl adipate	∞
Dimethyl acetamide	∞
Dimethyl formamide	∞
Dimethyl phthalate	∞
Dimethyl sulphoxide	∞
Dioctyl phthalate	i.
Dioxane	∞
Diphenyl ether	∞
Dipropylene glycol	∞
Dodecyl alcohol	∞
E	
Eosinic acid	10%
Ephedrine (1/2 H2O)	20%
Ester waxes	i.
Ethanol	∞
Ethyl acetate	∞
Ethylbenzene	∞
Ethylene diglycol	∞
Ethylene glycol	∞
Ethylene glycol acetate	∞
2-Ethylhexenol	∞
Ethyl urethane	50%
Ethylene chloride	∞
Eucalyptus oil	10%
F	
Formamide	∞
Furfural	∞
G	
Gelatin	i.
Glacial acetic acid	∞
Glycerol	∞
Glycerol monoestearate	sl.s.c.
Glycerol triacetate	∞
Glycol	∞
Gum arabic	i.
H	
Hexachlorophene	45%
Hydrochloric acid, 37%	∞
I	
Iodine	20%
Iron (III) chloride • 6 H_2O	*50%
Isobutanol	∞
Isobutyl acetate	∞
Isodecyl alcohol	∞
Isopropanol	∞
Isotridecyl alcohol	∞
L	
Lactic acid (90%)	∞
Lavender oil	10%
Lead acetate	1%
Lead stearate	i.
Lecithin	i.
Lithium stearate	i.
M	
Magnesium chloride • 4 H_2O	*25%
Manganese (II) chloride • 4 H_2O	*40%
Menthol	10%
Mercury (II) acetate	*10%
Methanol	∞
Methoxybutyl acetate	∞
Methyl acetate	∞
Methyl diglycol	∞
Methyl ethyl ketone	∞
Methyl glycol	∞
Methyl glycol acetate	∞
Methyl methacrylate	∞
Methyl salicylate	∞
Methylene chloride	∞
Mineral oils	i.
Morpholine	∞
N	
Naphthalene	10%
b-Naphtanol	40%
Nitrobenzene	∞
Nitromethane	∞
O	
Octyl alcohol	∞
Oleic acid	∞
P	
Paraffi n oil	i.
Paraldehyde	50%
PEG laurate	∞
PEG sorbitan oleate	sl.s.c.
Perchloroethylene	43%
Petroleum jelly	i.
Phenacetin	10%
Phenol	50%
Phenol (90%)	∞
Phenothiazine	15%
Phenyl acetate	∞
Phenylmercuric acetate	10%
Phenyl salicylate	50%
Phosphoric acid (85%)	∞
Piperazine	10%
Polyethylene glycol 4000 (soluble when heated)	i.
Polypropylene glycol 400	∞
Potassium iodide	*15%
Propanol	∞
1,2.Propylene glycol	∞
Pyridine	∞
Pyrocatechol	50%
R	
Resorcinol	50%
S	
Saccharin	10%
Salicylaldehyde	∞
Salicylic acid	30%
Sodium chloride	0.3%
Sodium cyclamate	3%
Sodium nitrite	0.4%
Sodium sulphate	i.
Sorbic acid	5%
Sorbitol	sl.s.c.
Stearic acid	sl.s.c.
Stearylamine	i.
Styrene	∞
Styrene oxide	∞
Sulphanilamide	10%
Sulphathiazole	10%
Sulphuric acid , 50%	∞
T	
Tannin	50%
Terpineol	∞
Tetrahydrofuran	∞
Tetralin	55%
Thiourea	10%
Thymol	50%
Tin (II) chloride • 2H_2O	*55%
Trichlorobutyl alcohol	10%
1,1,1-Trichloroethane	∞
Trichloroethylene	∞
Trichloroethyl phosphate	∞
Triethanolamine	∞
Triethylene glycol	∞
U	
Urea	3%
V	
Vanillin	10%
Vegetable oils	i.
W	
White spirit	i.
X	
Xylene	∞
Xylenol	∞
Z	
Zinc chloride • 2H_2O	*20%

Figures in % (m/m)

∞ = miscible in all proportions

sl.s.c. = slightly soluble at room temperature but soluble at 70 - 80°C

i. = insoluble

* When heated to about 100°C these metal salts go into solution and form highly viscous liquids with PEG 400 that are stable even at room temperature.

PHYSICAL FORMS OF PEG

All solid PEG (1500-35000) are available as flakes with sizes of about 0.3 to 2 cm. PEG grades 3000 to 20000 are available in powder form (P), the grades 4000 to 8000 also as fi ne powders (PF) and 3350 to 4000 as spray dried powders (PS).

Solid PEG are used in powder form wherever it is necessary for them to be intimately drymixed with component of a different kind, for example in tablet manufacture, or in dry granulation.

To convey an impression of the particle size distribution, an average particle size analysis of the Clariant powder grades is given in the next table.

Particle size distribution of PEG powder (typical values measured with Crystalsizer)

Micron	Powder (P) 3000-20000 %	Fine powder (PF) 4000-8000 %	Spray dried powder (PS) 3350-4000 %
< 90	*10-30*	*75-95*	*max. 15*
90-200	*10-30*	*5-25*	*20-45*
> 200	*50-75*	*max. 5*	*35-70*

Power density (kg/m³)

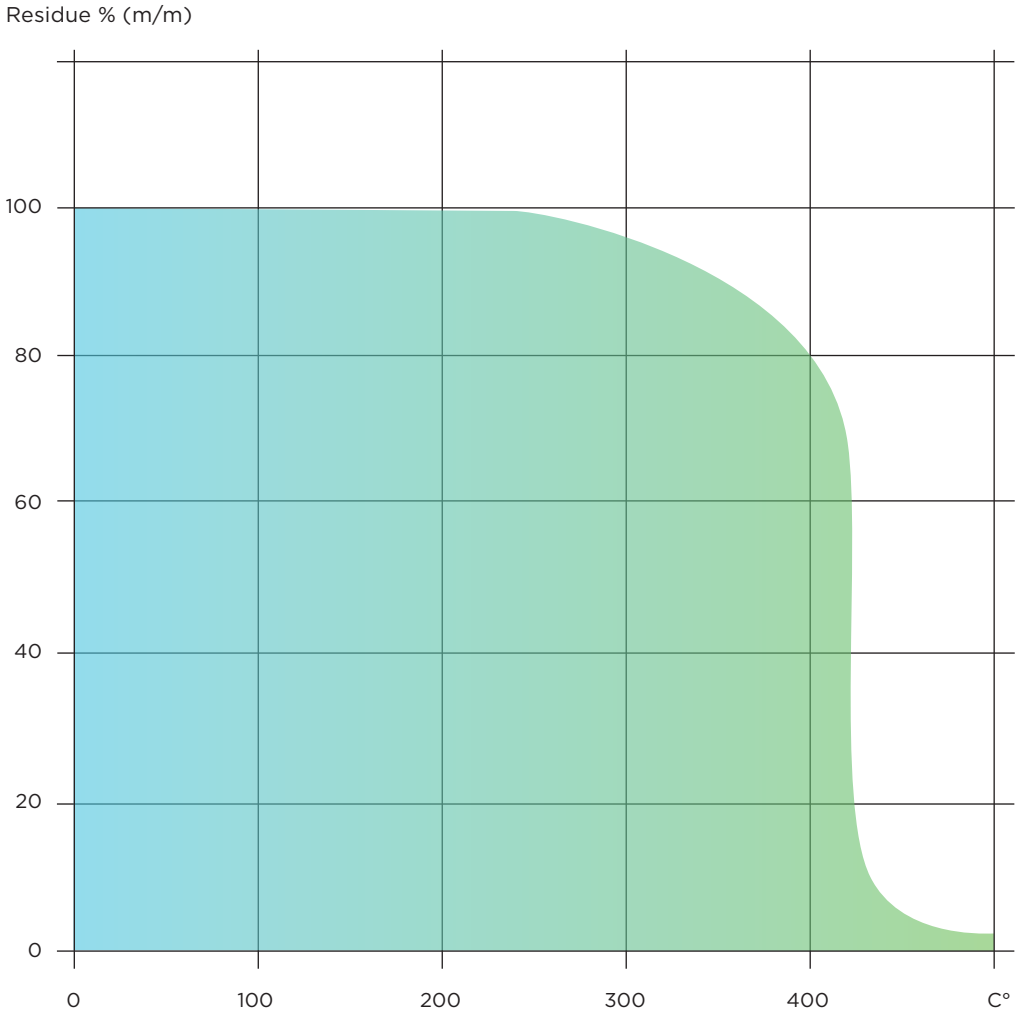
Flakes (S)	Powder (P)	Fine powder (PF)	Spray dried powder (PS)
400-500	*500-700*	*450-550*	*430-720*

PYROLYSIS

When air is excluded (14), PEG chain breaks down only at temperatures above 250°C, the chain length and the molar mass being insignificant factors in the range of about 300 to 6000. The rate of decomposition of PEG is shown by the following thermogravimetric (TG) curve.

The thermogravimetric curve was plotted by means if a combined DTA/TG instrument in a nitrogen atmosphere at a heat-up rate of 5°C/min.

Thermogravimetric curve for PEG 4000 under exclusion of air



MOLAR MASS DISTRIBUTION OF PEG

The various PEG grades are not uniform chemical compounds but rather mixtures of similar polymer members of the homologous PEG series.

Bis-trimethylsilyl derivatives are suitable for analysis of PEG by gas chromatography (15). By the use of gas chromatography we were able to determine the composition of our PEG 200, 300 and 400 as follows (16):

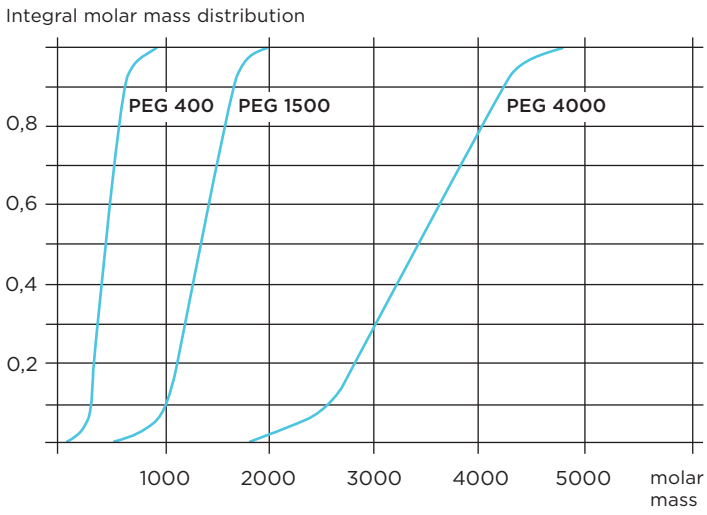
Polyglykol 200 USP is available as special type in pharma quality with a specifi ed Mono- and Diethylene Glycol content of max. 0.20%.

Information on the molar mass distribution of PEG grades is given by column chromatographic analyses based on the different migration rates of the fractions in microporous gel (GPC, gel permeation chromatography) (17, 18).

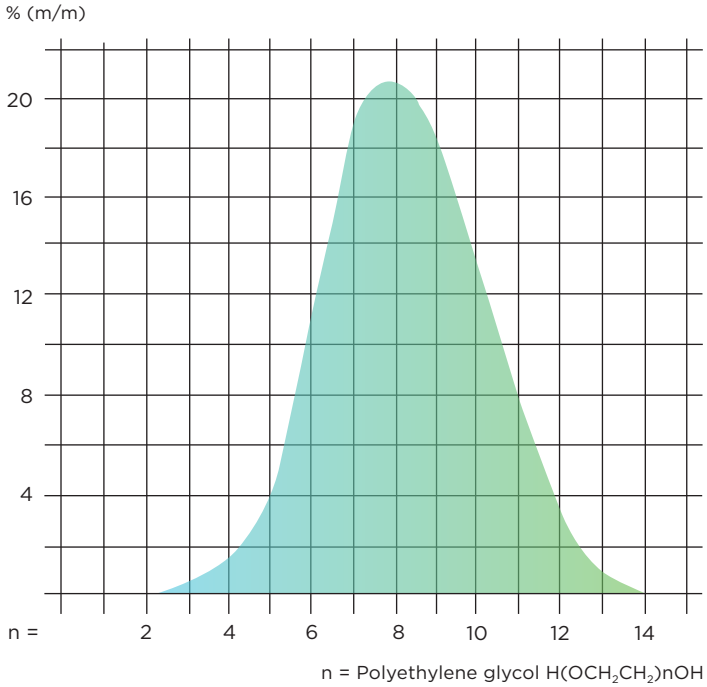
When our PEG 400, 1500 and 4000, dissolved in tetrahydrofuran, were fractionated over Styragel, the molar mass distribution was very narrow.

	PEG 200 %	**PEG 200 USP %**	**PEG 300 %**	**PEG 400 %**
Monoethylene glycol	*0.1*	—	—	—
Diethylene glycol	*3.4*	*0.1*	*0.2*	—
Triethylene glycol	*21.2*	*28.9*	*2.4*	*0.1*
Tertaethylene glycol	*31.2*	*37.6*	*9.0*	*0.7*
Pentaethylene glycol	*24.4*	*21.8*	*16.4*	*2.1*
Hexaethylene glycol	*14.0*	*8.8*	*25.5*	*7.2*
Heptaethylene glycol	*5.4*	*2.3*	*25.2*	*4.4*
Octaethylene glycol	*0.3*	*0.4*	*15.0*	*19.1*
Nonaethylene glycol	—	*0.1*	*4.2*	*19.2*
Decaethylene glycol	—	—	*2.0*	*15.7*
Undecaethylene glycol	—	—	*0.1*	*10.2*
Dodecaethylene glycol	—	—	—	*5.9*
Tridecaethylene glycol	—	—	—	*3.4*
Tetradecaethylene glycol	—	—	—	*1.5*
Pentadecaethylene glycol	—	—	—	*0.5*

GPC analysis of PEG 400, 1500 and 4000

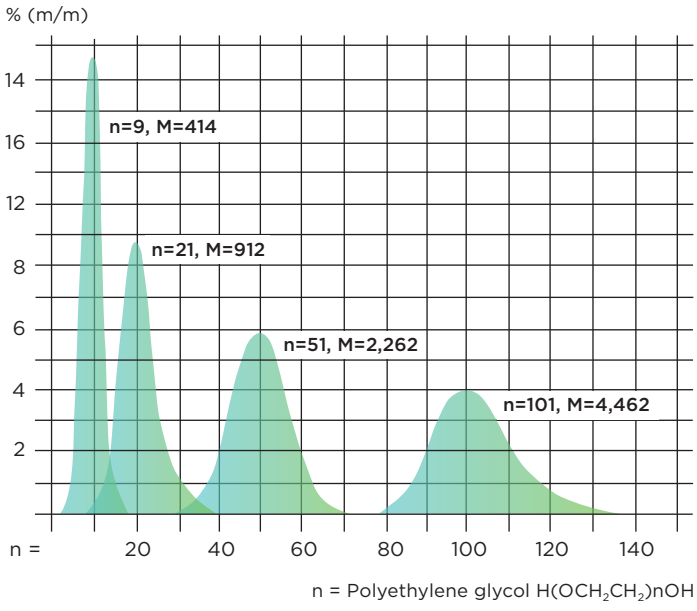


Molar mass distribution of PEG 400



Peak area (percentages by weight) determined by gas chromatography

Molar mass distribution of PEG 400 - 4000



Distribution is in accordance with Poisson's formula

Physiological Properties

Polyethylene glycols show outstanding toxicological safety regarding acute and chronic oral toxicity, embryotoxicity or skin compatibility (19,20) supported by parental / absorption / excretion investigations (21,22). Therefore they have been used for many years in cosmetics, foodstuffs (26) and the pharmaceutical industry and are registered in all relevant pharmacopoeias.

ANIMAL TOXICITY

• Acute oral toxicity
Macrogols (polyethylene glycols) are considered as practically non-toxic compounds. Acute oral toxicity, expressed as the median lethal dose (LD50), is reported to be 30.000 to 50.000 mg/kg body weight in various animal species. Higher molecular weight PEG exhibit even greater LD50 -values above 50.000 mg/kg body weight.

• Chronic oral toxicity
Smyth et al. (27) summarized the extensive feeding studies they conducted with Macrogols. For example polyethylene glycols having average molecular weights of 400, 1500 and 4000 caused no adverse effect in dogs when fed two percent in their diet for one year. Several percent of Macrogols can be tolerated in the diet of rats without appreciable effects, indicated that they are exceptionally low in chronic oral toxicity.

• Eye irritation
Macrogols do not cause appreciable irritation to the eyes of rabbits (28).

• Skin irritation and sensitization
Although early reports by Smyth et al. (29) reported that skin sensitization was observed in guinea pigs tested with certain Macrogols, later studies show that currently produced materials are without irritation or sensitizing properties (27).

• Dermal absorption
As concluded by Smyth et al. (27) the lethal dose via dermal application of Macrogols is so large as to defy the establishment of LD50 values.

• Toxicokinetic studies / metabolism
Toxicokinetic studies on absorption, metabolism, distribution, and excretion revealed that low molecular weight Macrogols are absorbed from the rat intestine only to a very slight extent. Higher molecular weight Macrogols are not absorbed at all. Excretion of Macrogols is mainly via feces without any biotransformation.

HUMAN TOXICITY

• Oral toxicity
Studies with human volunteers who received oral doses of 10 grams were tolerated without any toxicological or clinical symptoms (30).

• Eye irritation
No cases of injury to human eyes have been reported nor would any be expected.

• Skin irritation and sensitization
Although early reports by Smyth et al. (29) reported that skin sensitization was observed among a few human subjects tested with certain Macrogols, later studies show that currently produced materials are without irritations or sensitizing properties (27).

• ADI-value
The acceptable daily intake (ADI-value) for polyethylene glycols in foodstuffs is defi ned by the World Health Organization (WHO) as a maximum of 10 mg/kg body weight (31).

Identification Analysis

QUALITATIVE DETECTION WITH TETRAIODOBISMUTHIC ACID

The modified Dragendorff reagent is of an intense yellow colour and immediately gives a bright orange precipitate in the presence of free PEG and PEG derivatives (ethoxylates) (32). The reagent is suitable for a simple spot test and is used in paper and thin-layer chromatography.

The reagent is prepared as follows

	SOLUTION A
1,7 g 20 ml 100 ml	basic bismuth nitrate are dissolved in glacial acetic acid. This solution is diluted up to with demineralized water
	SOLUTION B
40 g 100 ml	potassium iodide are dissolved in demineralized water
	SOLUTION C
100 ml + 140 g + 200 g 1000 ml	Solution A Solution B glacial acetic acid are made up to with demineralized water
	SOLUTION D
20 g 80 ml	barium chloride are dissolved in demineralized water
	READY-TO-USE MODIFIED DRAGENDORFF REAGENT
100 ml +50 ml	Solution C Solution D

THIN-LAYER CHROMATOGRAPHY

A mixture of chloroform/methanol/ water in the ration: 3:25:12 may be used as the mobile phase. Water-saturated n-butanol has proved very successful as a solvent system for simpler separating operations (33-36).

METHODS OF DETERMINATION INVOLVING COMPLEX FORMATION

Due to their ether characteristics, PEG are capable of forming complexes which are difficult to dissolve. Precipitation with silicot ungstic acid in the presence of barium chloride is used to determine PEG gravimetrically (37). PEG can also be determined quantitatively by precipitation with sodium tetraphenyl borat (38). The modified Dragendorff reagent can be employed for the detection of PEG and for sedimetric determination (28). Phosphomolybdic acid is used for colorimetric determination (37).

None of the above-mentioned quantitative methods of precipitation is very easy to carry out, particularly as the molar mass of PEG in question has to be know in order to be able to evaluate the results.

To determine PEG in the molar mass range from 300 to 1000 colorimetrically, complexes of PEG with ammonium cobalt thiocyanate are suitable (39).

METHODS OF DETERMINATION INVOLVING ETHER CLEAVAGE

Another method of determining PEG is the Zeisel method of ether cleavage with hydrogen iodide (40 - 43).

Applications of PEG
Pharmaceutical Industry

PEG AS EXCIPIENTS

• Liquids
The very good solvent power leads to a broad use of low molecular weight PEG 200 to 400 in liquid preparations such as drops, parenterals or fillings for gelatin capsules. Polyethylene glycol does not soften gelatin. The liquid PEG have a slightly bitter taste, which can easily be adjusted by suitable additives (sweeteners). Solid PEG grades show a neutral taste.

• Ointment basics
It is very interesting that solid PEG are not soluble in liquid polyethylene glycols. Blending pasty or solid PEG together with liquid PEG will lead to a white, pasty ointment with good solubility in water, good dissolving properties and suitable for many active substances.

The three most common PEG ointment mixtures are

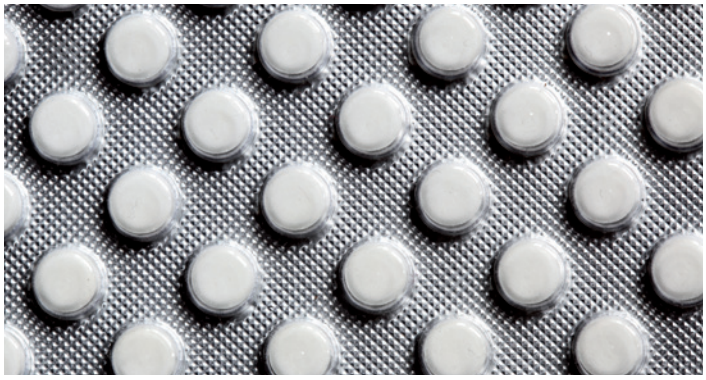
40%	*Polyglykol 3350*
+ 60%	*Polyglykol 400*
50%	*Polyglykol 3000 or Polyglykol 3350 (both types comply with Macrogol 4000 of the Japanese Ph.)*
+ 50%	*Polyglykol 400*
50%	*Polyglykol 1500*
+ 50%	*Polyglykol 300, offered for example as Lanogen® 1500.*

PEG bases can also be combined with other base, e.g. cetyl alcohol, cetyl stearyl alcohol, stearic acid, 1,2 propylene glycol, glycerol, glycerol monostearate and PEG sorbitan monooleate.

- Ammonium bituminosulphonicum
- Benzalkonium chloride
- Bismuth gallate, basic
- Camphor
- Chloramphenicol
- Diphenhydramine
- Hydrocortisone acetate
- Iodochlorohydroxyquinoline
- Nitrofurantoin
- Nitrofurazone
- Phenoxyethyl alcohol
- Polymyxin B
- Prophenpyridamine
- Sulphanilamide
- Sulphathiazole
- Sulphisomidine
- Trypafl avin
- Undecylenic acid and its salts

• Suppositories
Solid polyglycols are preferred bases for suppository masses. Numerous actives can be dissolved in PEG and have then a good bioavailability (53 – 54). The dissipation of the active takes place not only by melting within the body but also by dissolving the body fluids. During the manufacturing they show easy release from the mold, high stability and no refrigeration is required (55) during storage. The desired solidity can be adjusted by choosing the molecular weight and suitable ratios. For example 25% PEG 1000 and 75% PEG 1500 S give very soft masses, whereas 25 % PEG 4000 S and 75% PEG 6000 S will give more solid products (56).

• Tablets
The manufacture of tablets requires numerous excipients with different functions, several of them covered by PEG. Polyglykols may be carriers, solubilizers and absorption improvers for active substances, usually processed in the form of a melt (melt granulation), of course restricted to cases where the active substances withstand heating to about 70°C.



They also act as lubricants and binders (57) during the tablet processing. The relatively low melting point favour a sintering or compression technique. At the same time PEG has a plasticizing effect which facilitates the shaping of the tablet mass in the compression process and may counteract capping. Solid PEG are also frequently used in tablet coatings. The flexibility of sugar-coated tablets is increased by PEG and since polyethylene glycol acts as a anticaking agent, the cores are prevented from sticking together. With usually used film formers in sugar-free coatings PEG acts as softener.

PEG AS ACTIVES

• Ophthalmic demulcents
Polyethylene glycol 300 and 400 are listed as active ingredients in ophthalmic demulcents in amounts of 0.2 to 1% (58). Polyethylene glycols are treated as one class of compounds, also reflected by the use of one single CAS-number for the whole class of polyethylene glycols, it is likely that higher molecular weight PEG show similar properties for this application. Thus polyethylene glycol 6000 is also listed as an ophthalmic demulcent active ingredient (59).

• Laxatives
Since polyethylene glycol is both highly water soluble and not absorbed by humans (60), it is superior to solutions of other difficult to absorb materials with an osmotic mode of action, such as e.g. mannitol. PEG cause fewer side effects such as nausea or gas formation (61). Since up to now there is no review article available dealing with the osmotic activity of PEG, only some examples from the literature are cited here in the appendix (62 – 64).

The USP/NF describes a blend in the monograph “PEG 3350 and Electrolytes for Oral Solution” which contains a detailed description of all potential individual salt components to be used in addition to the polyglycol with a mean molecular weight of 3350 (65). The existence of this monograph explains why the mean molecular weight of 3350 is used so frequently in laxative preparations, although PEG with other molecular weights would have an essentially equivalent effect. The confusing nomenclatures (see page 7) also contribute to the use of the type 3350, since this type is registered in Japan (under the name “4000”) (66).

Remarks on the Manufacture of Laxatives on an Industrial Scale:
During the manufacture of laxative blends, the homogenous distribution of all ingredients is very important. A key criteria is the particle size distribution of all the ingredients, which are normally used in powder form. The more similar the particle size distributions of the different powders, the easier it will be to produce a homogenous blend. On the other hand the powder must not be too fine, since the generation of dust complicates the final filling of the material. Also the moisture content of the hygroscopic polyethylene glycol plays an important role, since “moist” polyglycols lead to sticking and lumping in the filling equipment.

• Organ preservations
A very specific and interesting application is the use of linear high molecular weight polyethylene glycol (20000 daltons) in compositions that exhibit anti-apoptotic activity and can be used therefore to protect, preserve or restore cell, tissue or organ function (67). In this application the polyethylene glycol must be seen as the active ingredient. The full explanation, why PEG shows the anti-apoptotic activity and why longer chains are more efficient than short ones is missing yet. Collins (68) suggests that the higher molecular weight PEG has a direct tolerogenic action on donor antigen in the transplanted organ. He assumes that some sort of attachment of PEG to transplantation antigens must have occurred, without chemical combination, but this is not proved. An earlier explanation from Daniel (69) is that an essential component of the medium is a non toxic solute which does not cross the cell membrane a low temperatures and could therefore counterbalance the osmotic effect of the intracellular proteins.

PEG AS REACTION COMPOUNDS

With the who OH-groups at the ends of the polyethylene glycol molecules, all reactions typical for alcohols are possible, such as esterification, carbonates and carbamates formation. To avoid chain-building reactions Methylether-capped PEG, so called Methylpolyethylene glycols, are available. Those MPEG are only able to react at one end of the molecule. The wide field of PEG conjugation to proteins and other organic molecules, e.g. anticancer drugs, would exceed the scope of this text. Harris (70) as well as later Greenwald (71) took carefully together overviews over the so called PEGnology. A first easy to read an shorter introduction might be for example the summaries of Bonora (72) or Veronese (73). Concerning anti-cancer drugs, polyethylene glycol may work also without linked to other molecules in some cases. In one animal test, polyglycol was found to prevent colon cancer (74), which should also prove true in humans (75, 76).

INCOMPATIBILITY

PEG are unsuitable as based for bacitraicine and penicillin G an W (compete inactivatio (77)); for sulphanilthiocarbamide (evaluation of hydrogen sulphide); acetylsalicylic acid (release of salicylic acid due to transesterification (78)); and also where discoloration is undesirable (79).

Substances capable of forming precipitates with PEG in aqueous solution at particular concentrations are, for instance:

- phenol
- cresols
- resorcinol
- salicylic acid
- ß-naphthol
- tannin
- potassium iodide

Applications of PEG
Cosmetic Industry

PEG CAN BE USED IN THE FOLLOWING COSMETIC PREPARATIONS:

• Creams, lotions, facial lotions
In creams, as in all preparations that tend to dry out, PEG have a moisture- stabilizing effect and also a conditioning effect on the skin treated (80, 81). After application, they leave a pleasant feel on the skin similar to the natural replacement of oils without producing any sensation of stickiness.

In lotions and face lotions PEG acts as a cleansing agent.

In after-shave lotions PEG has the additional function of a non-greasy lubricant and perfume stabilizer. The most suitable type is PEG-8 (Polyglykol 400).

• Deodorant, perfume and insect-repellent sticks
PEG are ideal carriers for sodium stearate and sodium aluminium hydroxylactate. Unlike ethanol or isopropanol, they are not volatile and thus permit reliable control of deodorant, perfume and insect-repellent sticks (82-84). The most suitable grades are the liquid types PEG-4 to PEG-12 (Polyglykol 200 USP to Polyglykol 600). PEG prove to be outstanding solubilizers for hexachlorophene, dimethyl phthalate, azulene, aluminium hydroxychloride (Locron ®), etc.

• Lipsticks
PEG can be used in lipsticks as solubilizers for tetrabromofluorescein and its derivatives. The solubility in PEG-8 (Polyglykol 400) is about 10%. Higher additions of PEG should be avoided because of their good solubility in water, since dyes then tend to “bleed”.

• Toothpastes
Since PEG are non-toxic and not-irritant, they meet the requirements for incorporation in toothpastes (85 - 88), where their main function is to improve the consistency and storage stability. Thus glycerol and sorbitol can be replaced by PEG in toothpaste formulations. With increasing molar mass the slightly bitter taste of PEG, which can be easily counteracted by sweeteners, is less pronounced. PEG-4 to PEG-40 (Polyglykol 200 USP to Polyglykol 2000 S) are recommended. PEG has been proven to be highly successful in the production of transparent toothpastes. By using PEG, the refractive index of the mixture, which usually contains a large amount of silicic acid, can be adjusted to achieve good transparency. (88, 90)

• Soaps, hand-cleanings pastes and detergent sticks
PEG-450 (Polyglykol 20000 S) is particularly suitable for use as a milling aid in toilet soap manufacture. Not only does it facilitate mechanical plasticization, it also improves the sharpness of the moulded bar contours. It stabilizes the perfume and later prevents the soap from frying out and cracking. Initial lathering is accelerated without affecting the foaming characteristics. PEG prevent handcleansing pastes form drying out and leave a pleasant feel on the skin once they have dried. Very soft smooth shaving creams can also be produced with PEG. Soap-free blocks (detergent blocks) can be moulded or pressed when PEG are incorporated. In this application PEG-32 to PEG-450 in the relative molar mass range of 1500 to 20000 are suitable as readily water-soluble carriers (90).

The strength and solubility in water can be adjusted by the addition of a small amount of cetyl alcohol.

• Bath oils and foam baths
In formulations of bath oils, etc. PEG-4 to PEG-40 assist the solubilizing action of the active substances for perfume oils. In addition, consistency and skin compatibility are improved.

• Denture cleaners, bath cubes, effervescent tablets
PEG are excellent binder when bath salts, denture cleaners etc. are pressed into tablets. By choosing the appropriate grade, e.g. PEG-75 to PEG-450 (Polyglykol 3350 P to Polyglykol 20000 P), and by incorporating suitable amounts, the dissolving rate can be controlled as required.

• Hair care products
PEG having proved successfully as an additives for improving the consistency of non-greasy haircare products, which can be washed off after use with clear water, a requirement that is met by PEG, especially PEG-8 (Polyglykol 400).

• Hair styling
The efficacy of aerosol hair spray and styling products is based on synthetic resins such as cellulose derivatives, polyvinyl alcohol and acetate, polyvinyl pyrrolidone, etc. As a plasticizer and antistatic agent, PEG-8 counteracts the tendency of these substances to dry to a brittle film (91).


BODY SHAPER

Safety and Handling

PEG are non-toxic and physiologically safe so no special safety precautions need to be taken when handling them.

For many applications, particularly in pharmaceuticals, cosmetics and foodstuffs packging, the physiological safety of PEG is important. When administered orally and cutaneously they are to be rated as non-toxic. The vapour pressure of PEG is so low that inha lation of relevant amounts is impossible.

Because of their good physiological tolerability PEG were first included in the US pharmacopoeia already in 1950. Since then they have been listed in numerous pharmacopoeias.

The tolerability of PEG in animals improves as the degree of polymerization rises.

PEG have no toxic or irritant effect on the skin. Because of low toxicity it was not possible to establish an exact LD50 resulting from skin penetration.

The CAS-number for all Polyethylene glycols is 25322-68-3.

ECOLOGICAL DATA

The behaviour of PEG in effluent is a matter of crucial importance, e.g. in their industrial use in the textile sector and in metal processing. The rate of biodegradation of PEG decreases with increosing molar mass. PEG up to molar mass 1500 are regarded as readily biodegrad able (Zahn-Wellens test). It must, however, be borne in mind that the activated sludge requires a certain time to adapt. In some cases the degradation of high molar mass PEG was also observed. The microbiological degrada tion of other substances is not inhibited by the presence of PEG. The toxic inhibition limit for bacteria in the fermentation tube test is 5000 mg/l.

Investigations within our own labs have shown that even in concentrations of 10000 mg/kg (1%) polyethylene glycols have no adverse effect on fish (crucian carp). Polyethylene glycols in concentration up to 10000 mg/l exhibit no harmful effect of any kind towards daphnia and protozoa.

The German water hazard class is WGK 1.

WASTE DISPOSAL

Any PEG to be disposed of waste can be taken, in accordance with the local regulations, to a special waste incineration plant. None of PEG, in concentrations up to 10,000 mg/l water, demonstrates an acute harmful effect on fi sh or bacteria.

PEG with molar masses of 200 to 1500 have good biodegradability. It is therefore possible to take them to a biological sewage treatment plant after consulting the operator provided the water and waste regulations permit.

Heating values	**MJ/kg**
PEG 200	*23.7*
PEG 300	*24.0*
PEG 400	*25.6*
PEG 600	*26.0*
PEG 3000	*26.7*

Storage

RECOMMENDED CONDITIONS

PEG are stable for 2 years when stored in the original sealed containers in a cool, dry place.

Furthermore the containers should not be exposed to direct sun light. Ambient temperatures for long term storage are preferably between 10°C and 25°C and between 0°C and 30°C as maximum. Storage at higher temperatures is possible only for a short time and should be kept below the solidifi cation point of the products (for Polyglykol 1000 to 35000).

It is essential to ensure storage in a dry place because liquid PEG are hygroscopic and the solid grades immediately in water. Each time the containers are opened, they should be resealed to make them airtight. Even with sealed laboratory containers it is impossible to prevent atmospheric oxygen and moisture acting on PEG owing to frequent opening (92). We therefore recommend that laboratory samples should also not be stored longer than 2 years.

The most suitable material for storage tanks is stainless steel, pure aluminium, rubber-or polyethylene-lined containers and storage tanks made from glass-fibre-reinforced polyester (GRP). The tank should be ventilated by means of a silica gel dryer. Conventional steel tanks are of limited suitability because after pro longed storage the product may become discoloured owing to traces of iron. Liquid PEG should not be stored in internally lacquered containers because normal coatings are dissolved (epoxy and stoving enamels are resistant, however).

PEG 600 to 1000 solidify when stored in a cool place and must be melted before use. This is best carried out in heating chambers, but the outside temperature should not exceed about 60°C. This must also be ensured when electrical drum heaters are used. Electrical immersion heaters are no suitable for melting owing to the high thermal stress occurring.

The recommended method of storing PEG 800 to 8000 in the molten state is in stainless steel or aluminium containers fi tted with an external, heating coll. The storage temperature should not exceed 70°C, and it is advisable to thoroughly mix the contents of the storage container with a dry nitrogen stream or a circulating pump.

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