

SEÑORA DIRECTORA
DIRECCIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

Asunto:	Solicitud No.:	13145004
	Oficio No.:	3681
	Referencia:	Respuesta examen de patentabilidad

MAURICIO JARAMILLO CAMPUZANO, identificado como aparece al pie de mi firma, en calidad de apoderado de la sociedad solicitante **LABORATORIOS SENOSIAIN S.A DE C.V**, doy respuesta al **Oficio No. 3681**, de conformidad con el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina.

1. MODIFICACIONES A UNA SOLICITUD EN TRÁMITE

El solicitante aporta un nuevo capítulo reivindicatorio, conformado por 6 reivindicaciones, en el que se han realizado las siguientes modificaciones:

- Se modificó la reivindicación 1, para incluir la celulosa microcristalina, lactosa monohidrato y estearato de magnesio, así como otros diluentes aglutinantes, diluentes y deslizantes mencionados en la descripción de la presente solicitud.
- Se modificó la reivindicación 6 para incorporar las etapas 6 a 8 del método, las cuales actualmente se encuentran identificadas mediante los incisos f), g) y h).

Asimismo, y siguiendo la sugerencia del Examinador, se modificó el título de la solicitud como sigue:

“COMPRIMIDO FARMACÉUTICO DE LIBERACIÓN CONTROLADA PARA ADMINISTRACIÓN ORAL QUE COMPRENDE CIPROFLOXACINA CLORHIDRATO EN DOS TIPOS DE GRANULOS; DE LIBERACION INMEDIATA Y DE LIBERACIÓN RETARDADA”

Estas modificaciones se ajustan al artículo 34 de la Decisión 486 de 2000, toda vez que no amplían el alcance de protección de la solicitud presentada originalmente y además encuentran soporte en la descripción de la solicitud.

2. TÍTULO

Como se indicó anteriormente, el Solicitante acepta modificar el título de la invención conforme a lo sugerido por el Examinador, por lo que se entiende por superada la objeción.

3. ARGUMENTOS A FAVOR DE LA CLARIDAD DE LA SOLICITUD

3.1. El Examinador señala que los componentes: celulosa microcristalina, lactosa monohidrato y estearato de magnesio son características esenciales del comprimido de liberación controlada definido en la reivindicación 1, de tal manera que se sugiere incluir estas características esenciales en la reivindicación 1.

3.2. En respuesta, los tres componentes arriba señalados tienen la función de diluyente aglutinante (celulosa microcristalina), diluyente (lactosa monohidrato) y deslizante (estearato de magnesio). Estos componentes son aditivos universalmente reconocidos para formar comprimidos, pero no tienen efecto alguno sobre la liberación del principio activo, toda vez que los excipientes involucrados en el control de la liberación del principio activo son HPMC de bajo peso molecular y etilcelulosa, los cuales ya se encuentran reclamados en la reivindicación 1.

3.3. El solicitante respetuosamente considera que la inclusión de los tres excipientes celulosa microcristalina, lactosa monohidrato y estearato de magnesio en la reivindicación 1 como la única posibilidad de diluyente aglutinante, diluyente y deslizante, resultaría en una excesiva restricción, toda vez que existen otros diluentes, diluentes aglutinantes y deslizantes reconocidos en la técnica, que fácilmente podrían generar una composición farmacéutica diferente sin caer en el alcance de protección de la materia amparada por la reivindicación 1.

3.4. Considerando lo anterior, y también siguiendo las sugerencias del Examinador, el solicitante ha incorporado los tres componentes: celulosa microcristalina, lactosa monohidrato y estearato de magnesio en la reivindicación 1, así como otros diluentes aglutinantes, diluentes y

deslizantes mencionados en la descripción de la presente solicitud. Los diluentes enlistados en la actual reivindicación 1 son intercambiables. Lo mismo puede decirse de los deslizantes y los diluentes aglutinantes. Esto se puede comprobar en el *Handbook of Pharmaceutical Excipients*, 5ª edición, de la editorial Pharmaceutical Press (<https://gmpua.com/RD/RD/HandbookPharmaceutical%20Excipients.pdf>). Adjuntamos copia de las páginas relacionadas con estos aditivos para pronta referencia.

3.5. Por ejemplo, en el caso de los diluentes aglutinantes, la actual reivindicación 1 reclama celulosa microcristalina, polivinilpirrolidona e hidroxipropilcelulosa. En las páginas 132, 336 y 611 del *Handbook of Pharmaceutical Excipients* se muestran las propiedades de estos tres ingredientes. Se puede comprobar que pertenecen a la misma categoría funcional.

3.6. En el caso de los deslizantes, la actual reivindicación 1 reclama estearato de magnesio, ácido esteárico, estearato de glicerilo, polietilenglicol, lauril sulfato de sodio, estearil fumarato de sodio y talco. A partir de la información contenida en las páginas 430, 308, 545, 687, 705, 737 y 767 del *Handbook of Pharmaceutical Excipients*, se puede comprobar que pertenecen a la misma categoría funcional.

3.7. De igual manera, en el caso de los diluentes, la actual reivindicación 1 reclama lactosa monohidrato, celulosa microcristalina, dextrosa, sacarosa y manitol. A partir de la información contenida en las páginas 132, 231, 389, 449 y 744 del *Handbook of Pharmaceutical Excipients*, se puede comprobar que pertenecen a la misma categoría funcional.

3.8. La información proporcionada por el *Handbook of Pharmaceutical Excipients* además permite confirmar que ninguno de los diluentes, deslizantes y diluentes aglutinantes actualmente reclamados, se utiliza como modificador de la liberación de principios activos.

3.9. Por todo lo anteriormente mencionado, se entiende por superada la objeción de claridad a la reivindicación 1.

3.10. Finalmente, el Examinador considera que las etapas 6 a 8 del método son esenciales para la invención definida en la reivindicación 6. En respuesta, se incorporan las etapas 6 a 8 en la reivindicación 6, mismas etapas que actualmente se encuentran identificadas mediante los incisos f), g) y h).

4. PETICIÓN

Teniendo en cuenta que se ha dado respuesta a todas las observaciones realizadas por su Despacho, que no se encontraron como fundadas ninguna de las oposiciones, y que no se encontraron documentos del estado del arte que anticipen el objeto de la solicitud, amablemente se solicita proceder al otorgamiento de la solicitud de patente.

5. ANEXOS

- Capítulo reivindicatorio modificado conformado por seis (6) reivindicaciones.
- *Handbook of Pharmaceutical Excipients* (páginas de interés).

5. NOTIFICACIONES

Recibiré notificaciones en la secretaría de su Despacho; en mis oficinas de abogado ubicadas en la Calle 67 No. 7 – 35, oficina 1204, teléfono 3192900, Bogotá D.C., Colombia, o; al correo electrónico patentes@gomezpinzon.com.

Atentamente,

MAURICIO JARAMILLO C.
C.C. 80.421.942 de Bogotá
T.P. 74.555 del C.S.J.

CMR

Handbook of Pharmaceutical Excipients

FIFTH EDITION

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Magnesium Stearate

1 Nonproprietary Names

BP: Magnesium stearate
JP: Magnesium stearate
PhEur: Magnesii stearas
USPNF: Magnesium stearate

2 Synonyms

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

3 Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

4 Empirical Formula and Molecular Weight

$C_{36}H_{70}MgO_4$ 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

5 Structural Formula

$[CH_3(CH_2)_{16}COO]_2Mg$

6 Functional Category

Tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams. See also Section 18.

8 Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for magnesium stearate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Microbial limits	+	+	+
Aerobic microbes	$\leq 1000/g$	$\leq 10^3/g$	$\leq 10^3/g$
Fungi and yeasts	$\leq 500/g$	—	$\leq 500/g$
Acidity or alkalinity	+	+	+
Acid value of the fatty acid	—	195–210	—
Freezing point	—	$\geq 53^\circ C$	—
Nickel	—	≤ 5 ppm	—
Cadmium	—	≤ 3 ppm	—
Specific surface area	—	—	+
Loss on drying	$\leq 6.0\%$	$\leq 6.0\%$	$\leq 6.0\%$
Chloride	$\leq 0.1\%$	$\leq 0.1\%$	$\leq 0.1\%$
Sulfate	$\leq 1.0\%$	$\leq 0.5\%$	$\leq 1.0\%$
Lead	—	≤ 10 ppm	$\leq 0.001\%$
Heavy metals	≤ 20 ppm	—	—
Relative stearic/palmitic content	+	+	+
Organic volatile impurities	—	—	+
Assay (dried, as Mg)	4.0–5.0%	4.0–5.0%	4.0–5.0%

10 Typical Properties

Crystalline forms: high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk): $0.159 g/cm^3$

Density (tapped): $0.286 g/cm^3$

Density (true): $1.092 g/cm^3$

Flash point: $250^\circ C$

Flowability: poorly flowing, cohesive powder.

Melting range:

117–150°C (commercial samples);

126–130°C (high purity magnesium stearate).

Solubility: practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Specific surface area: $1.6\text{--}14.8 m^2/g$

11 Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Stearic Acid

1 Nonproprietary Names

BP: Stearic acid
JP: Stearic acid
PhEur: Acidum stearicum
USPNF: Stearic acid

2 Synonyms

Cetylacetic acid; *Crodacid*; E570; *Edenor*; *Emersol*; *Hystrene*; *Industrene*; *Kortacid* 1895; *Pearl Steric*; *Pristerene*; stereophanic acid; *Tegostearic*.

3 Chemical Name and CAS Registry Number

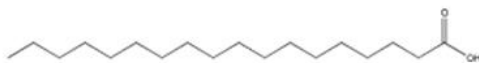
Octadecanoic acid [57-11-4]

4 Empirical Formula and Molecular Weight

$C_{18}H_{36}O_2$ 284.47 (for pure material)

The USPNF 23 describe stearic acid as a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$). In the USPNF 23, the content of stearic acid is not less than 40.0% and the sum of the two acids is not less than 90.0%. The USPNF 23 also contains a monograph for purified stearic acid; see Section 17. The PhEur 2005 contains a single monograph for stearic acid but defines stearic acid 50, stearic acid 70, and stearic acid 95 as containing specific amounts of stearic acid ($C_{18}H_{36}O_2$); see Section 9.

5 Structural Formula



6 Functional Category

Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant;⁽¹⁻³⁾ see Table I, although it may also be used as a binder⁽⁴⁾ or in combination with shellac as a tablet coating. It has also been suggested that stearic acid may be used as a sustained-release drug carrier.⁽⁵⁾

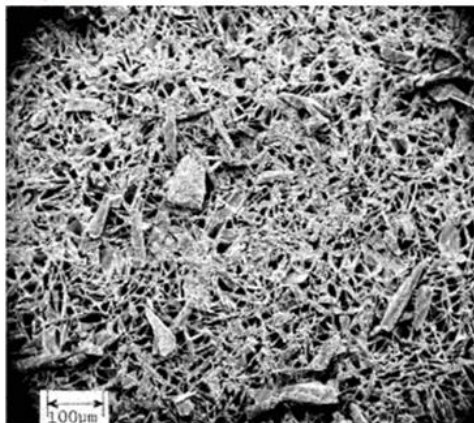
In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation of creams.^(6,7) The partially neutralized stearic acid forms a creamy base when mixed with 5–15 times its own weight of aqueous liquid; the appearance and plasticity of the cream being determined by the proportion of alkali used.

Stearic acid is used as the hardening agent in glycerin suppositories.

Stearic acid is also widely used in cosmetics and food products.

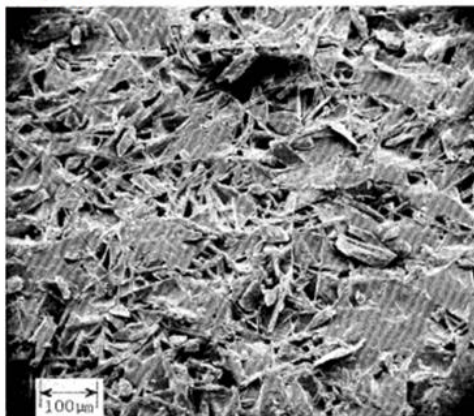
SEM: 1

Excipient: Stearic acid, 95% (*Emersol* 153)
Manufacturer: Emery Industries
Lot No.: 18895
Magnification: 120×
Voltage: 10 kV



SEM: 2

Excipient: Stearic acid, food grade (*Emersol* 6332)
Manufacturer: Emery Industries
Lot No.: 18895
Magnification: 120×
Voltage: 10 kV



Glyceryl Monostearate

1 Nonproprietary Names

BP: Glyceryl monostearate 40–55

JP: Glyceryl monostearate

PhEur: Glyceroli monostearas 40–55

USPNF: Glyceryl monostearate

Note that the USPNF 23 also includes a specification for mono- and di-glycerides that corresponds to glyceryl monostearate 40–55 in the PhEur 2005.

2 Synonyms

Capmul GMS-50; Cutina GMS; 2,3-dihydroxypropyl octadecanoate; glycerine monostearate; glycerin monostearate; glycerol monostearate; glycerol stearate; glyceryl stearate; GMS; Imuvitor 191; Imuvitor 900; Kessco GMS; Lipo GMS 410; Lipo GMS 450; Lipo GMS 600; monoester with 1,2,3-propanetriol; monostearin; Myvaplex 600P; Myvatex; 1,2,3-propanetriol octadecanoate; Protachem GMS-450; Rita GMS; stearic acid, monoester with glycerol; stearic monoglyceride; Stepan GMS; Tegin; Tegin 503; Tegin 515; Tegin 4100; Tegin M; Unimate GMS.

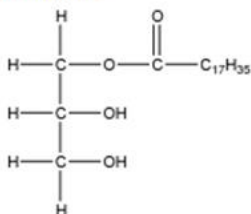
3 Chemical Name and CAS Registry Number

Octadecanoic acid, monoester with 1,2,3-propanetriol [31566-31-1]

4 Empirical Formula and Molecular Weight

$C_{21}H_{42}O_4$ 358.6

5 Structural Formula



6 Functional Category

Emollient; emulsifying agent; solubilizing agent; stabilizing agent; sustained-release ingredient; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

The many varieties of glyceryl monostearate are used as nonionic emulsifiers, stabilizers, emollients, and plasticizers in a variety of food, pharmaceutical, and cosmetic applications. It acts as an effective stabilizer, that is, as a mutual solvent for

polar and nonpolar compounds that may form water-in-oil or oil-in-water emulsions.^(1,2) These properties also make it useful as a dispersing agent for pigments in oils or solids in fats, or as a solvent for phospholipids, such as lecithin.

Glyceryl monostearate has also been used in a novel fluidized hot-melt granulation technique for the production of granules and tablets.⁽³⁾

Glyceryl monostearate is a lubricant for tablet manufacturing and may be used to form sustained-release matrices for solid dosage forms.^(4–6) Sustained-release applications include the formulation of pellets for tablets⁽⁷⁾ or suppositories⁽⁸⁾ and the preparation of a veterinary bolus.⁽⁹⁾ Glyceryl monostearate has also been used as a matrix ingredient for a biodegradable, implantable, controlled-release dosage form.⁽¹⁰⁾

When using glyceryl monostearate in a formulation, the possibility of polymorph formation should be considered. The α -form is dispersible and foamy, useful as an emulsifying agent or preservative. The denser, more stable, β -form is suitable for wax matrices. This application has been used to mask the flavor of clarithromycin in a pediatric formulation.⁽¹¹⁾

8 Description

While the names glyceryl monostearate and mono- and di-glycerides are used for a variety of esters of long-chain fatty acids, the esters fall into two distinct grades:

40–55 percent monoglycerides: the PhEur 2005 describes glyceryl monostearate 40–55 as a mixture of monoacylglycerols, mostly monostearoylglycerol, together with quantities of di- and triacylglycerols. It contains 40–55% of monoacylglycerols, 30–45% of diacylglycerols, and 5–15% of triacylglycerols. This PhEur grade corresponds to mono- and di-glycerides USPNF, which has similar specifications (not less than 40% monoglycerides).

90 percent monoglycerides: the USPNF 23 (Suppl. 1) describes glyceryl monostearate as consisting of not less than 90% of monoglycerides, chiefly glyceryl monostearate ($C_{21}H_{42}O_4$) and glyceryl monopalmitate ($C_{19}H_{38}O_4$).

The commercial products are mixtures of variable proportions of glyceryl monostearate and glyceryl monopalmitate.

Glyceryl monostearate is a white to cream-colored, waxlike solid in the form of beads, flakes, or powder. It is waxy to the touch and has a slight fatty odor and taste.

9 Pharmacopeial Specifications

Table I compares the specifications for the 40–55% grades. Glyceryl monostearate PhEur and mono- and di-glycerides USPNF. PhEur divides glyceryl monostearate 40–55 into three types according to the proportion of stearic acid ester in the mixture, and those specifications are presented in Table II. Table III presents the specifications for glyceryl monostearate USPNF (90% monoglycerides). Since the JP specifications are broad enough to encompass both grades, JP is included in both Table I and Table III.

Sodium Stearyl Fumarate

1 Nonproprietary Names

BP: Sodium stearyl fumarate
PhEur: Natrii stearylis fumaras
USPNF: Sodium stearyl fumarate

2 Synonyms

Fumaric acid, octadecyl ester, sodium salt; *Pruv*; sodium monostearyl fumarate.

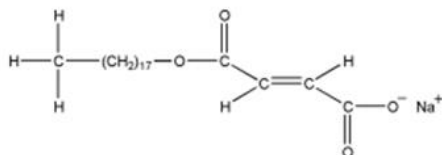
3 Chemical Name and CAS Registry Number

2-Butenedioic acid, mono-octadecyl ester, sodium salt [4070-80-8]

4 Empirical Formula and Molecular Weight

$C_{22}H_{39}NaO_4$ 390.5

5 Structural Formula



6 Functional Category

Tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium stearyl fumarate is used as a lubricant in capsule and tablet formulations at 0.5–2.0% w/w concentration.^(1–9) It is also used in certain food applications; see Section 16.

8 Description

Sodium stearyl fumarate is a fine, white powder with agglomerates of flat, circular-shaped particles.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium stearyl fumarate.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Water	≤ 5.0%	≤ 5.0%
Lead	—	≤ 0.001%
Heavy metals	—	≤ 0.002%
Related substances	+	—
Sodium stearyl maleate	—	≤ 0.25%
Stearyl alcohol	—	≤ 0.5%
Saponification value (anhydrous basis)	—	142.2–146.0
Organic volatile impurities	—	+
Assay (anhydrous basis)	99.0–101.5%	99.0–101.5%

10 Typical Properties

Acidity/alkalinity: pH = 8.3 for a 5% w/v aqueous solution at 90°C.

Density: 1.107 g/cm³

Density (bulk): 0.2–0.35 g/cm³

Density (tapped): 0.3–0.5 g/cm³

Melting point: 224–245°C (with decomposition)

Solubility: see Table II.

Table II: Solubility of sodium stearyl fumarate.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Practically insoluble
Chloroform	Practically insoluble
Ethanol	Practically insoluble
Methanol	Slightly soluble
Water	1 in 20 000 at 25°C 1 in 10 at 80°C 1 in 5 at 90°C

Specific surface area: 1.2–2.0 m²/g

11 Stability and Storage Conditions

At ambient temperature, sodium stearyl fumarate is stable for up to 3 years when stored in amber glass bottles with polyethylene screw caps.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Sodium stearyl fumarate is reported to be incompatible with chlorhexidine acetate.⁽¹⁰⁾

13 Method of Manufacture

Stearyl alcohol is reacted with maleic anhydride. The product of this reaction then undergoes an isomerization step followed by salt formation to produce sodium stearyl fumarate.

Talc

1 Nonproprietary Names

BP: Purified talc
JP: Talc
PhEur: Talcum
USP: Talc

2 Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; *Luzenac Pharma*; magnesium hydrogen metasilicate; *Magsil Osmanthus*; *Magsil Star*; powdered talc; purified French chalk; *Purtalc*; soapstone; steatite; *Superiore*.

3 Chemical Name and CAS Registry Number

Talc [14807-96-6]

4 Empirical Formula and Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_3(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

5 Structural Formula

See Section 4.

6 Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, see Table I,⁽¹⁻³⁾ although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products,⁽⁴⁻⁶⁾ Talc is also used as a lubricant in tablet formulations;⁽⁷⁾ in a novel powder coating for extended-release pellets;⁽⁸⁾ and as an adsorbant.⁽⁹⁾

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves; see Section 14. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder; see Section 11.

Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Table I: Uses of talc.

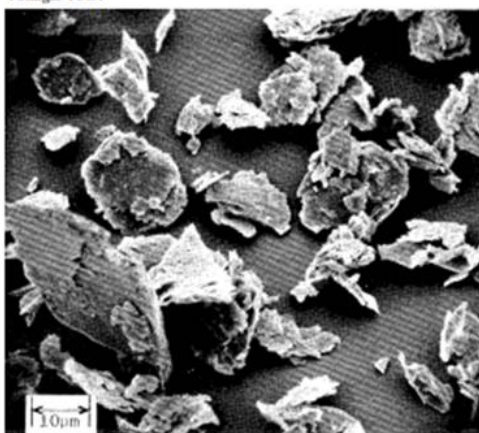
Use	Concentration (%)
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0
Tablet and capsule diluent	5.0–30.0

8 Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

SEM: 1

Excipient: Talc (*Purtalc*)
Manufacturer: Charles B Chrystal Co., Inc.
Lot No.: 1102A-2
Magnification: 1200×
Voltage: 10 kV



9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Acidity/alkalinity: pH = 7–10 for a 20% w/v aqueous dispersion.

Hardness (Mohs): 1.0–1.5

Moisture content: talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.

Particle size distribution: varies with the source and grade of material. Two typical grades are ≥99% through a 74 μm (#200 mesh) or ≥99% through a 44 μm (#325 mesh).

Refractive index: $n_D^{20} = 1.54–1.59$

Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.

Specific gravity: 2.7–2.8

Specific surface area: 2.41–2.42 m²/g

Sodium Lauryl Sulfate

1 Nonproprietary Names

BP: Sodium lauryl sulfate
JP: Sodium lauryl sulfate
PhEur: Natrii laurilsulfas
USPNF: Sodium lauryl sulfate

2 Synonyms

Dodecyl sodium sulfate; *Elfan 240*; sodium dodecyl sulfate; sodium laurilsulfate; sodium monododecyl sulfate; sodium monolauryl sulfate; *Texapon K12P*.

3 Chemical Name and CAS Registry Number

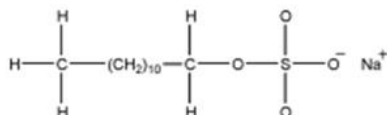
Sulfuric acid monododecyl ester sodium salt [151-21-3]

4 Empirical Formula and Molecular Weight

$C_{12}H_{25}NaO_4S$ 288.38

The USPNF 23 describes sodium lauryl sulfate as a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate ($C_{12}H_{25}NaO_4S$). The PhEur 2005 states that sodium lauryl sulfate should contain not less than 85% of sodium alkyl sulfates calculated as $C_{12}H_{25}NaO_4S$.

5 Structural Formula



6 Functional Category

Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium lauryl sulfate is an anionic surfactant employed in a wide range of nonparenteral pharmaceutical formulations and cosmetics; see Table I.

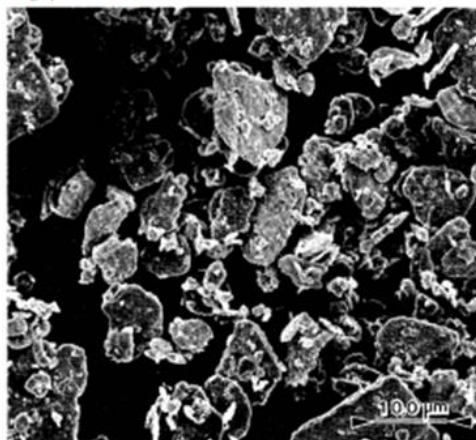
It is a detergent and wetting agent effective in both alkaline and acidic conditions. In recent years it has found application in analytical electrophoretic techniques: SDS (sodium dodecyl sulfate) polyacrylamide gel electrophoresis is one of the more widely used techniques for the analysis of proteins;⁽¹⁾ and sodium lauryl sulfate has been used to enhance the selectivity of micellar electrokinetic chromatography (MEKC).⁽²⁾

Table I: Uses of sodium lauryl sulfate.

Use	Concentration (%)
Anionic emulsifier, forms self-emulsifying bases with fatty alcohols	0.5–2.5
Detergent in medicated shampoos	≈10
Skin cleanser in topical applications	1
Solubilizer in concentrations greater than critical micelle concentration	>0.0025
Tablet lubricant	1.0–2.0
Wetting agent in dentifrices	1.0–2.0

SEM: 1

Excipient: Sodium lauryl sulfate
Manufacturer: Canadian Alcolac Ltd.
Magnification: 120×



8 Description

Sodium lauryl sulfate consists of white or cream to pale yellow-colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Acidity/alkalinity: pH = 7.0–9.5 (1% w/v aqueous solution)

Acid value: 0

Antimicrobial activity: sodium lauryl sulfate has some bacteriostatic action against Gram-positive bacteria but is

Polyethylene Glycol

1 Nonproprietary Names

BP: Macrogols
JP: Macrogol 400
Macrogol 1500
Macrogol 4000
Macrogol 6000
Macrogol 20000
PhEur: Macrogola
USPNF: Polyethylene glycol

2 Synonyms

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

3 Chemical Name and CAS Registry Number

α -Hydro- ω -hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

4 Empirical Formula and Molecular Weight

$\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_m\text{CH}_2\text{OH}$ where m represents the average number of oxyethylene groups.

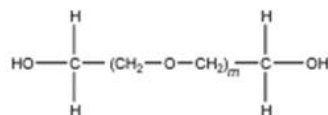
Alternatively, the general formula $\text{H}(\text{OCH}_2\text{CH}_2)_n\text{OH}$ may be used to represent polyethylene glycol, where n is a number m in the previous formula + 1.

See Table I for the average molecular weights of typical polyethylene glycols. Note that the number that follows PEG indicates the average molecular weight of the polymer.

Table I: Structural formula and molecular weight of typical polyethylene glycol polymers.

Grade	m	Average molecular weight
PEG 200	4.2	190–210
PEG 300	6.4	285–315
PEG 400	8.7	380–420
PEG 540 (blend)	—	500–600
PEG 600	13.2	570–613
PEG 900	15.3	855–900
PEG 1000	22.3	950–1050
PEG 1450	32.5	1300–1600
PEG 1540	28.0–36.0	1300–1600
PEG 2000	40.0–50.0	1800–2200
PEG 3000	60.0–75.0	2700–3300
PEG 3350	75.7	3000–3700
PEG 4000	69.0–84.0	3000–4800
PEG 4600	104.1	4400–4800
PEG 8000	181.4	7000–9000

5 Structural Formula



6 Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.⁽¹⁾

Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin; see Section 14. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases.⁽²⁾ Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases,⁽³⁾ for which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats.

Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules.⁽⁴⁾ However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5%.

Lactose, Monohydrate

1 Nonproprietary Names

BP: Lactose monohydrate
PhEur: Lactosum monohydricum
JP: Lactose
USPNF: Lactose monohydrate

2 Synonyms

See Tables II and III.

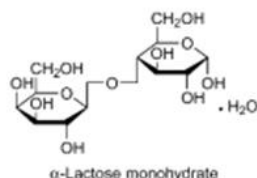
3 Chemical Name and CAS Registry Number

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate [64044-51-5]

4 Empirical Formula and Molecular Weight

C₁₂H₂₂O₁₁·H₂O 360.31

5 Structural Formula



The USPNF 23 describes lactose monohydrate as a natural disaccharide, obtained from milk, which consists of one galactose and one glucose moiety. The PhEur 2005 describes lactose monohydrate as the monohydrate of O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose. It is stated in the USPNF 23 that lactose monohydrate may be modified as to its physical characteristics, and may contain varying proportions of amorphous lactose.

6 Functional Category

Binding agent; diluent for dry-powder inhalers; tablet binder; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas.⁽¹⁻¹³⁾ Lactose is also used as a diluent in dry-powder inhalation.⁽¹⁴⁻¹⁶⁾ Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of

encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions.

Direct-compression grades of lactose monohydrate are available as granulated/agglomerated α-lactose monohydrate, containing small amounts of anhydrous lactose.

Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation.

Other directly compressible lactoses are spray-dried lactose and anhydrous lactose. See Lactose, Spray-Dried, Lactose, Anhydrous.

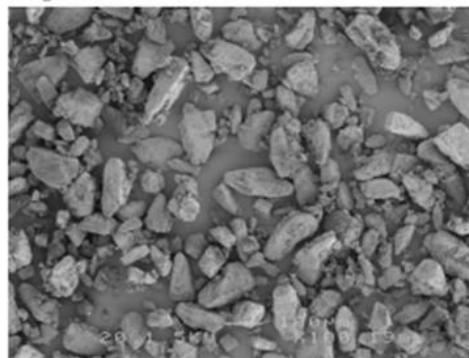
8 Description

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α-lactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. The stable crystalline forms of lactose are α-lactose monohydrate, β-lactose anhydrous, and stable α-lactose anhydrous.

Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

SEM: 1

Excipient: Pharmatose 125M
Manufacturer: DMV International
Magnification: 100×
Voltage: 1.5 kV



Dextrose

1 Nonproprietary Names

BP: Glucose monohydrate
JP: Glucose
PhEur: Glucosum monohydricum
USP: Dextrose

2 Synonyms

Blood sugar; *Caridex*; corn sugar; *C*PharmDex*; *Dextrofin*; D-(+)-glucopyranose monohydrate; grape sugar; *Lycadex PF*; *Roferose*; starch sugar; *Tabfine D-100*.

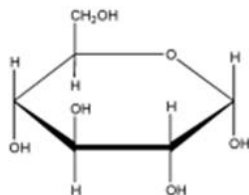
3 Chemical Name and CAS Registry Number

D-(+)-Glucose monohydrate [5996-10-1]
See also Section 17.

4 Empirical Formula and Molecular Weight

$C_6H_{12}O_6 \cdot H_2O$ 198.17 (for monohydrate)
See also Section 17.

5 Structural Formula



Anhydrous material shown.

6 Functional Category

Tablet and capsule diluent; therapeutic agent; tonicity agent; sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Dextrose is widely used in solutions to adjust tonicity and as a sweetening agent. Dextrose is also used as a wet granulation diluent and binder, and as a direct-compression tablet diluent and binder, primarily in chewable tablets. Although dextrose is comparable as a tablet diluent to lactose, tablets produced with dextrose monohydrate require more lubrication, are less friable, and have a tendency to harden.⁽¹⁻³⁾ The mildly reducing properties of dextrose may be used when tableting to improve the stability of active materials that are sensitive to oxidation.

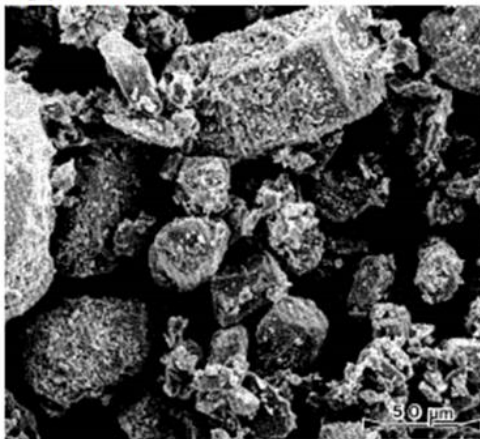
Dextrose is also used therapeutically and is the preferred source of carbohydrate in parenteral nutrition regimens.

8 Description

Dextrose occurs as odorless, sweet-tasting, colorless crystals or as a white crystalline or granular powder. The JP 2001 describes dextrose as dextrose anhydrous; the PhEur 2005 specifies dextrose as either dextrose anhydrous or dextrose monohydrate; and the USP 28 specifies dextrose as dextrose monohydrate.

SEM: 1

Excipient: Dextrose anhydrous (granular)
Manufacturer: Mallinckrodt Specialty Chemicals Co.
Lot No.: KKKZ
Magnification: 180×



9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Data are shown for dextrose monohydrate; see Section 17 for data for dextrose anhydrous.

Acidity/alkalinity: pH = 3.5–5.5 (20% w/v aqueous solution)

Density (bulk): 0.826 g/cm³

Density (tapped): 1.020 g/cm³

Density (true): 1.54 g/cm³

Heat of solution: 105.4 J/g (25.2 cal/g)

Melting point: 83°C

Moisture content: anhydrous dextrose absorbs significant amounts of moisture at 25°C and a relative humidity of about 85% to form the monohydrate. The monohydrate similarly only absorbs moisture at around 85% relative humidity and 25°C. See Figure 1.

Mannitol

1 Nonproprietary Names

BP: Mannitol
JP: D-Mannitol
PhEur: Mannitolum
USP: Mannitol

2 Synonyms

Cordycepic acid; C*PharmMannidex; E421; manna sugar; D-mannite; mannite; Mannogem; Pearlitol.

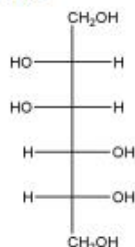
3 Chemical Name and CAS Registry Number

D-Mannitol [69-65-8]

4 Empirical Formula and Molecular Weight

C₆H₁₄O₆ 182.17

5 Structural Formula



6 Functional Category

Diluent; diluent for lyophilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.

7 Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.^(1,2)

Mannitol may be used in direct-compression tablet applications,^(3–7) for which the granular and spray-dried forms are available, or in wet granulations.⁽⁸⁾ Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and ‘mouth feel’.^(9,10)

In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial.^(11–20) A pyrogen-free form is available specifically for this use.

Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations,⁽²¹⁾ and as a carrier in dry powder inhalers.^(22,23) It is also used as a diluent in rapidly dispersing oral dosage forms.^(24,25) It is used in food applications as a bulking agent.

Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure. Given orally, mannitol is not absorbed significantly from the GI tract, but in large doses it can cause osmotic diarrhea; see Section 14.

8 Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol.

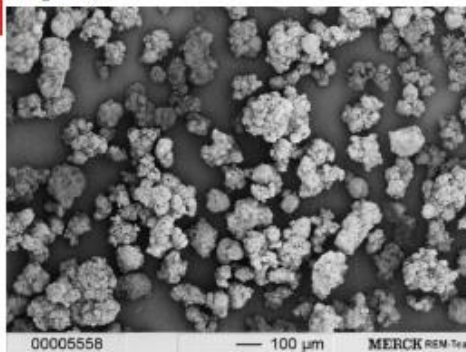
Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.⁽²⁶⁾

9 Pharmacopeial Specifications

See Table I.

SEM: 1

Excipient: Mannitol
Manufacturer: Merck
Magnification: 50×
Voltage: 3.5 kV



Sucrose

1 Nonproprietary Names

BP: Sucrose
JP: Sucrose
PhEur: Saccharum
USPNF: Sucrose

2 Synonyms

Beet sugar; cane sugar; α -D-glucopyranosyl- β -D-fructofuranoside; refined sugar; saccharose; sugar.

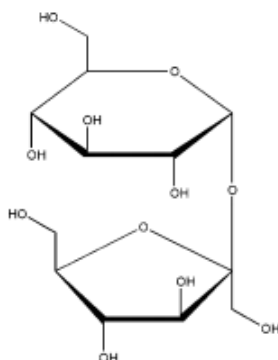
3 Chemical Name and CAS Registry Number

β -D-fructofuranosyl- α -D-glucopyranoside [57-50-1]

4 Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$ 342.30

5 Structural Formula



6 Functional Category

Base for medicated confectionery; coating agent; granulating agent; sugar coating adjunct; suspending agent; sweetening agent; tablet binder; tablet and capsule diluent; tablet filler; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Sucrose is widely used in oral pharmaceutical formulations. Sucrose syrup, containing 50–67% w/w sucrose, is used in tableting as a binding agent for wet granulation. In the powdered form, sucrose serves as a dry binder (2–20% w/w) or as a bulking agent and sweetener in chewable tablets and lozenges.^(1,2) Tablets that contain large amounts of sucrose may harden to give poor disintegration.

Sucrose syrups are used as tablet-coating agents at concentrations between 50% and 67% w/w. With higher concentrations, partial inversion of sucrose occurs, which makes sugar coating difficult.

Sucrose syrups are also widely used as vehicles in oral liquid-dosage forms to enhance palatability or to increase viscosity.^(3,4)

Sucrose has been used as a diluent in freeze-dried protein products.^(5,6)

Sucrose is also widely used in foods and confectionery, and therapeutically in sugar pastes that are used to promote wound healing.^(7,8) See Table I.

Table I: Uses of sucrose.

Use	Concentration (% w/w)
Syrup for oral liquid formulations	67
Sweetening agent	67
Tablet binder (dry granulation)	2–20
Tablet binder (wet granulation)	50–67
Tablet coating (syrup)	50–67

8 Description

Sucrose is a sugar obtained from sugar cane (*Saccharum officinarum* Linné (Fam. Gramineae)), sugar beet (*Beta vulgaris* Linné (Fam. Chenopodiaceae)), and other sources. It contains no added substances. Sucrose occurs as colorless crystals, as crystalline masses or blocks, or as a white crystalline powder; it is odorless and has a sweet taste.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Density (bulk):

0.93 g/cm³ (crystalline sucrose);

0.60 g/cm³ (powdered sucrose).

Density (tapped):

1.03 g/cm³ (crystalline sucrose);

0.82 g/cm³ (powdered sucrose).

Density (true): 1.6 g/cm³

Dissociation constant: $pK_a = 12.62$

Flowability: crystalline sucrose is free flowing, whereas powdered sucrose is a cohesive solid.

Melting point: 160–186°C (with decomposition)

Moisture content: finely divided sucrose is hygroscopic and absorbs up to 1% water.⁽⁹⁾ See Figure 1.

Osmolarity: a 9.25% w/v aqueous solution is isoosmotic with serum.

Particle size distribution: powdered sucrose is a white, irregular-sized granular powder. The crystalline material consists of colorless crystalline, roughly cubic granules. See Figures 2 and 3.

Cellulose, Microcrystalline

1 Nonproprietary Names

BP: Microcrystalline cellulose
JP: Microcrystalline cellulose
PhEur: Cellulosum microcristallinum
USPNF: Microcrystalline cellulose

2 Synonyms

Avicel PH; Cellex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; VivaPur.

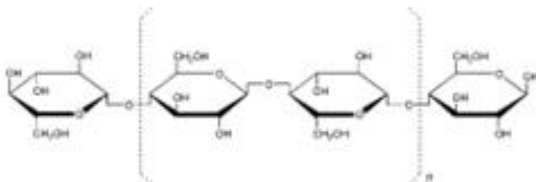
3 Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ $\approx 36\,000$
where $n \approx 220$.

5 Structural Formula



6 Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.⁽¹¹⁻¹⁷⁾ In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant⁽⁸⁾ and disintegrant properties that make it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products; see Table I.

8 Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Table I: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20-90
Antiadherent	5-20
Capsule binder/diluent	20-90
Tablet disintegrant	5-15
Tablet binder/diluent	20-90

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for microcrystalline cellulose.

Test	JP 2001	PhEur 2005 (Suppl 5.1)	USPNF 23
Identification	+	+	+
Characters	+	+	—
pH	5.0-7.0	5.0-7.5	5.0-7.5
Bulk density	+	—	+
Loss on drying	$\leq 7.0\%$	$\leq 7.0\%$	$\leq 7.0\%$
Residue on ignition	$\leq 0.05\%$	—	$\leq 0.1\%$
Conductivity	+	+	+
Sulfated ash	—	$\leq 0.1\%$	—
Ether-soluble substances	$\leq 0.05\%$	$\leq 0.05\%$	$\leq 0.05\%$
Water-soluble substances	+	$\leq 0.25\%$	$\leq 0.25\%$
Heavy metals	≤ 10 ppm	≤ 10 ppm	$\leq 0.001\%$
Organic volatile impurities	—	—	+
Microbial limits	+	+	+
Aerobic	—	$\leq 10^3$ /g	≤ 1000 cfu/g
Molds and yeasts	—	$\leq 10^2$ /g	≤ 100 cfu/g
Solubility	—	+	—
Particle size distribution	—	—	+

10 Typical Properties

Angle of repose:

49° for *Ceolus KG*;
34.4° for *Emcocel 90M*.⁽⁹⁾

Density (bulk):

0.337 g/cm³;
0.32 g/cm³ for *Avicel PH-101*.⁽¹⁰⁾
0.29 g/cm³ for *Emcocel 90M*.⁽⁹⁾
0.29 g/cm³ for *VivaPur 101*.

Density (tapped):

0.478 g/cm³;
0.45 g/cm³ for *Avicel PH-101*;
0.35 g/cm³ for *Emcocel 90M*.⁽⁹⁾

Density (true): 1.512-1.668 g/cm³

Flowability: 1.41 g/s for *Emcocel 90M*.⁽⁹⁾

Melting point: chars at 260-270°C.

Moisture content: typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.⁽¹¹⁾ See Table III.

Povidone

1 Nonproprietary Names

BP: Povidone
JP: Povidone
PhEur: Povidonum
USP: Povidone

2 Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula and Molecular Weight

(C₆H₉NO)_n 2500–3 000 000

The USP 28 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a *K*-value, in the range 10–120. The *K*-value is calculated using Fikentscher's equation:⁽¹⁾

$$\log z = c \left[\frac{7.5k^2}{1 + 1.5kc} \right] + k$$

where *z* is the relative viscosity of the solution of concentration *c* (in % w/v), and *k* is the *K*-value $\times 10^{-3}$.

Alternatively, the *K*-value may be determined from the following equation:

$$K\text{-value} = \sqrt{\frac{300c \log z (c + 1.5c \log z)^2 + 1.5}{0.15c + 0.003c^2}}$$

where *z* is the relative viscosity of the solution of concentration *c* (in % w/v).

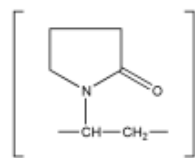
Approximate molecular weights for different povidone grades are shown in Table I.

Table I: Approximate molecular weights for different grades of povidone.

<i>K</i> -value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5 Structural Formula



6 Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.^(2,3) Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.^(4–6) Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone. See Table II.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations; see Section 14.

Table II: Uses of povidone.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

8 Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone *K*-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

9 Pharmacopeial Specifications

See Table III.

Hydroxypropyl Cellulose

1 Nonproprietary Names

BP: Hydroxypropylcellulose
JP: Hydroxypropylcellulose
PhEur: Hydroxypropylcellulosum
USPNF: Hydroxypropyl cellulose

2 Synonyms

Cellulose, hydroxypropyl ether; E463; hypolose; *Klucel*; *Methocel*; *Nisso HPC*; oxypropylated cellulose.

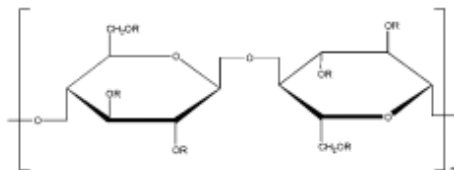
3 Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether [9004-64-2]

4 Empirical Formula and Molecular Weight

The PhEur 2005 and USPNF 23 describe hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight has a range of 50 000–1 250 000; see also Section 10.

5 Structural Formula



R is H or $[\text{CH}_2\text{CH}(\text{CH}_3)\text{O}]_m\text{H}$

6 Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations; see Table I.

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder,⁽¹⁾ film-coating,⁽²⁾ and extended-release-matrix former.^(3–5) Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes.^(6–10) Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.⁽¹¹⁾ The release rate of a drug increases with decreasing viscosity of

hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Aqueous solutions containing hydroxypropyl cellulose along with an amount of methyl cellulose or ethanolic solutions have been used.^(12–14) Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. Environmental concerns have limited the use of ethanol in film coating solutions. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant; see Hydroxypropyl Cellulose, Low-substituted.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations.^(15–17)

Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Table I: Uses of hydroxypropyl cellulose.

Use	Concentration (%)
Extended release-matrix former	15–35
Tablet binder	2–6
Tablet film coating	5

8 Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder. See also Section 10.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for hydroxypropyl cellulose.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Apparent viscosity	+	+	+
Appearance of solution	+	+	—
pH (1 in 100)	5.0–7.5	5.0–8.5	5.0–8.0
Loss on drying	≤ 5.0%	≤ 7.0%	≤ 5.0%
Residue on ignition	≤ 0.5%	—	≤ 0.2%
Sulfated ash	—	≤ 1.6%	—
Arsenic	≤ 2 ppm	—	—
Chlorides	+	≤ 0.5%	—
Lead	—	—	≤ 0.001%
Heavy metals	≤ 20 ppm	≤ 20 ppm	20 µg/g
Silica	—	≤ 0.6%	—
Organic volatile impurities	—	—	+
Sulfate	≤ 0.048%	—	—
Assay of hydroxypropoxy groups	53.4–77.5%	—	≤ 80.5%

Sucralose

1 Nonproprietary Names

USPNF: Sucralose

2 Synonyms

Splenda; TGS; 1',4',6'-trichlorogalactosucrose; 4,1',6'-trichloro-4,1',6'-trideoxy-galacto-sucrose.

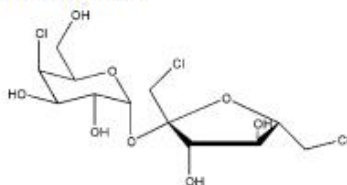
3 Chemical Name and CAS Registry Number

1,6-Dichloro-1,6-dideoxy- β -D-fructofuranosyl-4-chloro-4-deoxy- α -D-galactopyranoside [56038-13-2]

4 Empirical Formula and Molecular Weight

$C_{12}H_{19}Cl_3O_8$ 397.64

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Sucralose is used as a sweetening agent in beverages, foods, and pharmaceutical applications. It has a sweetening power approximately 300–1000 times that of sucrose and has no aftertaste. It has no nutritional value, is noncariogenic, and produces no glycemic response. See also Table I.

Table I: Uses of sucralose.

Use	Concentration (%)
Food products	0.03–0.24

8 Description

Sucralose is a white to off-white colored, free-flowing, crystalline powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for sucralose.

Test	USPNF 23
Identification	+
Specific rotation	+84.0° to +87.5°
Water	≤ 2.0%
Residue on ignition	≤ 0.7%
Heavy metals	≤ 0.001%
Limit of hydrolysis products	≤ 0.1%
Limit of methanol	≤ 0.1%
Related compounds	≤ 0.5%
Assay (dried basis)	98.0–102.0%

10 Typical Properties

Acidity/alkalinity: pH = 5–6 (10% w/v aqueous solution at 20°C)

Density (bulk): 0.35 g/cm³

Density (tapped): 0.62 g/cm³

Density (true): 1.63 g/cm³

Melting point: 130°C (for anhydrous crystalline form); 36.5°C (for pentahydrate).

Particle size distribution: 90% < 12 μ m in size.

Partition coefficient: log₁₀ P = –0.51 (octanol:water)

Refractive index: 1.33 to 1.37

Solubility: freely soluble in ethanol (95%), methanol, and water; slightly soluble in ethyl acetate.

Specific rotation $[\alpha]_D^{20}$: +84.0° to +87.5° (1% w/v aqueous solution); +68.2° (1.1% w/v solution in ethanol).

Viscosity: 0.6–3.8 mPa s

11 Stability and Storage Conditions

Sucralose is a relatively stable material. In aqueous solution, at highly acidic conditions (pH < 3), and at high temperatures (≥ 35°C), it is hydrolyzed to a limited extent, producing 4-chloro-4-deoxygalactose and 1,6-dichloro-1,6-dideoxyfructose. In food products, sucralose remains stable throughout extended storage periods, even at low pH. However, it is most stable at pH 5–6.

Sucralose should be stored in a well-closed container in a cool, dry place, at a temperature not exceeding 21°C. Sucralose, when heated at elevated temperatures, may break down with the release of carbon dioxide, carbon monoxide, and minor amounts of hydrogen chloride.

12 Incompatibilities

13 Method of Manufacture

Sucralose may be prepared by a variety of methods that involve the selective substitution of three sucrose hydroxyl groups by chlorine. Sucralose can also be synthesized by the reaction of sucrose (or an acetate) with thionyl chloride.