



124
763
170

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF:

EXPEDIENTE

06 100.792

TÍTULO SOLICITADO:

SÓLIDOS SUPERSATURADOS ESTABILIZADOS DE DROGAS LIPOFÍLICAS.

PUBLICACIÓN:

Gaceta 587 de 18/01/2008 numero de publicación 1237

PRIORIDAD:

EP 04075714.8 de 10/03/2004

US 60/551.330 de 10/03/2004

SOLICITANTE:

SCHERING AKTIENGESELLSCHAFT

APODERADO:

J. IAN RAISBECK

TRÁMITE:

REMISIÓN DE INFORMACIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de la firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del C.S.J, obrando en nombre y representación de **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, sociedad comercial constituida y vigente de acuerdo con las leyes de la República de Colombia, con domicilio y sede principal en Cali, de manera respetuosa, y con el propósito de coadyuvar en la decisión que sobre la solicitud de patente de la referencia deberá adoptarse próximamente, por este escrito me permito remitir información fundamentada que demuestra que la solicitud en mención no cumple el requisito de nivel inventivo exigido por la Decisión 486 de 2000, y que por ello debería el Despacho abstenerse de concederle el privilegio de patente solicitado.

Además de la defensa del orden jurídico vigente en materia de propiedad industrial, el presente escrito se fundamenta en la necesidad de evitar que la concesión de la

solicitud vulnere la libre competencia, y restrinja el mercado farmacéutico en perjuicio de los consumidores colombianos.

I. INCUMPLIMIENTO DE REQUISITOS DE PATENTABILIDAD

La composición farmacéutica en forma de polvos, tabletas, cápsulas y píldoras, que contiene como principio activo derivados de moléculas esteroides; y en general el proceso por el cual se obtienen, y que consta de una primera preparación de una solución supersaturada del esteroide en un solvente (etanol, triglicérido parcialmente sintético o aceite vegetal); posteriormente mezclar dicha solución supersaturada con sílice amorfa (con área superficial específica de por lo menos $250\text{m}^2/\text{g}$) y eliminar finalmente el solvente de la mezcla; carece por completo de los requisitos fundamentales para otorgársele el privilegio de patente de invención, veamos:

1.1. LA FORMULACIÓN Y EL PROCESO DE PREPARACIÓN DE LA MISMA, INCLUIDOS EN EL CAPITULO REIVINDICATORIO DE LA SOLICITUD COLOMBIANA EN TRAMITE CARECE DE NIVEL INVENTIVO.

El uso de excipientes con buenas propiedades adsorbentes y absorbentes, como cualquier persona medianamente versada en la materia reconoce, son utilizados ampliamente para contener compuestos líquidos o semisólidos que de otra manera no podrían incluirse en la mezcla de polvos o de gránulos en una formulación sólida. En el caso de la solicitud colombiana en trámite, se menciona la utilización de sílice amorfa con un tamaño de partícula tal que cubre un área superficial específica de por lo menos $250\text{m}^2/\text{g}$, la cual es la encargada de adsorber y absorber en su estructura las moléculas esteroides que se encuentran dispersas en la solución supersaturada. El tamaño de partícula que se maneja y que permite el valor de área superficial mencionado anteriormente, también es un factor que cualquier persona medianamente versada en la materia reconoce, y es que al utilizar un material de cierto tamaño de partícula, al disminuirlo aun mas, el área del material que se expone al medio aumenta.

El óxido de silicio o dióxido de silicio (SiO_2) es un compuesto de silicio y oxígeno, llamado comúnmente sílice. Es uno de los componentes de la arena. Una de las formas en que aparece naturalmente es el cuarzo, cuando su estado es cristalino. Si se encuentra en estado de amorfo (sílice amorfa) suele incluir un porcentaje elevado de

agua. Por esta gran capacidad adsorbente y absorbente el dióxido de silicio es un excelente desecante, esto significa que atrae la humedad del ambiente en que se encuentra.

En este sentido es obvia la aplicación de la sílice amorfa en el proceso de obtención de las formulaciones descritas en la solicitud colombiana, ya que sus características de agente adsorbente y absorbente, ampliamente reconocidas en el estado de la técnica¹, permiten concluir que al adicionarse en la solución supersaturada de moléculas esteroides, este material atraerá a dichas moléculas de una manera eficaz, gracias a su considerable área superficial específica, de manera que al retirar el solvente de la solución, las moléculas esteroides queden incluidas en la sílice amorfa.

Es tan reconocida y amplia la utilización de la sílice amorfa en la industria farmacéutica, que existen productos comercializados bajo el nombre, por ejemplo, de Aerosil® o de Aeroperl®, que contienen dicha sílice amorfa en una formula coloidal que permite su aplicación de manera estandarizada. Aerosil® por ejemplo, es un producto que fue desarrollado en 1942 por Degussa AG en Alemania. Este Aerosil® es dióxido de sílice puro, obtenido a través de la evaporización de tetracloruro de silicio, oxidado a altas temperaturas junto con hidrógeno y oxígeno, que resulta en un agregado primario de nanopartículas con un flujo extraordinario.

Tanto Aeroperl² como Aerosil³ contienen las características que fundamentan su inclusión y utilidad en la preparación de la formulación de la solicitud colombiana, veamos:

▶AEROPERL® 300 Pharma

¹ REMINGTON. The Science and Practice of Pharmacy. 20 th. Ed. Páginas 1046 y 1047.

² AEROPERL® 300 Pharma Colloidal Silicon Dioxide. Degussa Product Information.

³ AEROSIL® 200 Pharma Colloidal Silicon Dioxide. Degussa Product Information

3
126
168
172

Applications and Properties

Applications

- Pharmacy
 - Carrier for liquid and pasty (active) ingredients
 - Converts liquid and pasty substances into free-flowing powders
 - Adsorbent
 - Desiccant

Properties

- Dust free and easy handling
- High purity
- Excellent flow both loaded and unloaded

Physico-chemical Data

Properties	Unit	Typical Value
Specific surface area (BET)	m ² /g	approx. 300
Average granule size	µm	approx. 30
Tapped density (approx. value)* acc. to DIN EN ISO 787/11, Aug. 1983	g/l	approx. 280
Loss on drying (moisture) Tested according to USP/NF and Ph. Eur.	wt. %	≤ 2.5
Loss on ignition Tested according to USP/NF	wt. %	≤ 2.0
pH Tested according to USP/NF and Ph. Eur.		3.5 - 5.5
SiO ₂ - content Tested according to USP/NF and Ph. Eur.	wt. %	99.0 - 100.5
Chloride Tested according to Ph. Eur.	ppm	< 250
Heavy metals Tested according to Ph. Eur.	ppm	< 25
Arsenic Tested according to USP/NF	ppm	< 8

AEROSIL® 200 Pharma

Applications and Properties

Applications

- Pharmacy, especially semi-solid and liquid dosage forms

Properties

- Used as viscosity increasing agent to thicken and thixotropize liquids
- Improves storage and temperature stability of semi-solid and liquid dosage forms
- Improves distribution of active pharmaceutical ingredients
- Desiccant for moisture-sensitive actives
- Free flow and anti-caking agent to improve powder properties

Physico-chemical Data

Properties	Unit	Typical Value
Specific surface area (BET)	m ² /g	200 ± 25
Tapped density (approx. value)* acc. to DIN EN ISO 787/11, Aug. 1983	g/l	approx. 50
pH Tested according to Ph. Eur., USP/NF		3.5 - 5.5
Chloride Tested according to Ph. Eur., JP	ppm	≤ 250; ≤ 110
Heavy Metals Tested according to Ph. Eur., JP	ppm	≤ 25; ≤ 40
SiO ₂ - content Tested acc. to Ph. Eur., USP/NF, JP	wt. %	99.9 - 100.5; ≥ 98.0
Loss on Drying (moisture) Tested according to USP/NF, JP	wt. %	≤ 2.5; ≤ 7.0
Loss on Ignition Tested acc. to Ph. Eur., USP/NF, JP	wt. %	≤ 5.0; ≤ 2.0; ≤ 12.0
As - content Tested according to USP/NF, JP	ppm	≤ 8.0; ≤ 5.0
Organic Volatile Impurities Tested according to USP/NF		pass
Volume Test Tested according to JP	ml	≥ 70
Ca - content Tested according to JP		pass
Fe - content Tested according to JP	ppm	≤ 500
Al - content Tested according to JP		pass

Hasta este punto, podemos ver claramente que en el estado de la técnica se encuentra la información suficiente para que cualquier persona medianamente versada en la materia derive la aplicación de las propiedades de la sílice amorfa con un valor de área

superficial específica considerable para adsorber las moléculas esteroidales de la solución supersaturada y posteriormente retirar el solvente, quedando el principio activo incluido en este excipiente.

Esta supuesta lógica inventiva se puede desvirtuar aún más si se tiene en cuenta que existe información que involucra la misma relación entre compuestos de carácter esteroideal y la sílice amorfa o compuestos con características similares a esta:

- La patente americana US 4056468 publicada el 01 de noviembre de 1977 y titulada "ISOLATION OF COMPONENT MATERIALS OF AQUEOUS SOLUTIONS SOLUBLE IN LIPOPHILIC SOVENTS" revela:

1. In a process for the isolation of lipophilic solvent-soluble components from an aqueous solution containing lipophilic components comprising contacting the aqueous solution with one or both of a silica gel-based or kieselguhr-based concentration agent to absorb said aqueous solution therein and subsequently extracting substantially only the lipophilic solvent-soluble components from the aqueous solution absorbed in the concentration agent with a lipophilic solvent, the improvement which comprises employing as the concentration agent a flowable silica gel of kieselguhr or a mixture thereof, having an average particle size of 0.05 to 1.0 mm., an average pore volume of 0.2 to 3 ml./g. and a specific surface to 0.2 to 50 m²/g., and said extracting is conducted without substantial simultaneous desorption of the water of said absorbed aqueous solution, said lipophilic solvent-soluble components being at least one analgesic, sedative, hypnotic, anti-epileptic, psychopharmaceutical, sympathicomimetic, anti-histamine, narcotic, alkaloid, antibiotic, lipid, triglyceride, fatty acid, steroid or porphyrin.

5128
968
179

The process according to the invention has special importance for the investigation of body fluids, especially urine, blood, plasma and serum, as well as gastric juice, lymph fluids, brain and spinal fluid. Furthermore, aqueous fluids are also of importance which have been obtained from tissue material or parts of organs. However, in addition, any other desired aqueous solutions can also be extracted, e.g., extracts from plants and drugs (e.g., opium tinctures, extracts of hashish and tobacco), as well as wash liquids and waste waters. From all of these fluids, the component materials soluble in lipophilic solvents can be isolated quickly, satisfactorily and quantitatively.

The process according to the invention has special importance in diagnosis and for testing of body fluids for their content of pharmaceuticals, drugs, toxic materials or pharmaceutical metabolites. Thus, e.g., according to the process of this invention, there have already been detected and determined analgesics, sedatives, hypnotics, anti-epileptics, psychopharmaceuticals, sympathicomimetics, anti-histaminics, narcotics, alkaloids and antibiotics or their metabolites. However, in addition, there have also been extracted and investigated metabolites natural to the body, e.g., lipids, triglycerides, fatty acids, steroids and porphyrins.

Como se puede apreciar, se hace mención aquí de la gel de sílice (sílica gel) en la separación de compuestos esteroideos, por ejemplo de fluidos orgánicos, compuesto que al igual que Aerosil o Aeroperl, es una forma granular y porosa de dióxido de silicio, pero fabricada sintéticamente a partir de silicato sódico.

- La patente europea EP 0329347 publicada el 23 de agosto de 1989 y titulada "IMPROVEMENTS IN OR RELATING TO METHODS OF REMOVING STEROLS AND/OR OTHER STEROIDAL COMPOUNDS FROM EDIBLE FATS AND/OR OILS AND/OR OIL FROM WHICH SUCH STEROLS AND/OR OTHER STEROIDAL COMPOUNDS HAVE BEEN REMOVED" revela:

This invention relates to methods of removing sterols and/or other steroidal compounds from edible fats and/or oils and/or fats and/or oils from which such sterols and/or other steroidal compounds have been removed and/or sterols and/or other steroidal compounds so removed from fats and/or oils and in particular relates to the production of cholesterol reduced milk fat suitable for the processed food industry.

(...)

28. A method as set forth in claim 27, wherein said extraction is by one of steam distillation, carbon absorption column, silica reverse phase absorption, solvent/sorbent extraction or reverse osmosis membrane.

En este documento se puede apreciar que nuevamente la sílica se utiliza para extraer compuestos esteroidales (en especial colesterol) de la leche y derivados de la leche.

En conclusión, con el conocimiento básico de cualquier persona medianamente versada en la materia, específicamente a lo relacionado con las características de la sílice amorfa y su utilidad como absorbente y/o adsorbente, presentes en productos estandarizados y comercializados tales como los acá mencionados; y la información acerca de la relación entre dichas características de la sílice y los esteroides, el proceso a través del cual se consigue el material sólido en polvo con que se fabrican las tabletas, capsulas o pildoras de la solicitud colombiana, se resume a la posterior aplicación de los procesos y previos ensayos de formulación y preformulación que se reconocen en el estado de la técnica para este tipo de formulaciones sólidas de administración oral.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

III. PRUEBAS

Ruego que se tengan como tales las siguientes, sin perjuicio de aquellas que el Despacho considere oficiosamente, las siguientes:

- La patente americana US 4056468 publicada el 01 de Noviembre de 1977 y titulada "ISOLATION OF COMPONENT MATERIALS OF AQUEOUS SOLUTIONS SOLUBLE IN LIPOPHILIC SOVENTS" columna 6 y capítulo reivindicatorio.
- La patente Europea EP 0329347 publicada el 23 de Agosto de 1989 y titulada "IMPROVEMENTS IN OR RELATING TO METHODS OF REMOVING STEROLS AND/OR OTHER STEROIDAL COMPOUNDS FROM EDIBLE FATS AND/OR OILS AND/OR OIL FROM WICH SUCH STEROLS AND/OR OTHER STEROIDAL COMPOUNDS HAVE BEEN REMOVED" página 2 y capítulo reivindicatorio.
- REMINSNGTON. The escience and Practice of Pharmacy. 20 th. Ed. Páginas 1046 y 1047.
- AEROPERL® 300 Pharma Colloidal Silicon Dioxide. Degussa Product Information.
- AEROSIL® 200 Pharma Colloidal Silicon Dioxide. Degussa Product Information.

United States Patent [19]

Breiter et al.

[11] 4,056,468

[45] Nov. 1, 1977

[54] ISOLATION OF COMPONENT MATERIALS OF AQUEOUS SOLUTIONS SOLUBLE IN LIPOPHILIC SOLVENTS

[75] Inventors: Joachim Breiter; Roland Helger, both
of Darmstadt, Germany

[73] Assignee: Merck Patent Gesellschaft mit
beschränkter Haftung, Darmstadt,
Germany

[21] Appl. No.: 553,023

[22] Filed: Feb. 25, 1975

[30] Foreign Application Priority Data

Mar. 2, 1974 Germany 2410033

[51] Int. Cl.² B01D 15/00

[52] U.S. Cl. 210/31 R; 23/230 B

[58] Field of Search 23/230 B; 210/24, 31 C;
210/41, 31 R, 40; 252/449, 451

[56] References Cited

U.S. PATENT DOCUMENTS

3,494,875 2/1970 Page et al. 252/449
3,761,227 9/1973 Conrad et al. 23/230 B
3,888,972 6/1975 Kiselev et al. 252/449

FOREIGN PATENT DOCUMENTS

1,353,861 1/1964 France 252/449

OTHER PUBLICATIONS

Kesner et al., "Determination of Total Organic Acids in
Urine by Extraction with Organic Solvents," *Clinical
Chemistry*, vol. 19, No. 6, 1973, pp. 593-596.

Primary Examiner—Wilbur L. Bascomb, Jr.

Assistant Examiner—Ivars Cintins

Attorney, Agent, or Firm—Millen & White

[57] ABSTRACT

Process for the isolation of component materials of
aqueous solutions by adsorption of the aqueous solu-
tions on concentration agents based on silica gel and/or
kieselguhr and subsequent extraction of the component
materials with lipophilic solvents, which employs as
concentration agents flowable silica gels and/or kiesel-
guhrs with an average particle size of 0.05 to 1.0 mm.,
an average pore volume of 0.2 to 3 ml./g., and a specific
surface of 0.2 to 50 m²/g.

11 Claims, No Drawings

9
132
279
177

nated hydrocarbons, such as dichloromethane, chloroform, tetrachloromethane, 1,2-dichloroethane and 1,1,2-trichloroethane; and aromatic and aliphatic hydrocarbons, e.g., benzene, toluene, pentane, hexane, heptane, petroleum ether and cyclohexane. All these solvents can be used alone or in admixture. In principle, all organic solvents can be used which also according to the previously known processes have been regarded as suitable for the dissolving of the component materials from aqueous solutions. A special advantage of the concentration agents employed in the process of this invention consists in the possibility of using for the extraction lower aliphatic alcohols, e.g., organic solvents miscible with water. In this way, in many cases, the quantity of the necessary amount of solvent is reduced. One can e.g., achieve quantitative extractions with amounts of solvent which, from the point of view of volume, are about the same as the volume of the starting aqueous solution. This was hitherto not possible. In the case of mixtures of the water-miscible solvents with water-insoluble solvents (e.g., chloroform/isopropanol 80/20 vol. %) if the proportion of the water-miscible solvent is not too high (<30 vol. %), a satisfactory extraction is achieved with the water surprisingly remaining bound in the concentration agent. Furthermore, according to a special embodiment of the process of this invention, extractions can also be carried out if necessary with, e.g., lower aliphatic alcohols alone or in admixture with a small proportion of a water-insoluble lipophilic solvent. These lower aliphatic alcohols are able to split component materials of serum, e.g., triglycerides bound to protein, bound to the concentration agents. The triglycerides thereby become extractable. Small amounts of water possibly co-extracted in the case of this process are unimportant in the subsequent analysis.

The process according to the invention has special importance for the investigation of body fluids, especially urine, blood, plasma and serum, as well as gastric juice, lymph fluids, brain and spinal fluid. Furthermore, aqueous fluids are also of importance which have been obtained from tissue material or parts of organs. However, in addition, any other desired aqueous solutions can also be extracted, e.g., extracts from plants and drugs (e.g., opium tinctures, extracts of hashish and tobacco), as well as wash liquids and waste waters. From all of these fluids, the component materials soluble in lipophilic solvents can be isolated quickly, satisfactorily and quantitatively.

The process according to the invention has special importance in diagnosis and for testing of body fluids for their content of pharmaceuticals, drugs, toxic materials or pharmaceutical metabolites. Thus, e.g., according to the process of this invention, there have already been detected and determined analgesics, sedatives, hypnotics, anti-epileptics, psychopharmaceuticals, sympathicomimetics, anti-histaminics, narcotics, alkaloids and antibiotics or their metabolites. However, in addition, there have also been extracted and investigated metabolites natural to the body, e.g., lipids, triglycerides, fatty acids, steroids and porphyrins.

In some cases, it is expedient to convert the component materials present in the body fluids, by a pH change, into the undissociated and consequently into a form more soluble in the lipophilic solvents. Enzymatic splittings, e.g., of conjugated metabolites, such as glucuronides and sulphates, can also be carried out in the aqueous solution to be investigated, e.g., after being

brought together with the concentration agent. Since the concentration agent to be employed according to the invention is neutral and insensitive to pH value changes, there can be applied thereto any desired aqueous solution. In the extracts obtained, there can be detected and determined the component materials of the initial aqueous solutions according to methods known and described in detail in the literature. In many cases, it is especially advantageous to prepare, with the help of lipophilic solvents, a solution whose volume corresponds to that of the original sample, since the values obtained for the component materials are then identical with those of the aqueous solution. It is, of course, also possible according to the process of this invention, to prepare lipophilic solvent solutions with substantially higher concentrations of the sought component materials, whereby the detection or the determination of these materials can be made substantially easier. For this purpose, e.g., several extracts can be concentrated and combined.

The extracts obtained are especially suitable for gas and thin layer chromatographic detection of the component materials. However, all other known detection and determination methods can also be employed, e.g., photometric or colorimetric methods as well as fluorimetric, immunologic and radioimmunologic methods.

In many cases, by the process of this invention, standardized processes for the determination of particular component materials of aqueous solutions are possible. In order to make this standardization easier and also to make possible large-scale tests, the concentration agents according to the invention are expediently offered in particular finished packings. The finished packings contain the concentration agents in amounts of about 0.5 to 50 g., whereby the amount is adjusted to the intended purpose of use. Although the packing can be in any desired form, e.g., pillow- or sphere-shaped bags, column packings, e.g., glass or synthetic resin columns of about 5 to 20 cm. length and a diameter of 1 to 3 cm., are preferred.

Also suitable are, e.g., plastic single-use syringes commercially available for injection purposes, if a lipophilic solvent is selected to which the synthetic resin material is stable. The aqueous solution then only needs to be applied to or drawn into such a syringe packed with the concentration agent, so that mixing with the concentration agent occurs spontaneously. In this form, the adsorbed sample is readily transportable. The extraction of the component materials from the concentration agent can be conducted centrally at another place. The transport of liquid samples intended for the investigation is, in this way, considerably simplified. This makes easier screening programs and large scale investigations for the testing for the misuse of pharmaceuticals or drugs.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

10
135
972
178

of an estriol standard solution (100 µg/ml.) was added to one sample and 0.2 ml. ethanol was added to the other. 1 ml. of each of these solutions was put onto the column and the elution was done with 6 ml. of ether. 0.2 ml. of a 2% hydroquinone solution in ethanol were added to the eluate and they then were evaporated to dryness. The determination was effected in a manner known as such, namely by heating with sulfuric acid. (Mitteilungen der Deutschen Gesellschaft fuer Klinische Chemie (3), 1970, page 9). In 4 samples of urine, the following estrogen values were found in 24 hours: 14.3, 19.4, 10.2 and 21.9 mg. estriol, respectively.

EXAMPLE 16

A combination of multiple extractions for the isolation and purification of compounds, for example, those contained in blood, can be achieved by the combination of two extraction columns.

For this purpose, a 50 ml. syringe, filled with 16 g. kieselguhr according to Example 2 and in followup, a 2 ml. syringe filled with 0.5 g. of the same kieselguhr, were used. The small syringe was closed at the upper end by a stopper such as used for freeze-dried ampoules. The large column was equipped with a cannula at the outlet. After penetrating the stopper with this cannula, the eluate from the larger column flowed through the bed of the following smaller column.

To 4 ml. of fresh EDTA blood, 1 ml. of 0.025% solution of papaverine hydrochloride and 15 ml. of 0.025% aqueous ammonia was added. After 15 minutes, hemolysis was complete.

The blood thus prepared was loaded onto the larger column. The smaller column was loaded with 0.5 ml. of 0.2 N-sulfuric acid and conjunction between both the columns was effected. After 10 minutes, the larger column was eluted by 50 ml. ethyl acetate. The papaverine thus extracted from the larger column, was re-extracted when flowing through the second column into the sulfuric acid. The eluate (33 ml. after 20 min.) was discarded.

The columns were detached from each other and the aqueous phase in the smaller column was brought to a pH of 9.5 with gaseous NH_3 in accordance with Example 10. The column was eluted with 3.5 ml. ethyl acetate. The eluate was extracted with 4 ml. 1N hydrochloric acid and the upper phase was discarded. The acidic solution was measured in a spectrophotometer in 309 nm. in comparison to an extract from blood without added papaverine. The concentration found in the sample with papaverine hydrochloride was 232 µg., i.e., 92.1% of that added to the blood.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifica-

tions of the invention to adapt it to various usages and conditions.

What is claimed is:

1. In a process for the isolation of lipophilic solvent-soluble components from an aqueous solution containing lipophilic components comprising contacting the aqueous solution with one or both of a silica gel-based or kieselguhr-based concentration agent to absorb said aqueous solution therein and subsequently extracting substantially only the lipophilic solvent-soluble components from the aqueous solution absorbed in the concentration agent with a lipophilic solvent, the improvement which comprises employing as the concentration agent a flowable silica gel of kieselguhr or a mixture thereof, having an average particle size of 0.05 to 1.0 mm., an average pore volume of 0.2 to 3 ml./g. and a specific surface to 0.2 to 50 m²/g., and said extracting is conducted without substantial simultaneous desorption of the water of said absorbed aqueous solution, said lipophilic solvent-soluble components being at least one analgesic, sedative, hypnotic, anti-epileptic, psychopharmaceutical, sympathicomimetic, anti-histamine, narcotic, alkaloid, antibiotic, lipid, triglyceride, fatty acid, steroid or porphyrin.

2. A process according to claim 1, wherein the concentration agent is a silica gel with an average particle size of 0.15 to 0.4 mm., an average pore volume of 0.5 to 1.7 ml./g. and a specific surface of 0.3 to 20 m²/g.

3. A process according to claim 2 wherein the specific surface of the silica gel is not more than 0.8 m²/g.

4. A process according to claim 2 wherein said silica gel has a specific surface of 0.8 m²/g., an average pore diameter of 40,000 angstroms and a pore volume of 0.7 ml./g.

5. A process according to claim 1, wherein the concentration agent is a kieselguhr with an average particle size of 0.15 to 0.4 mm., an average pore volume of 0.5 to 1.7 ml./g. and a specific surface of 0.5 to 5 m²/g.

6. A process according to claim 1, wherein the aqueous solution is a body fluid.

7. A process according to claim 6, wherein the body fluid is a sample of urine.

8. A process according to claim 1, wherein the weight ratio of aqueous solution to concentration agent is from 1:0.4 to 1:1.25 for kieselguhr and from 1:0.9 to 1:1.7 for silica gel.

9. A process according to claim 1, wherein the solvent is a water immiscible organic solvent or mixtures thereof or is a mixture of water immiscible and water miscible organic solvents.

10. A process according to claim 9, wherein the water immiscible solvent is a chlorinated alkane and the water miscible solvent is isopropanol.

11. A process according to claim 1, wherein a measured amount of the concentration agent is packaged in a single-use container adapted to store the concentration agent with the aqueous solution adsorbed thereon prior to extraction of the lipophilic-soluble components from the aqueous solution absorbed in the concentration agent with a lipophilic solvent.

* * * * *

①⑫ **EUROPEAN PATENT APPLICATION**

①⑰ Application number: **89301304.5**

①⑮ Int. Cl.4: **A23D 5/00 , C11B 3/00 ,**
A23C 15/00 , A23C 19/00

①⑱ Date of filing: **10.02.89**

①⑳ Priority: **12.02.88 NZ 223508**

④③ Date of publication of application:
23.08.89 Bulletin 89/34

⑧④ Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

⑦① Applicant: **NEW ZEALAND DAIRY RESEARCH**
INSTITUTE
Dairy Farm Road Fitzherbert West
Palmerston North(NZ)

⑦② Inventor: **Keen, Alan Robert c/o New Zealand**
Dairy
Research Institute Dairy Farm Road
Fitzherbert Palmerston North(NZ)
Inventor: **Ward, David Douglas c/o New**
Zealand Dairy
Research Institute Dairy Farm Road
Fitzherbert Palmerston North(NZ)
Inventor: **Hobman, Peter Graeme c/o New**
Zealand Dairy
Research Institute Dairy Farm Road
Fitzherbert Palmerston North(NZ)

⑦④ Representative: **Brown, John David et al**
FORRESTER & BOEHMERT
Widenmayerstrasse 4/I
D-8000 München 22(DE)

⑤④ Improvements in or relating to methods of removing sterols and/or other steroidal compounds from edible fats and/or oils and/or fats and/or oil from which such sterols and/or other steroidal compounds have been removed.

⑤⑦ A solvent or solvent system to effect selected removal of the sterol or steroidal compound is added to and maintained in contact with liquid fat or oil for a desired time and the solvent and extracted components separate from the solvent. In the examples milk fat has cholesterol therein reduced and the milk fat containing a reduced amount of cholesterol used in foodstuffs. The extracted cholesterol is useful and fat remaining after the solvent has been removed is useful as a source of desirable flavours. The solvent may be subjected to a recovery process for reuse.

EP 0 329 347 A2

18
136
775
181

Improvements in or relating to methods of removing sterols and/or other steroidal compounds from edible fats and/or oils and/or oils from which such sterols and/or other steroidal compounds have been removed and/or sterols and/or other steroidal compounds so removed from fats and/or oils

This invention relates to methods of removing sterols and/or other steroidal compounds from edible fats and/or oils and/or fats and/or oils from which such sterols and/or other steroidal compounds have been removed and/or sterols and/or other steroidal compounds so removed from fats and/or oils and in particular relates to the production of cholesterol reduced milk fat suitable for the processed food industry.

5

SUMMARY OF THE INVENTION

10 It is an object of the present invention to provide a method of removing sterols and/or other steroidal compounds from edible fat and/or oils and/or fats and/or oils from which such sterols and/or steroidal compounds have been removed and/or sterols and/or other steroidal compounds which have been so removed from fats and/or oils which will at least provide the public with a useful choice.

Accordingly in one aspect the invention consists in a method reducing the amount of sterols and/or
15 other steroidal compounds present in edible fats and/or oils from said edible fats and/or oils, said method comprising the steps of:

adding a solvent and/or a modified solvent system said solvent and/or solvent system being selected to effect selective removal of the sterol and/or other steroidal compound 5;

20 maintaining the solvent in contact with the fat and/or oil in liquid condition for a predetermined length of time;

separating the solvent from the fat or oil and separating out extracted components from the solvent.

In a further aspect the invention consist in an edible fat and/or oil, the amount of sterols and/or other steroidal compounds in which has been reduced by a method according to the preceding paragraph.

In a still further aspect the invention consist in sterols and/or other steroidal compounds preferably
25 cholesterol removed from an edible fat and/or oil preferably milk fat by a method according to the above paragraph.

FIELD OF THE INVENTION

30

This invention relates to the removal of sterols from edible fats and/or oils and/or other steroidal compounds and especially the production of cholesterol-reduced milk-fat, suitable for the processed food industry. Particularly in milk fat systems, most of the natural colour and much of the desirable natural
35 flavour is retained.

A fat and/or oil reduced by low melting point lipid fractions remaining after removal of the solvent is useful as a source of desirable flavours.

BACKGROUND OF THE INVENTION

40

There are a number of well established procedures for the removal of colour and objectionable matter from edible oils and fats. Many of these processes rely on an active adsorbent such as carbon, clays,
45 aluminas, silicas and surface treated derivatives there of. Swern used such methods for bleaching oils [see Baileys Industrial Oils & Fat Products pp 771-77 (1964)]. Other such adsorption processes are available as known art, see U.S. Pat. Nos. 4,112,129; 3,450,541; 2,2118,819; 3,519,435 (Fractionation of Milk Fats); 4,443,379; and 4,005,228 (milkfat crystallising using acetone), New Zealand Patent No. 209508 and South African Patent No. 8516968 describe the use of appropriate absorbent systems for the removal of
50 cholesterol from milk fats and steroidal compounds from fats and/or oils.

Patents for cholesterol reduction in egg products also exist (see U.S. Patent Nos. 3,987,212; 3,941,892 and 3,563,765).

Very little information appears to exist for the reduction of cholesterol from milkfats. Belgium Patent no.

19
437
176
182

Decholesterolized anhydrous milkfat (DCAMF) was melted and added to a predetermined amount of emulsifiers, stabilizers, skim milk and flavours. The appropriate amount of DCAMF was selected so as to obtain cream or whole milk with the desired milkfat content. The mixture of ingredients was heated to a selected temperature and homogenized at selected pressures to produce a stable emulsion. The resultant cream or whole milk was subjected to UHT treatment then aseptically packed. The cream and whole milk was kept refrigerated until required. The UHT products obtained had excellent flavour and physical properties in which the cholesterol content was extremely low.

10 4. Butter

Method (a):

15 Decholesterolized milkfat is melted at minimum temperatures then maintained at 40° C in a suitable vat. The aqueous phase consisting of water, reconstituted skim milk solids, emulsifiers, stabilizers, flavour and salt (if required) was pasteurized and added to the vat. The contents of the vat were agitated and passed through a scrapped surface heat exchanger and pin worker and the butter thus produced was packaged and cooled. A butter with excellent flavour and containing low cholesterol content was obtained.

20

5. Ice-Cream

A suitable quantity of melted decholesterolized anhydrous milkfat was added to a formulation of reconstituted skim milk powder, sugar, emulsifiers, stabilizers, suitable flavours and corresponding colours which had been pasteurized. The mixture was passed through an ice-cream churn and the ice-cream produced packed and maintained suitably frozen. Ice cream with excellent flavour and with markedly reduced cholesterol content was obtained.

A suitable milkfat is thus obtained which has been used for the manufacture of a wide range of products (including dairy products) which are essentially free of cholesterol, i.e., butter, cheeses, cottage cheeses, ice-creams, and low cholesterol liquid milks of varying fat content. Where necessary flavour (natural, nature identical or artificial) can be used in the formulation of the products in order to restore the expected flavour of the product which is reduced due the initial treatment of the AMF.

While presently preferred embodiments have been described in particular, the invention may be otherwise embodied within the scope of the appended claims.

Although it is preferable to process liquified fat it is possible to obtain some reduction in cholesterol by processing fat in a solid, preferably particulate e.g. micronized state by reducing the size of particles of fat to a suitable size before processing either with or without heating the mixture of fat and solvent to or above a fat liquifying temperature.

40 The features disclosed in the foregoing description, in the following Claims and/or in the accompanying drawings may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

45 Claims

1. A method reducing the amount of sterols and/or other steroidal compounds present in edible fats and/or oils from said edible fats and/or oils, said method comprising the steps of:
adding a solvent and/or a modified solvent system said solvent and/or solvent system being selected to effect selective removal of the sterol and/or other steroidal compound 5;
maintaining the solvent in contact with the fat and/or oil in liquid condition for a predetermined length of time;

separating the solvent from the fat and/or oil and separating out extracted components from the solvent.

2. A method as claimed in Claim 1 wherein said solvent is lipophobic in nature.

55 3. A method as claimed in Claim 1 or Claim 2 which includes the step of thoroughly mixing said solvent with said fat and/or oil.

4. A method as claimed in anyone of the preceding claims including the step of removing cholesterol from milk fat.

177¹⁵
438
94
183

5. A method as claimed in anyone of Claims 1 to 3 including the steps of removing cholesterol from cream and/or other aqueous emulsions or colloidal suspensions of fats and/or oils and/or vegetable oils.
6. A method as claimed in any one of the preceding claims which includes the step of using methanol as said solvent.
7. A method as claimed in anyone of Claims 1 to 5 which includes the step of using methanol/water mixtures as said solvent.
8. A method as claim in anyone of Claims 1 to 7 which include the step of repeating the steps of anyone of Claims 1 to 7, a desired number of time using fresh solvent or solvent treated to a reusable condition at each repeat of said steps.
9. A method as claimed in anyone of Claims 1 to 7 which includes the step of subjecting the fat and/or oil to treatment by solvent in a column in which treated fat and/or oil and solvent are removable from one end of the column and fat and/or oil and fresh solvent or solvent treated to a reusable condition are added to the other end of the said column.
10. A method as claimed in any one of the preceding claims including the step of treating the separated solvent to a reusable condition.
11. A method as claimed in Claim 10 which includes the step of subjecting the used solvent to a recovery process selected from distillation; passage of the solvent through an adsorption medium selected from active carbon and reverse phase adsorbents solvent extraction of sterol and/or other steroidal compounds from remaining fat and/or oil; and passing the solvent through a membrane which separates the remaining fat and/or oil from the solvent.
12. A method of reducing the amount of sterols and/or steroidal compounds present in edible fats and/or oils from said edible fats and/or oils when effected substantially as herein described.
13. An edible fat and/or oil in which the amount of sterols and/or other steroidal compounds has been reduced by a method according to any one of the preceding claims.
14. Milk fat from which cholesterol has been removed by a method as claimed in anyone of Claims 1 to 12.
15. Food products including milk fat according to Claim 14.
16. Sterols and/or other steroidal compounds removed from an edible fat and/or oil by a method according to any one of Claims 1 to 12.
17. Cholesterol removed from a edible fat and/or oil by a method according to anyone of Claims 1 to 12.
18. A fat and/or oil residue remaining after removal of solvent from a mixture of fat and/or oil and solvent by a method according to anyone of Claims 1 to 12.
19. A method for the removal of steroidal material from fats and oils comprising:
 - (a) taking said fat or oil in either its solid or liquid state;
 - (b) adding a solvent or modified solvent system which has low solubility in the said fat or oil, said solvent system being selected to effect selective removal of steroidal material;
 - (c) mixing said fat or oil and solvent to create a solvent phase and fat or oil phase;
 - (d) separating said phases; and
 - (e) removing from said fat or oil phase any solvent therein.
20. A method as set forth in Claim 19 wherein said solvent to fat or oil ratio is greater than the solubility of the solvent system in the fat or oil.
21. A method set forth in Claim 1, wherein said solvent is added to said oil or fat at a temperature about equal to the temperature used to liquify said fat or oil.
22. A method as claimed in anyone of Claims 19 to 21, wherein said solvent is added to said oil or fat and the temperature adjusted to liquify said fat or oil.
23. A method as set forth in anyone of claim 19 to 23, wherein said solvent is added in a ratio of 5:1 solvent to fat or oil.
24. A method as set forth in anyone of claim 19 to 23, wherein steps (a) through (e) are repeated until substantially all of said sterol material is removed from said fat or oil.
25. A method as set forth in anyone of claims 19 to 24, wherein the fat is milkfat and the solvent is methanol or methanol/water mixtures.
26. A method as claimed in anyone of claims 19 to 25, wherein said separated solvent phase is extracted therefrom.
27. A method as set forth in claim 26, wherein said solvent extracted from said solvent phase is used in step (b).

17
410
279
189

Product Information

AEROPERL® 300 Pharma

Colloidal Silicon Dioxide

AEROPERL® 300 Pharma is a granulated high purity colloidal silicon dioxide for use in pharmaceutical products (tested according to USP/NF and Ph. Eur Monograph 0434).

Applications and Properties

Applications

- Pharmacy
 - Carrier for liquid and pasty (active) ingredients
 - Converts liquid and pasty substances into free-flowing powders
 - Adsorbent
 - Desiccant

Properties

- Dust free and easy handling
- High purity
- Excellent flow both loaded and unloaded

Physico-chemical Data

Properties	Unit	Typical Value
Specific surface area (BET)	m ² /g	approx. 300
Average granule size	µm	approx. 30
Tapped density (approx. value)* acc. to DIN EN ISO 787/11, Aug. 1983	g/l	approx. 280
Loss on drying (moisture)* Tested according to USP/NF and Ph. Eur.	wt. %	≤ 2.5
Loss on Ignition Tested according to USP/NF	wt. %	≤ 2.0
pH Tested according to USP/NF and Ph. Eur.		3.5 - 5.5
SiO₂ - content Tested according to USP/NF and Ph. Eur.	wt. %	99.0 - 100.5
Chloride Tested according to Ph. Eur.	ppm	< 250
Heavy metals Tested according to Ph. Eur.	ppm	< 25
Arsenic Tested according to USP/NF	ppm	< 8

* ex plant

The data represents typical values and not production parameters.

185
114
degussa.

creating essentials

280
186

Safety and Handling

With every sample or initial shipment of our products we will send a Material Safety Data Sheet. Of course, you can also request an MSDS or any other information regarding product safety at any time, or download it as a registered user at www.aerosil.com.

Packaging and Storage

AEROPERL® 300 Pharma is supplied in multiple layer 10 kg bags. We recommend to store the product in closed containers under dry conditions and to protect the material from volatile substances. Shrink-wrapped pallets should be resealed after the removal of individual bags.

AEROPERL® 300 Pharma should be used within 2 years after production.

Registration

AEROPERL® 300 Pharma

CAS-No.	EINECS	TSCA (USA), AICS (Australia), DSL (Canada)	ENCS (Japan)	ECL (Korea)	IECS (China)
112 945-52-5 (ex 7631-86-9)	231-545-4	Registered	1-548	KE-30953 (KE-31032)	Registered

► For further information please contact:

Commercial Contact

Degussa GmbH
Business Line Aerosil
Weissfrauenstrasse 9
D-60287 Frankfurt am Main,
Germany
Phone: +49 69/218-2532
Fax: +49 69/218-2533
E-Mail: aerosil@degussa.com
<http://www.aerosil.com>

NAFTA

Degussa Corporation
Business Line Aerosil
379 Interpace Parkway,
P. O. Box 677
Parsippany, NJ 07054-0677
Phone: +1 (800) AEROSIL
Phone: +1 (973) 541-8510
Fax: +1 (973) 541-8501

Asia (without Japan)

Aerosil Asia Marketing Office
c/o NIPPON AEROSIL CO., LTD.
P. O. Box 7015
Shinjuku Monolith 13F
3-1, Nishi-Shinjuku 2-chome
Shinjuku-ku, Tokyo
163-0913 Japan
Phone: +81-3-3342-1786
Fax: +81-3-3342-1761

Japan

NIPPON AEROSIL CO., LTD.
Sales & Marketing Division
P. O. Box 7015
Shinjuku Monolith 13F
3-1, Nishi-Shinjuku 2-chome
Shinjuku-ku, Tokyo
163-0913 Japan
Phone: +81-3-3342-1763
Fax: +81-3-3342-1772

Technical Contact

Degussa GmbH
Technical Service Aerosil
Rodenbacher Chaussee 4
P. O. Box 1345
D-63403 Hanau-Wolfgang,
Germany
Phone: +49 6181/59-3936
Fax: +49 6181/59-4489

NAFTA

Degussa Corporation
Technical Service Aerosil
2 Turner Place
Piscataway, NJ 08855-0365
Phone: +1 (888) SILICAS
Phone: +1 (732) 981-5000
Fax: +1 (732) 981-5275

Asia (without Japan)

Degussa GmbH
Technical Service Aerosil
Rodenbacher Chaussee 4
P. O. Box 1345
D-63403 Hanau-Wolfgang,
Germany
Phone: +49 6181/59-3936
Fax: +49 6181/59-4489

Japan

NIPPON AEROSIL CO., LTD.
Applied Technology Service
3 Mita-cho
Yokkaichi, Mie
510-0841 Japan
Phone: +81-593-45-5270
Fax: +81-593-46-4657

Please visit our website www.aerosil.com to find your local contact.

This information and all further technical advice are based on Degussa's present knowledge and experience. However, Degussa assumes no liability for providing such information and advice including the extent to which such information and advice may relate to existing third party intellectual property rights, especially patent rights. In particular, Degussa disclaims all CONDITIONS AND WARRANTIES, WHETHER EXPRESS OR IMPLIED, INCLUDING THE IMPLIED WARRANTIES OF FITNESS FOR A PARTICULAR PURPOSE OR MERCHANTABILITY. DEGUSSA SHALL NOT BE RESPONSIBLE FOR CONSEQUENTIAL, INDIRECT OR INCIDENTAL DAMAGES (INCLUDING LOSS OF PROFITS) OF ANY KIND. Degussa reserves the right to make any changes according to technological progress or further developments. It is the customer's responsibility and obligation to carefully inspect and test any incoming goods. Performance of the product(s) described herein should be verified by testing and carried out only by qualified experts. It is the sole responsibility of the customer to carry out and arrange for any such testing. Reference to trade names used by other companies is neither a recommendation, nor an endorsement of any product and does not imply that similar products could not be used.

15
142
181
187

Product Information

AEROSIL® 200 Pharma

Colloidal Silicon Dioxide

AEROSIL® 200 Pharma is a high purity amorphous anhydrous colloidal silicon dioxide for use in pharmaceutical products (tested according to USP/NF, Ph. Eur. Monograph 0434 and JP).

Applications and Properties

Applications

- Pharmacy, especially semi-solid and liquid dosage forms

Properties

- Used as viscosity increasing agent to thicken and thixotropize liquids
- Improves storage and temperature stability of semi-solid and liquid dosage forms
- Improves distribution of active pharmaceutical ingredients
- Dessicant for moisture-sensitive actives.
- Free flow and anti-caking agent to improve powder properties

Physico-chemical Data

Properties	Unit	Typical Value
Specific surface area (BET)	m ² /g	200 ± 25
Tapped density (approx. value)* acc. to DIN EN ISO 787/11, Aug. 1983	g/l	approx. 50
pH Tested according to Ph. Eur., USP/NF		3.5 - 5.5
Chloride Tested according to Ph. Eur., JP	ppm	≤ 250; ≤ 110
Heavy Metals Tested according to Ph. Eur., JP	ppm	≤ 25; ≤ 40
SiO₂ - content Tested acc. to Ph. Eur., USP/NF; JP	wt. %	99.9 - 100.5; ≥ 98.0
Loss on Drying (moisture)* Tested according to USP/NF; JP	wt. %	≤ 2.5; ≤ 7.0
Loss on Ignition Tested acc. to Ph. Eur., USP/NF; JP	wt. %	≤ 5.0; ≤ 2.0; ≤ 12.0
As - content Tested according to USP/NF; JP	ppm	≤ 8.0; ≤ 5.0
Organic Volatile Impurities Tested according to USP/NF		pass
Volume Test Tested according to JP	ml	≥ 70
Ca - content Tested according to JP		pass
Fe - content Tested according to JP	ppm	≤ 500
Al - content Tested according to JP		pass

* ex plant

The data represents typical values and not production parameters.

creating essentials

Safety and Handling

With every sample or initial shipment of our products we will send a Material Safety Data Sheet. Of course, you can also request an MSDS or any other information regarding product safety at any time, or download it as a registered user at www.aerosil.com.

Packaging and Storage

AEROSIL® 200 Pharma is supplied in multiple layer 10 kg bags. We recommend to store the product in closed containers under dry conditions and to protect the material from volatile substances. AEROSIL® 200 Pharma should be used within 2 years after production.

Registration

AEROSIL® 200 Pharma					
CAS-No.	EINECS	TSCA (USA), AICS (Australia), DSL (Canada)	ENCS (Japan)	ECL (Korea)	IECS (China)
112 945-52-5 7631-86-9	231-545-4	Registered	1-548	KE-30953 (KE-31032)	Registered

► For further information please contact:

Commercial Contact

Degussa GmbH
Business Line Aerosil
Weissfrauenstrasse 9
D-60287 Frankfurt am Main,
Germany
Phone: +49 69/218-2532
Fax: +49 69/218-2533
E-Mail: aerosil@degussa.com
<http://www.aerosil.com>

NAFTA

Degussa Corporation
Business Line Aerosil
379 Interpace Parkway,
P. O. Box 677
Parsippany, NJ 07054-0677
Phone: +1 (800) AEROSIL
Phone: +1 (973) 541-8510
Fax: +1 (973) 541-8501

Asia (without Japan)

Aerosil Asia Marketing Office
c/o NIPPON AEROSIL CO., LTD.
P. O. Box 7015
Shinjuku Monolith 13F
3-1, Nishi-Shinjuku 2-chome
Shinjuku-ku, Tokyo
163-0913 Japan
Phone: +81-3-3342-1786
Fax: +81-3-3342-1761

Japan

NIPPON AEROSIL CO., LTD.
Sales & Marketing Division
P. O. Box 7015
Shinjuku Monolith 13F
3-1, Nishi-Shinjuku 2-chome
Shinjuku-ku, Tokyo
163-0913 Japan
Phone: +81-3-3342-1763
Fax: +81-3-3342-1772

Technical Contact

Degussa GmbH
Technical Service Aerosil
Rodenbacher Chaussee 4
P. O. Box 1345
D-63403 Hanau-Wolfgang,
Germany
Phone: +49 6181/59-3936
Fax: +49 6181/59-4489

NAFTA

Degussa Corporation
Technical Service Aerosil
2 Turner Place
Piscataway, NJ 08855-0365
Phone: +1 (888) SILICAS
Phone: +1 (732) 981-5000
Fax: +1 (732) 981-5275

Asia (without Japan)

Degussa GmbH
Technical Service Aerosil
Rodenbacher Chaussee 4
P. O. Box 1345
D-63403 Hanau-Wolfgang,
Germany
Phone: +49 6181/59-3936
Fax: +49 6181/59-4489

Japan

NIPPON AEROSIL CO., LTD.
Applied Technology Service
3 Mita-cho
Yokkaichi, Mie
510-0841 Japan
Phone: +81-593-45-5270
Fax: +81-593-46-4657

Please visit our website www.aerosil.com to find your local contact.

This information and all further technical advice are based on Degussa's present knowledge and experience. However, Degussa assumes no liability for providing such information and advice including the extent to which such information and advice may relate to existing third party intellectual property rights, especially patent rights. In particular, Degussa disclaims all CONDITIONS AND WARRANTIES, WHETHER EXPRESS OR IMPLIED, INCLUDING THE IMPLIED WARRANTIES OF FITNESS FOR A PARTICULAR PURPOSE OR MERCHANTABILITY. DEGUSSA SHALL NOT BE RESPONSIBLE FOR CONSEQUENTIAL, INDIRECT OR INCIDENTAL DAMAGES (INCLUDING LOSS OF PROFITS) OF ANY KIND. Degussa reserves the right to make any changes according to technological progress or further developments. It is the customer's responsibility and obligation to carefully inspect and test any incoming goods. Performance of the product(s) described herein should be verified by testing and carried out only by qualified experts. It is the sole responsibility of the customer to carry out and arrange for any such testing. Reference to trade names used by other companies is neither a recommendation, nor an endorsement of any product and does not imply that similar products could not be used.

or glycerin, a mixture of liquefied phenol and an equal volume of glycerin is miscible with water. *Uses*: A formulation that facilitates the dispensing of concentrated phenol. Its therapeutic uses are described above under *Phenol*. It is a *pharmaceutical necessity* for *Phenolated Calamine Lotion* (see RPS-18 page 762).

PHOSPHORIC ACID

Orthophosphoric Acid; Syrupy Phosphoric Acid; Concentrated Phosphoric Acid

Phosphoric acid [7664-38-2] H_3PO_4 (98.00); contains 85 to 88%, by weight, of H_3PO_4 .

Preparation—Phosphorus is converted to phosphorus pentoxide P_2O_5 by exposing it to a current of warm air, then the P_2O_5 is treated with water to form phosphoric acid. The conversion of the phosphorus to the pentoxide takes place while the phosphorus, distilling from the phosphorus manufacturing operation, is in the vapor state.

Description—Colorless, odorless liquid of a syrupy consistency; specific gravity about 1.71.

Solubility—Miscible with water or alcohol, with the evolution of heat.

Uses—To make the diluted acid and as a weak acid in various pharmaceutical preparations. Industrially, it is used in dental cements and in beverages as an acidulant.

Diluted Phosphoric Acid [Dilute Phosphoric Acid]—Contains, in each 100 mL, 9.5 to 10.5 g of H_3PO_4 (98.00). **Preparation**: Mix phosphoric acid (69 mL) and purified water (qs) to make 1000 mL. **Description and Solubility**: Clear, colorless, odorless liquid; specific gravity about 1.057. Miscible with water or alcohol. *Uses*: A *pharmaceutical necessity*. It also has been employed in *lead poisoning* and in other conditions in which it is desired to administer large amounts of phosphate and at the same time produce a mild acidosis. It has been given in the dosage of 60 mL a day (5 mL/hr) under carefully controlled conditions.

POTASSIUM METAPHOSPHATE

Metaphosphoric acid (HPO_3), potassium salt

Potassium metaphosphate [7790-53-6] KPO_3 (118.07); a straight-chain polyphosphate, having a high degree of polymerization; contains the equivalent of 59 to 61% P_2O_5 .

Preparation—By thermal dehydration of monopotassium phosphate (KH_2PO_4).

Description—White, odorless powder.

Solubility—Insoluble in water; soluble in dilute solutions of sodium salts.

Uses—*Pharmaceutic aid* (buffering agent).

MONOBASIC POTASSIUM PHOSPHATE

For the full monograph, see page 1264.

Comments—A component of various buffer solutions. Medicinally, it has been used as a urinary acidifier.

PUMICE

Pumex

A substance of volcanic origin, consisting chiefly of complex silicates of aluminum, potassium, and sodium.

Description—Very light, hard, rough, porous, grayish masses or a gritty, grayish powder of several grades of fineness; odorless, tasteless, and stable in the air.

Three powders are available:

Pumice Flour or Superfine Pumice—Not less than 97% passes through a No 200 standard mesh sieve.

Fine Pumice—Not less than 95% passes through a No 150 standard mesh sieve, and not more than 75% passes through a No 200 standard mesh sieve.

Coarse Pumice—Not less than 95% passes through a No 60 standard mesh sieve, and not more than 5% passes through a No 200 standard mesh sieve.

Solubility—Insoluble in water and is not attacked by acids or alkali hydroxide solutions.

Uses—A *filtering and distributing medium* for pharmaceutical preparations. Because of its grittiness the powdered form is used in certain types of soaps and cleaning powders and also as a *dental abrasive*.

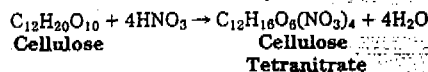
PYROXYLIN

Cellulose, nitrate; Soluble Guncotton

Pyroxylin [9004-70-0]; a product obtained by the action of a mixture of nitric and sulfuric acids on cotton, which consists chiefly of cellulose tetranitrate ($C_{12}H_{16}N_4O_{10}$).

Note—The commercially available form is moistened with about 30% of alcohol or other suitable solvent. The alcohol or solvent must be allowed to evaporate to yield the dried substance described in the *Pharmacopeia*.

Preparation—Shönbein, in 1846, found that nitric acid acts on cotton and produces a soluble compound. It subsequently was proved that this substance belongs to a series of closely related nitrates in which the nitric acid radical replaces the hydroxyl of the cellulose formula. This usually is indicated by taking the double empirical formula for cellulose $C_{12}H_{20}O_{10}$ and indicating replacement of four of the OH groups thus



The compound used in preparing collodion is a varying mixture of the di-, tri-, tetra-, and pentanitrates, but is mainly tetranitrate. The hexanitrate is the true explosive guncotton and is insoluble in ether, alcohol, acetone, or water.

Description—Light yellow, matted mass of filaments, resembling raw cotton in appearance but harsh to the touch; *exceedingly flammable*, burning, when unconfined, very rapidly and with a luminous flame; when kept in well-closed bottles and exposed to light, it is decomposed with the evolution of nitrous vapors, leaving a carbonaceous residue.

Solubility—Insoluble in water; dissolves slowly but completely in 25 parts of a mixture of 3 volumes of ether and 1 volume of alcohol; soluble in acetone or glacial acetic acid and precipitated from these solutions by water.

Uses—A *pharmaceutical necessity* for *Collodion*.

ROSIN

Resina; Colophony; Georgia Pine Rosin; Yellow Pine Rosin

A solid resin obtained from *Pinus palustris* Miller and from other species of *Pinus* Linné (Fam *Pinaceae*).

Constituents—American rosin contains *sylicic acid* [$C_{20}H_{30}O_2$], α -, β -, and γ -*abietic acids* [$C_{20}H_{30}O_2$], γ -*pinic acid* (from which α - and β -pinic acids are gradually formed), and *resene*. Some authorities also include *pimaric acid* [$C_{30}H_{50}O_2$] as a constituent. French rosin is called *galipot*.

Description—Sharply angular, translucent, amber-colored fragments, frequently covered with a yellow dust; fracture brittle at ordinary temperatures, shiny and shallow-conchoidal; odor and taste are slightly terebinthinate; easily fusible and burns with a dense, yellowish smoke, specific gravity 1.07 to 1.09.

Solubility—Insoluble in water; soluble in alcohol, ether, benzene, glacial acetic acid, chloroform, carbon disulfide, dilute solutions of sodium hydroxide and potassium hydroxide, or some volatile and fixed oils.

Uses—A *pharmaceutical necessity* for *Zinc-Eugenol Cement*. Formerly, and to some extent still, used as a component of plasters, cerates, and ointments, to which it adds adhesive qualities.

PURIFIED SILICEOUS EARTH

Purified Kieselguhr; Purified Infusorial Earth; Diatomaceous Earth; Diatomite

A form of silica [SiO_2] [7631-86-9] consisting of the frustules and fragments of diatoms, purified by boiling with acid, washing, and calcining.

Occurrence and Preparation—Large deposits of this substance are found in Virginia, Maryland, Nevada, Oregon, and California, usually in the form of masses of rocks, hundreds of feet in thickness. Under the microscope it is seen to consist largely of the minute siliceous frustules of diatoms. It must be purified carefully in a manner similar to that directed for *Talc* (page 1048) and thoroughly calcined. The latter treatment destroys the bacteria that are present in large quantities in the native earth.

Description—Very fine, white, light-gray or pale-buff mixture of amorphous powder and lesser amounts of crystalline polymorphs, including quartz and cristobalite; gritty, readily absorbs moisture and retains about four times its weight of water without becoming fluid.

Solubility—Insoluble in water, acids, or dilute solutions of alkali hydroxides.

Uses—Introduced into the USP as a *distributing and filtering medium* for aromatic waters; also suitable for filtration of elixirs. Like talc, it does not absorb active constituents.

COLLOIDAL SILICON DIOXIDE

Silica [7631-86-9] SiO_2 (60.08); a submicroscopic fumed silica prepared by the vapor-phase hydrolysis of a silicon compound.

Description—Light, white, nongritty powder of extremely fine particle size (about 15 nm).

Solubility—Insoluble in water or acids (except hydrofluoric); dissolved by hot solutions of alkali hydroxides.

Uses—A *tablet moisture adsorber, glidant*, and as a *suspending and thickening agent* in pharmaceutical preparations.

SODA LIME

A mixture of calcium hydroxide and sodium or potassium hydroxide or both.

It may contain an indicator that is inert toward anesthetic gases such as ether, cyclopropane, and nitrous oxide and that changes color when the soda lime no longer can absorb carbon dioxide.

Description—White or grayish white granules; if an indicator is added, it may have a color; absorbs carbon dioxide and water on exposure to air.

Uses—Neither a therapeutic nor a pharmaceutical agent. It is a reagent for the absorption of carbon dioxide in anesthesia machines, oxygen therapy, and metabolic tests. Because of the importance of the proper quality for these purposes it has been made official and standardized.

SODIUM BORATE

Sodium Tetraborate; Sodium Pyroborate; Sodium Baborate

Borax [1303-96-4] $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$ (381.37); *anhydrous* [1330-43-4] $\text{Na}_2\text{B}_4\text{O}_7$ (201.22).

Preparation—Found in immense quantities in California as a crystalline deposit. The earth, which is strongly impregnated with borax, is lixiviated; the solution is evaporated and crystallized.

Calcium borate, or *cotton balls*, also occurs in the borax deposits of California, and sodium borate is obtained from it by double decomposition with sodium carbonate.

Description—Colorless, transparent crystals, or a white, crystalline powder; odorless; the crystals often are coated with white powder because of efflorescence; solution alkaline to litmus and phenolphthalein; pH about 9.5.

Solubility—1 g in 16 mL water, 1 mL glycerin, or 1 mL boiling water; insoluble in alcohol.

Incompatibilities—Precipitates many *metals* as insoluble borates. In aqueous solution it is alkaline and precipitates *aluminum salts* as aluminum hydroxide, *iron salts* as a basic borate, and ferric hydroxide and *zinc sulfate* as zinc borate and a basic salt. *Alkaloids* are precipitated from solutions of their salts. Approximately equal weights of *glycerin* and boric acid react to produce a decidedly acid derivative generally called glyceroboric acid. Thus, the addition of glycerin to a mixture containing it overcomes incompatibilities arising from an alkaline reaction.

Uses—As a pharmaceutical necessity, it is used as an alkalinizing agent and as a buffer for alkaline solutions. Its alkalinizing properties provide the basis for its use in denture adhesives and its buffering action for its use in eyewash formulations.

SODIUM CARBONATE

Carbonic acid, disodium salt, monohydrate; Monohydrated Sodium Carbonate USP XV

Disodium carbonate monohydrate [5968-11-6] $\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}$ (124.00); *anhydrous* [497-19-8] (105.99).

Preparation—The initial process for its manufacture was devised by Leblanc, a French apothecary, in 1784, and consists of two steps: first, the conversion of common salt [NaCl] into sodium sulfate by heating it with sulfuric acid and, second, the decomposition of the sulfate by calcium carbonate (limestone) and charcoal (coal) at a high temperature to yield this salt and calcium sulfide. The carbonate then is leached out with water.

It currently is prepared by the electrolysis of sodium chloride, whereby sodium and chlorine are produced, the former reacting with water to produce sodium hydroxide and this solution treated with carbon dioxide to produce the salt. The process is used most extensively in localities where electric power is very cheap.

The monohydrated form is made by crystallizing a concentrated solution of this salt at a temperature above 35° (95°F) and stirring the liquid so as to produce small crystals. It contains about 15% water of crystallization.

Soda ash is a term designating a commercial quality of the anhydrous salt. Its annual production is very large, and it has a wide variety of applications, among which are the manufacture of glass, soap, and sodium salts; it also is used for washing fabrics.

Washing soda, or *sal soda*, is the salt with 10 molecules of water. It is in the form of colorless crystals that rapidly effloresce in the air.

Description—Colorless crystals or a white, crystalline powder, stable in air under ordinary conditions; when exposed to dry air above 50° it effloresces, and at 100° it becomes anhydrous; decomposed by weak acids, forming the salt of the acid and liberating carbon dioxide; aqueous solution alkaline to indicators (pH about 11.5).

Solubility—1 g in 3 mL water or 1.8 mL boiling water; insoluble in alcohol.

Incompatibilities—*Acids, acid salts, and acidic preparations* cause its decomposition. Most *metals* are precipitated as carbonates, hydroxides, or basic salts. *Alkaloids* are precipitated from solutions of their salts.

Uses—Occasionally, for dermatitis topically as a lotion; it has been used as a mouthwash and a vaginal douche. It is used in the preparation of the sodium salts of many acids. The USP recognizes it as a pharmaceutical aid used as an alkalinizing agent.

SODIUM HYDROXIDE

Caustic Soda; Soda Lye

Sodium hydroxide [1310-73-2] NaOH (40.00); includes not more than 3% Na_2CO_3 (105.99).

Caution—Exercise great care in handling it, as it rapidly destroys tissues.

Preparation—By treating sodium carbonate with milk of lime or by the electrolysis of a solution of sodium chloride as explained under *Potassium Hydroxide* (page 1211). It now is produced largely by the latter process. See also *Sodium Carbonate*, above.

Description—White, or nearly white, fused masses, small pellets, flakes, sticks, and other forms; hard and brittle and shows a crystalline fracture; exposed to the air, it rapidly absorbs carbon dioxide and moisture; melts at about 318°; specific gravity 2.13; when dissolved in water or alcohol or when its solution is treated with an acid, much heat is generated; aqueous solutions, even when highly diluted, are strongly alkaline.

Solubility—1 g in 1 mL water; freely soluble in alcohol or glycerin.

Incompatibilities—Exposed to air, it absorbs carbon dioxide and is converted to sodium carbonate. With *fats* and *fatty acids* it forms soluble soaps; with *resins* it forms insoluble soaps. See *Potassium Hydroxide* (page 1211).

Uses—Too alkaline to be of medicinal value but occasionally used in veterinary practice as a caustic. It is used extensively in pharmaceutical processes as an alkalinizing agent and is generally preferred to potassium hydroxide because it is less deliquescent and less expensive; in addition, less of it is required, since 40 parts of it are equivalent to 56 parts of KOH. It is a pharmaceutical necessity in the preparation of *Glycerin Suppositories*.

SODIUM STEARATE

Octadecanoic acid, sodium salt

Sodium stearate [822-16-2] $\text{C}_{18}\text{H}_{35}\text{NaO}_2$ (306.47) consists chiefly of sodium stearate and sodium palmitate $\text{C}_{16}\text{H}_{31}\text{NaO}_2$ = 278.41).

Preparation—Stearic acid is reacted with an equimolar portion of NaOH.

Description—Fine, white powder, soapy to the touch; usually has a slight, tallow-like odor; affected by light; solutions are alkaline to phenolphthalein TS.

Solubility—Slowly soluble in cold water or cold alcohol; readily soluble in hot water or hot alcohol.

Uses—Officially, a pharmaceutical aid used as an emulsifying and stiffening agent. It is an ingredient of glycerin suppositories. In dermatological practice it has been used topically in sycosis and other skin diseases.

STARCH

Corn Starch; Wheat Starch; Potato Starch

Starch [9005-25-8] consists of the granules separated from the mature grain of corn *Zea mays* Linné (Fam Gramineae) or of wheat *Triticum aestivum* Linné (Fam Gramineae) or from tubers of the potato *Solanum tuberosum* Linné (Fam Solanaceae).

Preparation—In making starch from corn, the germ is separated mechanically, and the cells softened to permit escape of the starch granules. This generally is done by permitting it to become sour and decomposed, stopping the fermentation before the starch is affected. On the small scale, it may be made from wheat flour by making a stiff ball of dough and kneading it while a small stream of water trickles upon it. It is carried off with the water, while the *gluten* remains as a soft, elastic mass; the latter may be purified and used for various purposes to which gluten is applicable. Commercially, its quality largely depends on the purity of the water used in its manufacture. It may be made from potatoes by first grating them, and then washing the soft mass upon a