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Performance Chemicals

Useful performance chemicals by Sanyo Chemical Industries' Group 136

Medical Use Polyethylene Glycol

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Medicines include those for internal use, external use for skin and mucous membranes, and direct injections into blood vessels. Depending on the use and purpose, there are various forms of medicines including powder, tablets, cream and liquid. Compounds other than the active pharmaceutical ingredients in medicines are called excipients (additives). They are intentionally formulated in order to assure stability, safety and uniformity depending on the characteristics of the medicines. They play specific functional roles in the facilitating dissolving or sustained release as required. Our polyethylene glycol (PEG) for medical use, MACROGOL products are one of pharmaceutical excipient.

Polyethylene Glycol

In 1960, our company developed, first in Japan, PEG products. They have been used for various uses. Among many of our PEG products, those used as medical ingredients or excipients are called MACROGOL. PEG is presented generally by the molecular formula as shown in **Fig. 1**. It is a polymer and has a molecular weight distribution. A molecular weight distribution is defined by a number-average molecular weight (Mn). We have PEG products whose Mn ranges between about 200 and 20,000. PEG products are liquid, paste or solid depending on the molecular weight. They features are [1] low toxicity, [2] high lubricity, [3] capability of mixing with other PEG products of different molecular weight and [4] high solubility with water and many types of organic solvent. Taking advantage of these favorable features, they have been used for various fields including medicines, medical excipients, hair care and skincare products, detergents, pigment dispersant, lubricant and binder.

We have six different types of medical use PEG products MACROGOL as shown in **Table 1**. They are listed by the Japanese Pharmacopoeia or Japanese Pharmaceutical Excipients. To ensure the safety and quality of the PEG products, they are manufactured under strict management system which is complying with standard for Good Manufacturing Practice [GMP] applicable for manufacturing and quality control in conformity with the self-imposed standard for pharmaceutical excipient GMP (**Fig. 2**).

Features of MACROGOL

(1) Appearance and Properties

MACROGOL is liquid, paste or solid (flake or powder) depending on the molecular weight (**Fig. 3**). Different grades of MACROGOL each having different properties e.g. vapor pressure (**Table 2**). They can be mixed together to produce medicines having desired hardness and viscosity.

(2) Solubility into solvent

Table 3 shows solubility of MACROGOL. At low temperatures, the higher molecular weight of MACROGOL, it shows the lower solubility into polar solvents. However, at 50°C, a high solubility is obtained regardless of the molecular

$$HOCH_2(CH_2OCH_2)_nCH_2OH$$

Fig. 1 Molecular formula of polyethylene glycol

Fig. 2 GMP-compliant plant

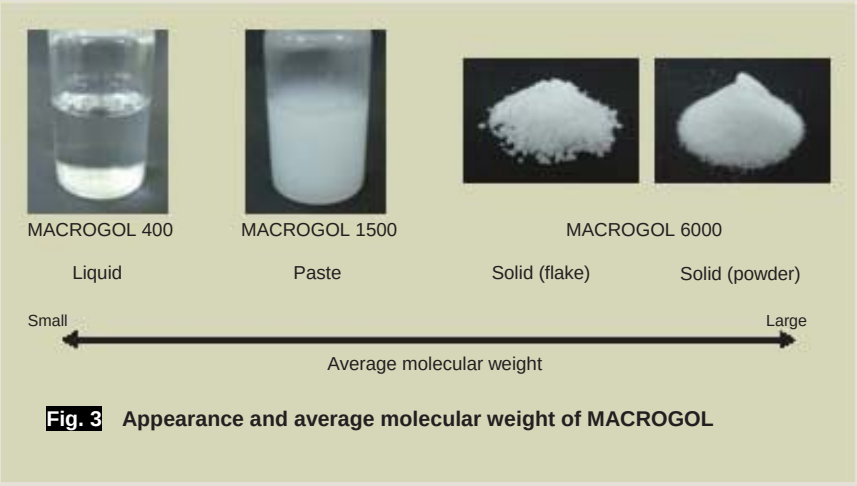

Fig. 3 **Appearance and average molecular weight of MACROGOL**

weight. MACROGOL hardly solves into nonpolar solvents even at high temperatures.

(3) Safety (toxicity)

MACROGOL has lower toxicity (in terms of LD_{50} [Acute Oral Toxicity]) (**Table 4**). MACROGOL of a larger molecular weight shows a lower toxicity.

(4) Change over time

According to the Japanese Pharmacopoeia or the Japanese Pharmaceutical Excipients, MACROGOL's pH value ranges widely between 4.0 and 7.0. This is because polyether compounds such as MACROGOL are subject to oxidative degradation. It is attributable to oxygen radicals, which can lead to decrease in pH value with time.

Figure 4 shows change of pH value with time for MACROGOL 1500. At higher storage temperature, the change proceeds faster. Therefore, to retard the change, they should be stored in a cool, dark place. MACROGOL is hygroscopic. They should therefore be kept away from moisture. MACROGOL of a larger molecular weight shows a lower hygroscopicity.

Applications of MACROGOL

(1) Pharmaceutical Excipients

There are about 70 different kinds of pharmaceutical excipients including diluents and binders.[1)] The pharmaceutical excipients not merely are additives for making pharmaceutical preparation according to the desired effects, but also

Table 1 **Physical-chemical characteristics of MACROGOL listed by the Japanese Pharmaceutical Excipients or the Japanese Pharmacopoeia**

Product name	MACROGOL 200	MACROGOL 400	MACROGOL 1500	MACROGOL 4000	MACROGOL 6000	MACROGOL 20000
Applicable official standard (list)	Japanese Pharmaceutical Excipients	Japanese Pharmacopoeia	Japanese Pharmacopoeia	Japanese Pharmacopoeia	Japanese Pharmacopoeia	Japanese Pharmacopoeia
Form	Colorless, transparent viscous liquid	Colorless, transparent viscous liquid	Paste in white	Powder in white	Powder or flake in white	Powder in white
Freezing point (°C)	-35 or below	6	40	55	58	60
Specific gravity (20/20°C)	1.120	1.120	-	-	-	-
pH*1	5.5	6	5.5	7	7	7
Mn*2	200	400	550*3	3,100	8,600	20,000
Water content (%)	1.0 or below	1.0 or below	1.0 or below	1.0 or below	1.0 or below	1.0 or below
Ignition residue (%)	0.10 or below	0.10 or below	0.10 or below	0.25 or below	0.25 or below	0.25 or below

*1 Measured with a sample of 5 g diluted with 100 mL water *2 Mn average molecular weight calculated based on the hydroxyl value measured according to JIS K1557 *3 Mixture of two different $HOCH_2(CH_2OCH_2)_nCH_2OH$ compounds whose "n" value is 5-6 and 28-36 respectively

The numbers that follow the word MACROGOL represent the average molecular weight. However, for MACROGOL 1500, 4000 and 6000 only, note that they do not represent the average molecular weight.

To use or handle our products, contact our sales office. Before use, read through the latest version of the safety data sheet (SDS). Users shall be responsible for determining suitability and safety of the product that they will use in each individual application.

Table 2 **Properties of MACROGOL**

Product name	MACROGOL 200	MACROGOL 400	MACROGOL 1500	MACROGOL 4000	MACROGOL 6000	MACROGOL 20000
Mn*1	200	400	550*3	3,100	8,600	20,000
Kinematic viscosity (mm^2/s [210°F])	4.1	7.1	16	80	800	14000
Vapor pressure (Pa [100°C])	1.3	1.2×10^{-2}	-	$<2.7\times10^{-10}$	$<2.7\times10^{-10}$	$<2.7\times10^{-10}$
Specific heat ($kJ\cdot kg^{-1}\cdot K^{-1}$)	2.2*2	2.2*2	2.3*3	2.3*3	2.3*3	2.5*3
Fusion heat ($kJ\cdot kg^{-1}$)	-	150	160	180	190	190
Surface tension (mN/m [25°C])	44.5	44.5	-	-	-	-

*1 Mn average molecular weight calculated based on the hydroxyl value measured according to JIS K1557 *2 Average value at temperature between 30 and 60°C *3 Average value at temperature between the freezing point and 100°C

Table 3 Solubility of MACROGOL

Product name	Measuring temperature	Water	Methanol	Ethanol	Diethyl ether
MACROGOL 200	20°C	A	A	A*1	D
	50°C	A	A	A*1	D
MACROGOL 1500	20°C	A	A	D*2	D
	50°C	A	A	A*1	D
MACROGOL 4000	20°C	B	C	D*2	D
	50°C	A	A	A*1	D
MACROGOL 20000	20°C	C	C	D*2	D

*1 95% ethanol *2 99.5% ethanol
Legend A: Dissolve ≥100 g with a solvent of 100 mL B: Dissolve 50 to <100 g with a solvent of 100 mL
C: Dissolve 1 to <50 g with a solvent of 100 mL D: Dissolve <1 g with a solvent of 100 mL

Table 4 Toxicity of MACROGOL

Product name	LD_{50}*1 (g/kg [oral, rat])
MACROGOL 200	28
MACROGOL 400	30
MACROGOL 1500	44
MACROGOL 4000	50
MACROGOL 6000	50

* 1 Registry of Toxic Effects of Chemical substances, Feb. 2003 (NIOSH)

lend [1] easy use (in handling and taking the drug), [2] stable quality (prevention of deterioration), [3] higher usefulness (helping the active ingredient to reach the target area; adjusting the manifestation of the medicinal effect) and [4] higher safety (e.g. reduction of side effects) to the drug.

(2) Examples of applications

Features such as lower toxicity , higher versatility and various forms of MACROGOL, make it useful as medical additive for various applications (**Table 5**).

MACROGOL in liquid can be used as a moisturizer, stabilizer for liquids for external use, and solubilizing agent for lipophilic drugs. It helps the drug permeating into the affected part effectively.

MACROGOL in paste, Vaseline-like pasty material, can be used for making an ointment of desired viscosity so that it can be spread uniformly over the affected part.

MACROGOL in flake or powder, paraffin-like solid material, has a moldability, so that it can be used for preparing suppositories. It can be used also as a tablet coating agent to increase the tablet's surface smoothness. It can harden the surface of tablets to improve their friability and flowability. Among many of MACROGOL application areas, here describes its use as a colon cleansing agent and precipitant for blood plasma fractionation as well that has not been much introduced to date.

(3) Colon cleansing agent

Before inspection or surgery for colorectal cancer or other colonic diseases, bowel preparation for colonic cleansing is necessary. Inadequate bowel preparation can lead to poor colonic visualization, missed lesions, or other risks of anastomotic failure or infectious diseases. Intestinal lavage is therefore essential. Colon cleansing agents are required to be [1] capable of facilitating quick, easy and efficient cleaning, [2] non-digestible and non-absorbable, and capable of passing out through the bowel easily, and [3] minimal patient's discomfort (easy to take). PEG formulation as colon cleansing agent is osmotically balanced for the kinds and concentration of the electrolytes while acting as an agent for retaining water in the bowel. The water and electrolytes concentrations in body fluids can be kept well balanced. Feces can be softened and discharged easily. PEG is non-digestible and non-absorbable so that it is directly discharged out of the body.[2] PEG based agents do not induce substantial shifts in fluid and electrolyte level or poor patient compliance, so that they have now been used most widely among other types of colon cleansing agents.

(4) Precipitant for plasma fractionation

An adult's blood volume is about 80 mL per 1 kg of body weight. Blood consists of cellular components of erythrocyte,

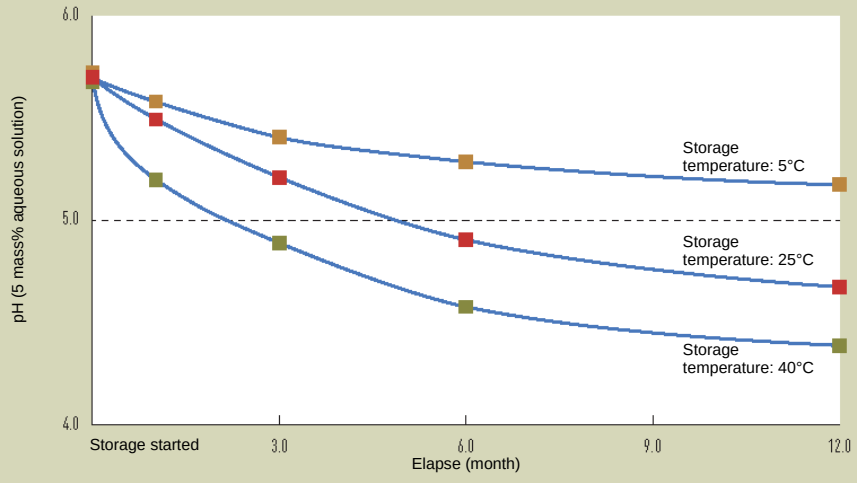

Fig. 4 Change over time (MACROGOL 1500)

Since pH value measurements shown here may not be the case depending on the storage conditions of the sample, they should be used for reference only.

Table 5 Application of MACROGOL

Use	Properties of medical drugs and additives
Base material for ointment	Adjusts application concentration and viscosity of the ointment, keeps it applied uniformly over the affected part, facilitates its sustainable permeation into the part, and absorbs body fluids oozing out of the affected part.
Base material for suppository	Mixing different MACROGOL products together will produce base materials having a desired melting point and dissolution rate. MACROGOL of a higher average molecular weight shows a higher storage stability.
Tablet binder	Available as a smoothing agent, coating agent or binder for manufacturing tablets. Compared to sugar coating agents, it can shorten the coating time, and impart better aesthetics and harder surface to tablets.

It can be used also as a solvent, stabilizer, plasticizer, surfactant, lubricant, cohesive agent, luster, binder, smoothing agent, moisturizer, emulsifier, pressure sensitive adhesive, adhesion enhancer, diluent, thickener, disintegrant, solubilizing agent, wetting agent, sugar coating agent, softener, wetting modifier, solubilizer, suspending agent, dispersant, desiccant and disintegrating agent, etc.

leucocyte and platelet, and liquid part called plasma. Cellular components account for about 45% of the entire constituents of blood while the remainder is plasma.

Biological medicals produced from blood e.g. donated blood are generally called blood products. They include blood component products (erythrocyte, leucocyte and platelet) intended for e.g. blood transfusion, and plasma derivatives. They are produced by refining proteins such as antibodies and blood clotting components.

MACROGOL can be used as a precipitant when separating and refining (fractionating) proteins from blood.

Plasma consists of about 7 to 8% of various types of proteins, about 90 to 91% of water, and the remainder of sugar and lipid. Plasma derivatives are obtained by physicochemically separating important proteins such as albumin

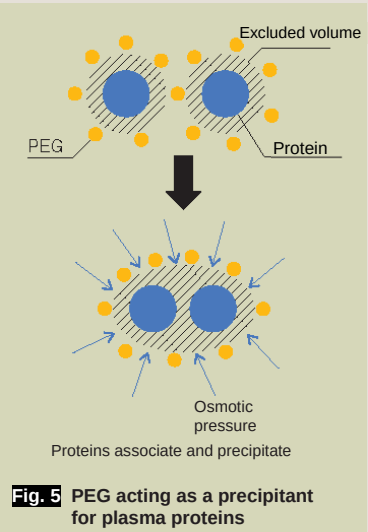

Fig. 5 PEG acting as a precipitant for plasma proteins

into individual components. Protein is a condensation polymer of 20 kinds of amino acids. It has a different molecular characteristic depending on the kinds and configuration of the composed amino acids. Moreover, plasma proteins show complicated molecular characteristics because they exist in the form of couples with sugar (glucose) chains and/or lipids (fats), Therefore, for fractionation (to separate and refine) plasma proteins, it is necessary to adjust processing parameters depending on many factors such as molecular characteristics, molecular weight and forms.

Fractionation processes include [1] PEG fractionation that uses PEG as a precipitant for proteins, [2] ethanol fractionation that adjusts five parameters of pH value, ionic strength, ethanol concentration, protein concentration and temperature to change the solubility of proteins, and [3] chromatography fractionation.[3)]

PEG precipitates proteins by reducing the dielectric constant and using the excluded volume effect. **Figure 5** shows its working mechanism. Osmotic pressures existing between the near-protein region where PEG cannot enter and the region in which PEG already exists move proteins so that they come closer to each other to achieve thermal stabilization.[4)] Another advantage of PEG is that it can precipitate while minimizing the modification of protein molecules. MACROGOL has been widely and effectively used for manufacturing medicines.

Prospects

At present, Japan has its own official medicines lists of the Japanese Pharmacopoeia and the Japanese Pharmaceutical Excipients. However, responding to globalization of pharmaceutical manufacturing businesses, Japan, America and EU countries are cooperating each other to develop a unified, international standard and list of medicines. Our company will enhance the PEG product lineups ensuring that they comply with the international quality standard so that we can globally contribute to the development of medicine.

Moreover, along the recent advancement in medicines, we shall continue developing new, need-oriented and high quality pharmaceutical excipients.

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