Nonionic Surfactants

A surfactant is a compound that can reduce the interfacial tension between 2 immiscible phases. This is because the molecule contains 2 localised regions, one hydrophilic in nature and the other hydrophobic. Nonionic surfactants differ from anionic surfactants (p.2138) by the absence of charge on, or ionisation of, the molecule; they are generally less irritant than anionic or cationic surfactants.

Hydrophilic groups include the oxyethylene group ($–O.CH_2.CH_2–$) and the hydroxyl group (–OH). By varying the number of these groups in a hydrophobic molecule, such as a fatty acid, substances are obtained that range from strongly hydrophobic and water-insoluble compounds, such as glyceryl monostearate, to strongly hydrophilic and water-soluble compounds, such as the macrogols. These 2 extreme types are not satisfactory as emulsifying agents, though they are useful stabilisers in the presence of efficient emulsifying agents. Between these extremes are the nonionic emulsifying agents in which the proportions of hydrophilic and hydrophobic groups are more evenly balanced; these include some of the macrogol esters and ethers, and sorbitan derivatives. Nonionic surfactants may be classified according to their *hydrophilic-lipophilic balance* (HLB). This is an arbitrary scale of values denoting the relative affinity of the surfactant for oil and water. Lipophilic surfactants have low HLB values (less than 10) and are generally used as antifoaming agents, water-in-oil emulsifying agents, and as wetting agents; hydrophilic surfactants have higher HLB values (greater than 10) and are generally used as oil-in-water emulsifying agents and solubilising agents.

Nonionic surfactants also have applications in the food, cosmetic, paint, pesticide, and textile industries as well as being used as oil slick dispersants. Some macrogol ethers such as nonoxinol 9 are used as spermicides.

By virtue of the processes used in their manufacture, nonionic surfactants are usually mixtures of related compounds; the properties of a particular material may vary from one manufacturer to another and there may be variation in batches from an individual source. Since nonionic surfactants do not ionise to any great extent in solution, they are generally compatible with both anionic and cationic substances, but they reduce the antimicrobial action of many preservatives.

The range of nonionic surfactants used in pharmaceutical practice is large and their classification can be varied and complex. The principal groups of nonionic surfactants are outlined below.

Glycol and glycerol esters are a group of nonionic surfactants consisting of fatty acid esters of glycols and glycerol. Hydrophobic properties predominate and these compounds are poor emulsifying agents if used alone, though they are useful stabilisers for both oil-in-water and water-in-oil emulsions. If a small amount of soap, sulfated fatty alcohol, or other surfactant is added to the esters, a 'self-emulsifying' product is formed, which is capable of producing satisfactory oil-in-water emulsions. **Acetoglycerides** are mixed glyceryl esters in which the glycerol is esterified partly with a fatty acid and partly with acetic acid.

Macrogol esters are polyoxyethylene esters of fatty acids, mainly stearates. The hydrophilic properties of the oxyethylene group are weaker than those of the hydroxyl group but by introducing a sufficient number into a fatty acid molecule, substances are produced in which the hydrophilic and hydrophobic properties are sufficiently well balanced for the esters to act as efficient oil-in-water emulsifying agents. They may also be used as wetting and solubilising agents. Since the ester linkage is prone to hydrolysis, these compounds are less resistant to acids and alkalis than the macrogol ethers.

Macrogol ethers are condensation products prepared by reaction between fatty alcohols or alkylphenols and ethylene oxide. The ether linkage confers good stability to acids and alkalis. Macrogol ethers are widely used in the preparation of oil-in-water emulsions and as wetting and solubilising agents.

Sorbitan derivatives are derivatives of the cyclic mono- or di-anhydrides of sorbitol. They consist of *sorbitan esters*, which are prepared by esterification of one or more of the hydroxyl groups in the anhydrides with a fatty acid such as stearic, palmitic, oleic, or lauric acid, and *polysorbates*, which are polyoxyethylene derivatives of the sorbitan esters. Sorbitan esters are oil-soluble, water-dispersible, nonionic surfactants and are effective water-in-oil emulsifiers. Polysorbates are more hydrophilic, water-soluble compounds and are used as oil-in-water emulsifying agents. By varying the number of oxyethylene groups in the molecule, and the type of fatty acid in the sorbitan ester, surfactants with a wide range of properties may be obtained.

Poloxamers are copolymers of polyoxyethylene and polyoxypropylene. They are used as oil-in-water emulsifiers and as solubilising and wetting agents in pharmaceutical preparations intended for internal use.

Other nonionic compounds with surface activity such as the higher fatty alcohols are covered in the chapter on Paraffins and Similar Bases (p.2028).

Diacetylated Monoglycerides

Monoglicéridos diacetilados.

Моноглицериды Диацетилированные

Pharmacopoeias. In *USNF*.

USNF 26 (Diacetylated Monoglycerides). Consists of glycerol esterified with edible fat-forming fatty acids and acetic acid. A clear liquid. Very soluble in alcohol 80%, in vegetable oils, and in mineral oils; sparingly soluble in alcohol 70%. Store in airtight containers. Protect from light.

Profile

Diacetylated monoglycerides have been used as plasticisers, pharmaceutical excipients, and food additives.

Diethylene Glycol Monopalmitostearate

Diethylene Glycol Monostearate; Diéthylène Glycol (Stéarate de); Diéthylènеglycol, palmitostéarate de; Diethylenglycoli Monopalmitostearas; Diethylenglycoli palmitostearas; Diethylenglykol monopalmitostearát; Diethylenglykol palmito stearát; Diethyleni Glycoli Stearas; Dietilenglicol, monopalmitoestearato de; Dietilenglikolio palmitostearatas; Dietiléнglikol-monopalmitát és monosztearát; Dietyleeniglykolipalmitostearaatti; Dietylenglykolpalmitostearat; Diglycol Stearate.

Диэтиленгликоля Монопальмитостеарат

CAS — 106-11-6 (diethylene glycol monostearate); 36381-62-1 (diethylene glycol monopalmitate).

Pharmacopoeias. In *Eur.* (see p.vii). *USNF* includes Diethylene Glycol Stearates.

Ph. Eur. 6.2 (Diethylene Glycol Palmitostearate). A mixture of diethylene glycol mono- and di-esters of stearic and palmitic acids produced by esterification of diethylene glycol and stearic acid of vegetable or animal origin. It contains 45.0 to 60.0% of monoesters and 35.0 to 55.0% of diesters, and a maximum of 2.5% of free diethylene glycol. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 43° to 50°. Protect from light.

USNF 26 (Diethylene Glycol Stearates). A mixture of diethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 45.0% of monoesters produced from the condensation of ethylene glycol and stearic acid of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 43° to 50°. Store in airtight containers.

Profile

Diethylene glycol monopalmitostearate has similar properties and uses to glyceryl monostearate or self-emulsifying glyceryl monostearate (p.1915). Diethylene glycol monolaurate and mono-oleate have also been used.

Ethylene Glycol Monopalmitostearate

Ethylene Glycol Monostearate; Ethylene Glycol Stearate; Éthylène Glycol (Stéarate d'); Éthylèneglycol, monopalmitostéarate d'; Ethyleneglycoli Monopalmitostearas; Ethylenglycoli monopalmitostearas; Ethylenglycoli Monostearas; Ethylenglykol-monopalmitostearát; Ethyleni Glycoli Stearas; Etilenglicol, monopalmitoestearato de; Etilenglikolio monopalmitostearatas; Etiléнglikol-monopalmitát és monosztearát; Etyleeniglykolimonopalmitostearaatti; Etylenglykolmonopalmitostearat.

Этиленгликоля Монопальмитостеарат

CAS — 111-60-4 (ethylene glycol monostearate); 4219-49-2 (ethylene glycol monopalmitate).

Pharmacopoeias. In *Eur.* (see p.vii). *USNF* includes Ethylene Glycol Stearates.

Ph. Eur. 6.2 (Ethylene Glycol Monopalmitostearate). A mixture of ethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 50% of monoesters produced from the condensation of ethylene glycol and stearic acid and not more than 5% of free ethylene glycol. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 54° to 60°. Protect from light.

USNF 26 (Ethylene Glycol Stearates). A mixture of ethylene glycol mono- and di-esters of stearic and palmitic acids. It contains not less than 50% of monoesters produced from the condensation of ethylene glycol and stearic acid of vegetable or animal origin. A white or almost white, waxy solid. Practically insoluble in water; soluble in hot alcohol and in acetone. M.p. 54° to 60°. Store in airtight containers.

Profile

Ethylene glycol monopalmitostearate has similar properties and uses to glyceryl monostearate or self-emulsifying glyceryl monostearate (p.1915). Ethylene glycol monolaurate and mono-oleate have also been used.

Glyceryl Behenate

Glicerol, behenato de.

Глицерил Бегенат

Pharmacopoeias. In *USNF*. *Eur.* (see p.vii) includes Glycerol Dibehenate.

Ph. Eur. 6.2 (Glycerol Dibehenate; Glyceroli Dibehenas). A mixture of diacylglycerols, mainly dibehenoylglycerol, together with variable quantities of mono- and triacylglycerols. It contains 15 to 23% of monoacylglycerols, 40 to 60% of diacylglycerols, and 21 to 35% of triacylglycerols, obtained by esterification of glycerol and behenic acid. A hard, waxy mass or powder or white or almost white, unctuous flakes. Practically insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane. M.p. 65° to 77°.

USNF 26 (Glyceryl Behenate). A mixture of glycerides of fatty acids, mainly behenic acid. A fine powder with a faint odour. M.p. about 70°. Practically insoluble in water and in alcohol; soluble in chloroform. Store in airtight containers at a temperature not exceeding 35°.

Profile

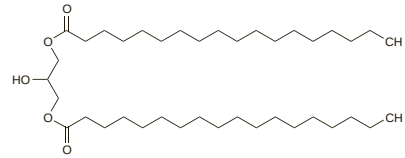
Glyceryl behenate is used as a lubricant and binder in tablet-making.

Glyceryl Distearate

Glicerin-disztearát; Glicerol, diestearato de; Glicerolio distearatas; Glycerol Distearate; Glycérol, distéarate de; Glyceroldistearat; Glycerol-distearát; Glyceroli distearas; Glyserolidistearaatti.

Глицерилдистеарат

CAS — 1323-83-7.



Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF*.

Ph. Eur. 6.2 (Glycerol Distearate). A mixture of diacylglycerols, mainly distearoylglycerol, together with variable quantities of mono- and triacylglycerols. It contains 8 to 22% of monoacylglycerols, 40 to 60% of diacylglycerols, and 25 to 35% of triacylglycerols, obtained by partial glycerolysis of vegetable oils containing triacylglycerols of palmitic or stearic acid or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

A hard, waxy mass or powder, or white or almost white, unctuous flakes. Practically insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane. M.p. 50° to 60° (types I and II) or 50° to 70° (type III).

USNF 26 (Glyceryl Distearate). A mixture of diglycerides, mainly glyceryl distearate, together with variable quantities of monoglycerides and triglycerides. It contains 8 to 22% of monoglycerides, 40 to 60% of diglycerides, and 25 to 35% of triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of palmitic or stearic acid or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

Hard, waxy mass or powder, or white or almost white flakes. Insoluble in water; partly soluble in hot alcohol; soluble in dichloromethane and in tetrahydrofuran. Store in airtight containers.

Profile

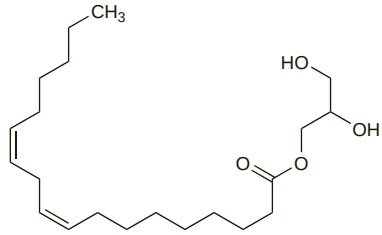
Glyceryl distearate is used as an emulsifying and/or solubilising agent.

Glyceryl Monolinoleate

Glicerin-monolinoleát; Glicerol, monolinoleato de; Glicerolio monolinoleatas; Glycerol Monolinoleate; Glycérol, monolinoléate de; Glyceroli monolinoleas; Glycerol-monolinolát; Glycerolmonolinoleat; Glyserolimonolinoleaatti; Monolinolein.

Глицерилмонолинолеат

CAS — 26545-74-4.



Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Glycerol Monolinoleate). A mixture of monoacylglycerols, mainly mono-oleoylglycerol and monolinoleoylglycerol, together with variable quantities of di- and triacylglycerols. It contains 32 to 52% of monoacylglycerols, 40 to 55% of diacylglycerols, and 5 to 20% of triacylglycerols, obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of linoleic acid. A suitable antoxidant may be added.

Amber, oily liquids which may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane. Store in airtight containers. Protect from light.

USNF 26 (Glyceryl Monolinoleate). A mixture of monoglycerides, mainly glyceryl mono-oleate and glyceryl monolinoleate, together with variable quantities of diglycerides and triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of linoleic acid. It contains 32 to 52% of monoglycerides, 40 to 55% of diglycerides, and 5 to 20% of triglycerides. A suitable antoxidant may be added.

Amber, oily liquids that may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane; soluble in tetrahydrofuran. Store in airtight containers.

Profile

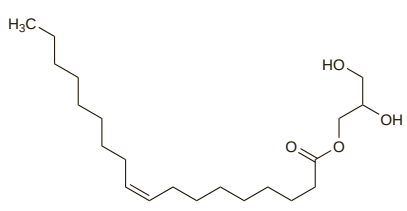
Glyceryl monolinoleate is used as an emulsifying and/or solubilising agent.

Glyceryl Mono-oleate

Glicerol, monooleato de; Glycérol, mono-oléate de; Glyceroli mono-oleas; Monolein.

Глицерилмоноолеат

CAS — 25496-72-4.



Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Glycerol Mono-oleates). Mixtures of monoacylglycerols, mainly mono-oleoylglycerol, together with variable quantities of di- and triacylglycerols. They are defined by the nominal content of monoacylglycerols and obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of oleic acid, or by esterification of glycerol by oleic acid. A suitable antoxidant may be added.

Amber, oily liquids which may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane. Store in airtight containers. Protect from light.

USNF 26 (Glyceryl Monooleate). A mixture of monoglycerides, mainly glyceryl mono-oleate, together with variable quantities of di- and triglycerides. It is obtained by partial glycerolysis of vegetable oil that consists mainly of triglycerides of oleic acid, or by esterification of glycerol with oleic acid of vegetable or animal origin. It is defined by the nominal content of monoglycerides. A suitable antoxidant may be added.

Amber, oily liquids that may be partially solidified at room temperature. Practically insoluble in water; freely soluble in dichloromethane; soluble in tetrahydrofuran. Store in airtight containers.

Profile

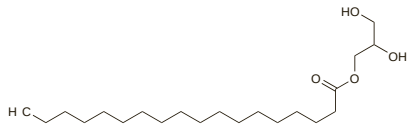
Glyceryl mono-oleate has similar properties to glyceryl monostearate or self-emulsifying glyceryl monostearate (below).

Glyceryl Monostearate

Gliceril, monoestearato de; Glicerin-monosztearát; Glicerolio monostearatas; Glicerolu monostearynian; Glycérol, monostéarate de; Glyceroli monostearas; Glycerolmonostearat; Glycerolmonostearát; Glyserolimonostearaatti; GMS; Monostearin.

Глицерилмоностеарат

CAS — 31566-31-1 (glyceryl monostearate); 26657-96-5 (glyceryl monopalmitate).



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 6.2 (Glycerol Monostearate 40-55). A mixture of monoacylglycerols, mainly monostearoylglycerol, together with variable quantities of di- and triacylglycerols. It contains 40 to 55% of monoacylglycerols, 30 to 45% of diacylglycerols, and 5 to 15% of triacylglycerols, obtained by partial glycerolysis of vegetable oils mainly containing triacylglycerols of palmitic or stearic acid, or by esterification of glycerol with stearic acid. The fatty acids may be of vegetable or animal origin.

A white or almost white, hard, waxy mass or unctuous powder or flakes. Practically insoluble in water; soluble in alcohol at 60°. M.p. 54° to 66°.

USNF 26 (Glyceryl Monostearate). It contains not less than 90% of monoglycerides of saturated fatty acids, chiefly glyceryl monostearate ($C_{21}H_{42}O_4$ = 358.6) and glyceryl monopalmitate ($C_{19}H_{38}O_4$ = 330.5). It may contain a suitable antoxidant.

A white to yellowish wax-like solid, beads, flakes, or powder with a slight, agreeable, fatty odour. M.p. not below 55°. Insoluble in water but may be dispersed in hot water with the aid of a small amount of soap or other suitable surfactant; soluble 1 in 10 of chloroform, 1 in 100 of ether and of methyl alcohol, 1 in 33 of isopropyl alcohol; dissolves in hot organic solvents such as alcohol, acetone, mineral or fixed oils, and benzene. Store in airtight containers. Protect from light.

Self-emulsifying Glyceryl Monostearate

Glicerol autoemulsionable, monoestearato de; Monostearato de glicerilo autoemulsionable; Monostearin Emulsificans; Self-emulsifying Mono- and Diglycerides of Food Fatty Acids; Self-emulsifying Monostearin.

Глицерилмоностеарат Самоэмульгирующийся

Pharmacopoeias. In *Br.*

BP 2008 (Self-emulsifying Glyceryl Monostearate). A mixture consisting principally of mono-, di-, and triglycerides of stearic and palmitic acids, and of minor proportions of other fatty acids; it may also contain free fatty acids, free glycerol, and soap. It contains not less than 30% of monoglycerides, not more than 7% of free glycerol, and not more than 6% of soap, calculated as sodium oleate, all calculated with reference to the anhydrous substance.

A white to cream-coloured, hard, waxy solid with a faint fatty odour. Dispersible in hot water; soluble in hot dehydrated alcohol and in hot liquid paraffin; soluble in hot vegetable oils, but may give turbid solutions at concentrations below 20%.

Incompatibility. Because of the presence of soap, self-emulsifying glyceryl monostearate is incompatible with acids and high concentrations of ionisable salts, hard water, calcium compounds, zinc oxide, and oxides of heavy metals.

Profile

Glyceryl monostearate is a poor water-in-oil emulsifying agent but it is a useful stabiliser of water-in-oil and oil-in-water emulsions in preparations for internal and external use. It has emollient properties. Glyceryl monostearate is also used in the food and cosmetic industries.

It is usual to add a small amount of soap, sulfated fatty alcohol, or other surfactant, to glyceryl monostearate, which has the effect of making the product self-emulsifying and capable of producing satisfactory oil-in-water emulsions. Self-emulsifying glyceryl monostearate is used as an emulsifying agent for oils, fats, solvents, and waxes in the preparation of bases of the non-emulsified, emulsified, and vanishing-cream types. It is not intended for inclusion in preparations for internal use.

Aqueous preparations containing self-emulsifying glyceryl monostearate should contain a preservative to prevent fungal or bacterial growth.

Macrogol Cetostearyl Ethers

Ceteareth Compounds; Macrogol, éteres cetoestearílicos de; Macrogol, ether cétostéarylique de; Macrogoli aether cetostearylicus; Makrogol-cetil-sztearil-éter; Makrogolcetostearyleter; Makrogolio cetostearilo eteris; Makrogolisetostearyylieeteri.

Полиэтиленгликоля и Цетостеарилового Спирта Эфиры

CAS — 68439-49-6.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Macrogol Cetostearyl Ether). A mixture of ethers of mixed macrogols with linear fatty alcohols, mainly cetostearyl alcohol. It may contain some free macrogols and it contains various amounts of free cetostearyl alcohol. The amount of ethylene oxide reacted with cetostearyl alcohol is from 2 to 33 units per molecule (nominal value). White or yellowish-white waxy, unctuous mass, pellets, microbeads, or flakes. Macrogol cetostearyl ether with low numbers of ethylene oxide units per molecule is practically insoluble in water; soluble in alcohol and in dichloromethane. Macrogol cetostearyl ether with higher numbers of ethylene oxide units per molecule is dispersible or soluble in water; soluble in alcohol and in dichloromethane. Macrogol cetostearyl ether solidifies at 32° to 52°. Store in airtight containers. The labelling states the amount of ethylene oxide reacted with cetostearyl alcohol (nominal value).

Cetomacrogol 1000 *(BAN, rINN)*

Cétomacrogol 1000; Cetomacrogolum 1000; Éter monocetílico de polietilenglicol 1000; Polyethylene Glycol 1000 Monocetyl Ether; Polyoxyethylene Glycol 1000 Monocetyl Ether.

Кетомакрогол 1000; Цетомакрогол 1000

CAS — 9004-95-9 (macrogol cetyl ethers); 68439-49-6 (macrogol cetostearyl ethers).

Description. Cetomacrogol 1000 is a macrogol ether containing 20 to 24 oxyethylene groups in the polyoxyethylene chain. It may be prepared from either cetyl alcohol or from cetostearyl alcohol. It is represented by the formula $CH_3.[CH_2]_m.[O.CH_2.CH_2]_n.OH$, where *m* may be 15 or 17 and *n* may be 20 to 24. The more specific term macrogol cetostearyl ether (22), representing such an ether in which *n* = 22, has replaced cetomacrogol 1000 in BP formulations.

Macrogol cetyl ethers are also sometimes termed ceteth compounds.

Pharmacopoeias. In *Int.*

Incompatibility. Cetomacrogol has been reported to be incompatible with phenols and to reduce the antibacterial activity of quaternary ammonium compounds. Cetomacrogol may separate from solutions in the presence of a high concentration of electrolytes.

Polyoxyl 20 Cetostearyl Ether

Polioxil 20, éter cetoestearílico de.

Полиоксиэтилендиола 20 и Цетостеариловой Кислоты Эфир

CAS — 68439-49-6.

Pharmacopoeias. In *USNF.*

USNF 26 (Polyoxyl 20 Cetostearyl Ether). A mixture of the monocetostearyl (mixed hexadecyl and octadecyl) ethers of mixed macrogols, the average polymer length being equivalent to 17.2 to 25.0 oxyethylene units. A cream-coloured waxy unctuous mass, melting, when heated, to a clear brownish-yellow liquid. Soluble in water, in alcohol, and in acetone; insoluble in petroleum spirit. A 10% solution in water has a pH of 4.5 to 7.5. Store at a temperature of 8° to 15° in airtight containers.

Profile

Macrogol cetostearyl ethers are used as surfactants and emulsifiers. Macrogol cetostearyl ether (22) is used with cetostearyl alcohol (for example, in the form of Cetomacrogol Emulsifying Wax BP 2008) as an emulsifying agent for making oil-in-water emulsions that are unaffected by moderate concentrations of electrolytes and that are stable over a wide pH range. It is also used to disperse volatile oils in water to form transparent sols.