CLARIANT

Your universally applicable polymer

POLYGLYKOLS® - POLYETHYLENE GLYCOLS

what is precious to you?

Polyglykols®
OUR PRODUCT RANGE

Clariant Trade Names For Polyethylene Glycols/Macrogols/PEGs

Clariant uses the name Polyglykol® as a trade name for polyethylene glycols also called as macrogols in European pharmaceutical industry. 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.

Polyglykol®
RANGE

POLYGLYKOL® 300
POLYGLYKOL® 400
POLYGLYKOL® 600
POLYGLYKOL® 1000
POLYGLYKOL® 1500 S

POLYGLYKOL® 2000 S
POLYGLYKOL® 3000 S / P
POLYGLYKOL® 3350 S / P / PS
POLYGLYKOL® 4000 S / P / PF / PS
POLYGLYKOL® 6000 S / P / PF

POLYGLYKOL® 8000 S / P / PF
POLYGLYKOL® 10000 S / P
POLYGLYKOL® 12000 S / P
POLYGLYKOL® 20000 S / P
POLYGLYKOL® 35000 S
LANOGEN® 1500

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).

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

Applications of **POLYGLYKOLS®**

PHARMACEUTICAL INDUSTRY

Polyglykols as Excipients

• Liquids

The high solvent power leads to a broad use of low molecular weight PEGs 200 to 400 in liquid preparations such as drops, parenterals or fillings for gelatin capsules. Polyethylene glycol does not soften gelatin. The liquid PEGs 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 PEGs are not soluble in liquid polyethylene glycols. Blending pasty or solid PEGs together with liquid PEGs 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 bases, e.g. cetyl alcohol, cetyl stearyl alcohol, stearic acid, 1,2 propylene glycol, glycerol, glycerol monostearate and PEG sorbitan mono oleate.

PEGs are not compatible, with paraffin wax, petroleum jelly, oleyl oleates and hydrogenated peanut oil. Examples of PEG-compatible pharmaceuticals are:

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

• Suppositories

Solid polyglycols are preferred bases for suppository masses. Numerous actives can be dissolved in PEGs resulting in a good bioavailability[1-2]. 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[3] 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 gives very soft masses, whereas 25% PEG 4000 S and 75% PEG 6000 S will give more solid products[4].

• Tablets

The manufacture of tablets requires numerous excipients with different functions, several of them covered by PEGs. 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[5] 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 PEGs are also frequently used in tablet coatings. The flexibility of sugar-coated tablets is increased by PEGs 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.

Polyglykols as Actives

• Ophthalmic demulcents

Polyethylene glycol 300 and 400 are listed as active ingredients in ophthalmic demulcents in amounts of 0.2 to 1%[6]. 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 PEGs show similar properties for this application. Thus polyethylene glycol 6000 is also listed as an ophthalmic demulcent active ingredient[7] .

• Laxatives

Since polyethylene glycol is both highly water soluble and not absorbed by humans[8], it is superior to solutions of other difficult to absorb materials with an osmotic mode of action, e.g. mannitol. PEGs cause fewer side effects such as nausea or gas formation[9]. Since up to now there is no review article available dealing with the osmotic activity of PEGs, only some examples from the literature are cited here in the appendix[10-12].

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[13]. The existence of this monograph explains why the mean molecular weight of 3350 is used so frequently in laxative preparations, although PEGs with other molecular weights would have an essentially equivalent effect. The confusing

nomenclatures also contribute to the use of the type 3350, since this type is registered in Japan under the name '4000'[14].

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 antiapoptotic activity that can be used therefore to protect, preserve or restore cell, tissue or organ function[15]. In this application the polyethylene glycol must be seen as the active ingredient. The full explanation, why PEG shows the antiapoptotic activity and why longer chains are more efficient than short ones is missing yet. Collins[15] 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[16] is that an essential component of the medium is a non toxic solute which does not cross the cell membrane at low temperatures and could therefore counterbalance the osmotic effect of the intracellular proteins.

Polyglykols as Reaction Compounds of Drug Delivery Systems

With the two 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 methyl-ether-capped PEGs, so called Methylpolyethylene glycols (MPEGs), are available. Those MPEGs 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[17] as well as later Greenwald[18] took carefully together overviews over the so called PEGnology. A first easy to read introduction might be for example the summaries of Bonora[19] or Veronese[20]. Concerning anticancer drugs, polyethylene glycols may also work without link to other molecules in some cases. In one animal test, polyglycol was found to prevent colon cancer[21], which should also prove true in humans[22-23].

INCOMPATIBILITY

PEGs are unsuitable as based for bacitraicine and penicillin G an W (compete inactivation[24]); for sulphanilthiocarbamide (evaluation of hydrogen sulphide); acetylsalicylic acid (release of salicylic acid due to transesterification[25]); and also where discoloration is undesirable[26].

Substances capable of forming precipitates with PEGs in aqueous solution at particular concentrations are for instance phenol, cresols, resorcinol, salicylic acid, ß-naphthol, tannin and potassium iodide.

COSMETIC INDUSTRY

PEGs can be used in the following cosmetic preparations:

- **Creams and Lotions**

In creams, as in all preparations that tend to dry out, PEGs have a moisture-stabilizing effect and also a conditioning effect on the skin treated[27-28]. 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, 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, anti perspirants and insect-repellent sticks**

PEGs are ideal carriers for sodium stearate and sodium aluminium hydroxylactate. Unlike ethanol or isopropanol, they are non volatile and thus permit reliable control of deodorant, perfume and insect-repellent sticks[29-31].

The most suitable grades are the liquid types PEG-4 to PEG-12 (Polyglykol® 200 USP to Polyglykol® 600).

PEGs prove to be outstanding solubilizers for hexachlorophene, dimethyl phthalate, azulene, aluminium hydroxychloride (Locron®), etc.

- **Lipsticks**

PEGs 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 PEGs are non-toxic and not irritant, they meet the requirements for incorporation in toothpastes[32-35], where their main function is to improve the consistency and storage stability.

Thus glycerol and sorbitol can be replaced by PEGs in toothpaste formulations.

With increasing molar mass the slightly bitter taste of PEGs, which can be easily counteracted by sweeteners, is less pronounced. PEG-6 to PEG-40 (300 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[36-37].

- **Soaps, hand-cleansing pastes and detergent sticks**

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 drying out and cracking. Initial lathering is accelerated without affecting the foaming characteristics. PEGs prevent hand-cleansing pastes from drying out and leave a pleasant feel on the skin.

Very soft, smooth shaving creams can also be produced with PEGs. Soap-free blocks (detergent blocks) can be moulded or pressed when PEGs 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[38].

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

- **Hair care products**

PEGs have proved successful as 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 PEGs, 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[39].

- **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**

PEGs 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.

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Technical **DATA**

POLYGLYKOL®	INCI PEG	PRODUCT DESCRIPTION at 20°C	HAZEN COLOUR 25% A.I. in Water (EN 1557)	MOLAR COLOUR MASS g / mol	OH VALUE mg KOH / g (DIN 55240)	SOLIDIFICATION POINT (Ph.Eur.) °C	VISCOSITY at 20°C m pa · s (DIN 51757)
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	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		max. 30	2700 - 3300	34 - 42	52 - 56	50% 75 - 95
3350	75	white waxy	max. 30	3050 - 3685	30 - 37	53 - 57	50% 85 - 105
4000	90	flakes	max. 30	3700 - 4400	25 - 30	53 - 58	50% 114-142
6000	150	powder	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)	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

VISCOSITY at 98.8°C = 270°F mm2 / s	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
5.4 - 6.4	5 - 7.5	—	max. 1	1.125	< 0.1	∞
6.8 - 8.0	5 - 7	—	max. 1	1.126	< 0.01	∞
9.9 - 11.3	5 - 7.5	—	max. 1	1.126	< 0.01	∞
16-19	5 - 7.5	—	max. 1	solidified melt 1.126	< 0.001	75
26 - 32	5 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	62
38 - 49	5 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	58
67 - 93	5 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	56
76 - 110	5 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	56
110 - 158	5 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	55
250 - 390	5 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	54
470 - 900	5 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	54
—	5 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	53
—	5 - 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 - 7	100 - 200	max. 1	solidified melt 1.20	< 0.001	50
—	5 - 7.5	—	max. 1	solidified melt 1.20	< 0.001	> 70

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ICS 2014/01