Handbook of Pharmaceutical Excipients

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Handbook of Pharmaceutical Excipients

FIFTH EDITION

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Sucralose

1 Nonproprietary Names

USPNF: Sucralose

2 Synonyms

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

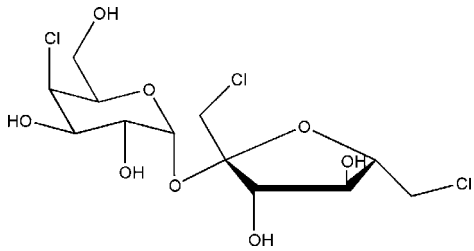
3 Chemical Name and CAS Registry Number

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/cm^3
Density (tapped): 0.62 g/cm^3
Density (true): 1.63 g/cm^3
Melting point: 130°C (for anhydrous crystalline form); 36.5°C (for pentahydrate).
Particle size distribution: 90% < 12 μm in size.
Partition coefficient: $\log_{10} P$ = —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.

14 Safety

Sucralose is generally regarded as a nontoxic and nonirritant material and is approved, in a number of countries, for use in food products. Following oral consumption, sucralose is mainly unabsorbed and is excreted in the feces.[1–3]

The WHO has set an acceptable daily intake for sucralose of up to 15 mg/kg body-weight.[4]

LD_{50} (mouse, oral): > 16 g/kg
LD_{50} (rat, oral): > 10 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

The FDA, in April 1998, approved sucralose for use as a tabletop sweetener and as an additive in a variety of food products. In the UK, sucralose was authorized for use in food products on a 2-year temporary basis in March 2002.[5] It is also accepted for use in many other countries worldwide. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Sucrose.

18 Comments

The sweetening effect of sucralose is not reduced by heating and food products containing sucralose may be subjected to high-temperature processes such as pasteurization, sterilization, UHT processing and baking. Sucralose is often blended with maltodextrin or dextrose as bulking agents in its granular form.

A specification for sucralose is contained in the Food Chemicals Codex (FCC).

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21 Authors

BA Langdon, MP Mullarney.

22 Date of Revision

26 August 2005.

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.

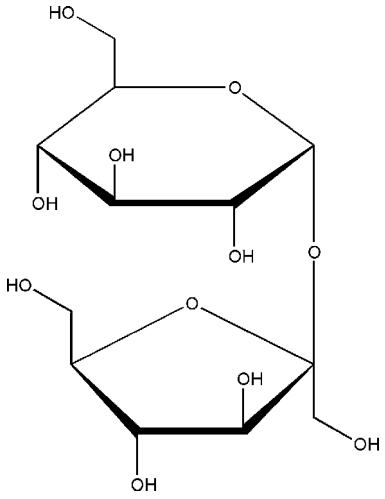
3 Chemical Name and CAS Registry Number

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/cm^3 (crystalline sucrose);
0.60 g/cm^3 (powdered sucrose).
Density (tapped):
1.03 g/cm^3 (crystalline sucrose);
0.82 g/cm^3 (powdered sucrose).
Density (true): 1.6 g/cm^3
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.

Table II: Pharmacopeial specifications for sucrose.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
Acidity or alkalinity	+	+	—
Specific optical rotation	+66.3° to +67.0°	+66.3° to +67.0°	⩾+65.9°
Color value	—	⩽45	—
Conductivity	+	+	—
Loss on drying	⩽0.1%	⩽0.1%	—
Bacterial endotoxins[a]	⩽0.25 IU/mg	⩽0.25 IU/mg	—
Dextrins[a]	+	+	—
Reducing sugars	—	+	—
Invert sugar	+	—	+
Chloride	—	—	⩽0.0035%
Sulfate	—	—	⩽0.006%
Sulfites	⩽15 ppm	⩽10 ppm	—
Calcium	—	—	⩽5 ppm
Heavy metals	—	—	⩽5 ppm
Lead	⩽0.5 ppm	⩽0.5 ppm	—
Residue on ignition	—	—	⩽0.05%
Organic volatile impurities	—	—	+

[a] If sucrose is to be used in large volume infusions.

Refractive index: n_D^{25} = 1.34783 (10% w/v aqueous solution)
Solubility: *see* Table III.
Specific gravity: *see* Table IV.

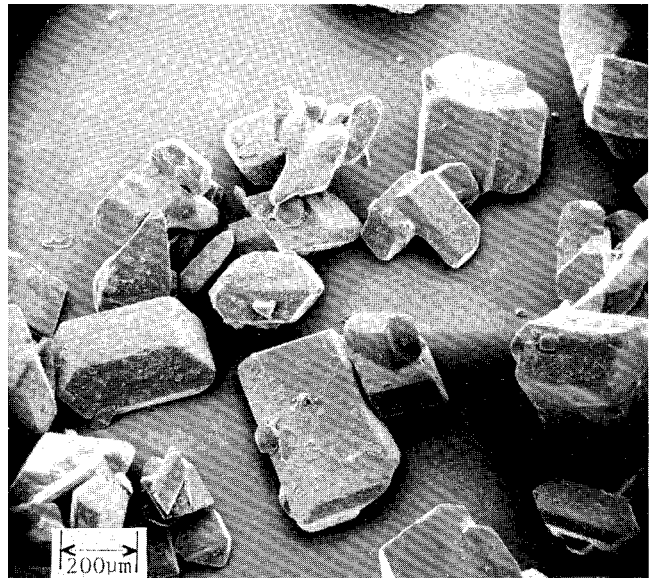
Table III: Solubility of sucrose.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Practically insoluble
Ethanol	1 in 400
Ethanol (95%)	1 in 170
Propan-2-ol	1 in 400
Water	1 in 0.5 1 in 0.2 at 100°C

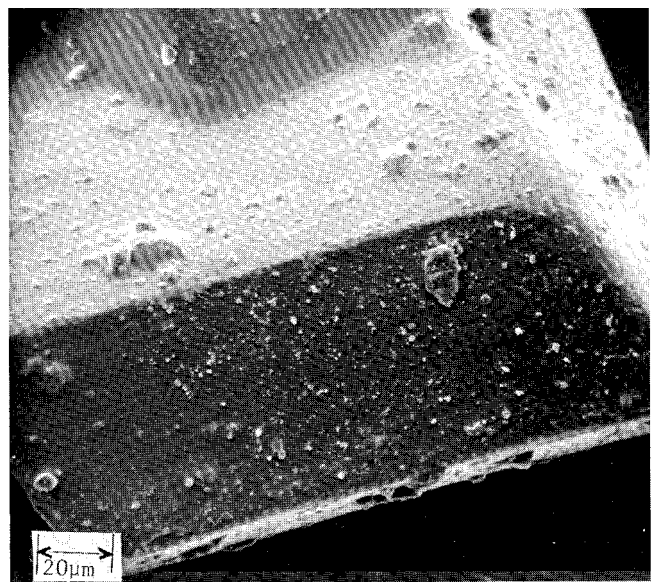
Table IV: Specific gravity of aqueous sucrose solutions.

Concentration of aqueous sucrose solution (% w/w)	Specific gravity at 20°C
2	1.0060
6	1.0219
10	1.0381
20	1.0810
30	1.1270
40	1.1764
50	1.2296
60	1.2865
70	1.3471
76	1.3854

SEM: 1
Excipient: Sucrose
Manufacturer: Great Western Sugar Co.
Lot No.: 1-2-80
Magnification: 60×
Voltage: 10 kV



SEM: 2
Excipient: Sucrose
Manufacturer: Great Western Sugar Co.
Lot No.: 1-2-80
Magnification: 600×
Voltage: 10 kV



11 Stability and Storage Conditions

Sucrose has good stability at room temperature and at moderate relative humidity. It absorbs up to 1% moisture, which is released upon heating at 90°C. Sucrose caramelizes when heated to temperatures above 160°C. Dilute sucrose solutions are liable to fermentation by microorganisms but resist decomposition at higher concentrations, e.g., above 60%

w/w concentration. Aqueous solutions may be sterilized by autoclaving or filtration.

When sucrose is used as a base for medicated confectionery, the cooking process, at temperatures rising from 110 to 145°C, causes some inversion to form dextrose and fructose (invert sugar). The fructose imparts stickiness to confectionery but prevents cloudiness due to graining. Inversion is accelerated particularly at temperatures above 130°C and by the presence of acids.

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

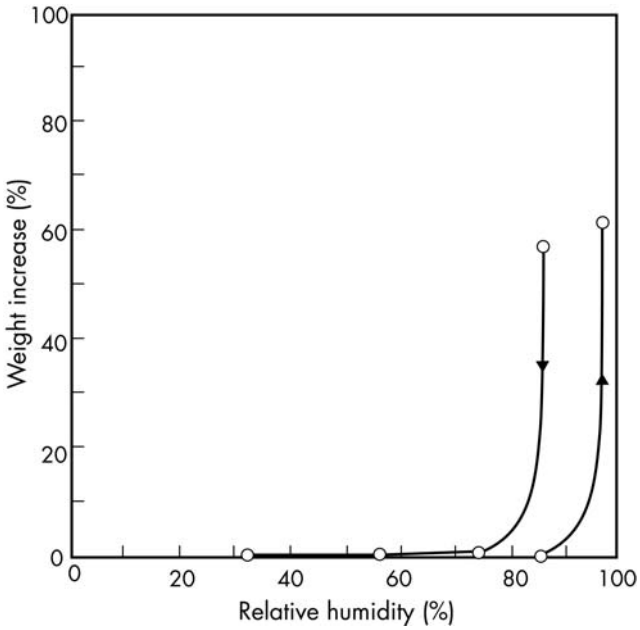


Figure 1: Moisture sorption–desorption isotherm of powdered sucrose.
Samples dried initially at 60°C over silica gel for 24 hours. Note: at 90% relative humidity, sufficient water was absorbed to cause dissolution of the solid.

12 Incompatibilities

Powdered sucrose may be contaminated with traces of heavy metals, which can lead to incompatibility with active ingredients, e.g. ascorbic acid. Sucrose may also be contaminated with sulfite from the refining process. With high sulfite content, color changes can occur in sugar-coated tablets; for certain colors used in sugar-coating the maximum limit for sulfite content, calculated as sulfur, is 1 ppm. In the presence of dilute or concentrated acids, sucrose is hydrolyzed or inverted to dextrose and fructose (invert sugar). Sucrose may attack aluminum closures.[10]

13 Method of Manufacture

Sucrose is obtained from the sugar cane plant, which contains 15–20% sucrose, and sugar beet, which contains 10–17% sucrose. Juice from these sources is heated to coagulate water-soluble proteins, which are removed by skimming. The resultant solution is then decolorized with an ion-exchange resin or charcoal and concentrated. Upon cooling, sucrose crystallizes out. The remaining solution is concentrated again and yields more sucrose, brown sugar, and molasses.

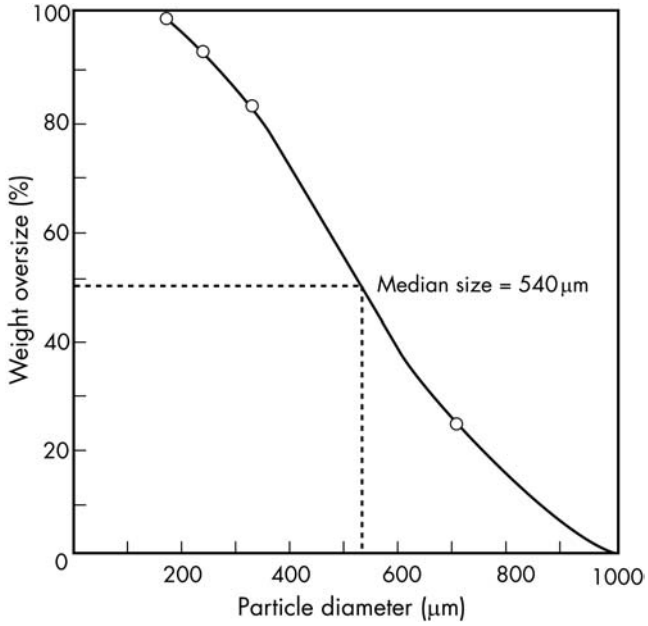


Figure 2: Particle size distribution of crystalline sucrose.

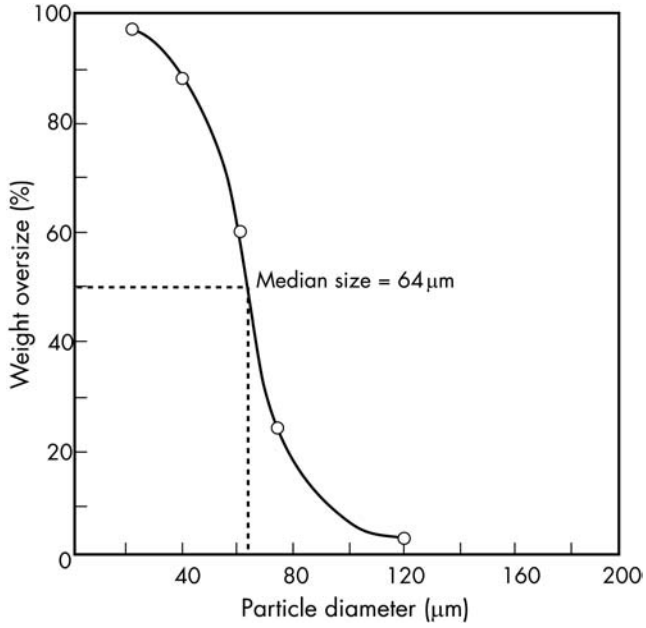


Figure 3: Particle size distribution of powdered sucrose.

14 Safety

Sucrose is hydrolyzed in the small intestine by the enzyme sucrase to yield dextrose and fructose, which are then absorbed. When administered intravenously, sucrose is excreted unchanged in the urine.

Although sucrose is very widely used in foods and pharmaceutical formulations, sucrose consumption is a cause of concern and should be monitored in patients with diabetes mellitus or other metabolic sugar intolerance.[11]

Sucrose is also considered to be more cariogenic than other carbohydrates since it is more easily converted to dental plaque.

For this reason, its use in oral pharmaceutical formulations is declining.

Although sucrose has been associated with obesity, renal damage, and a number of other diseases, conclusive evidence linking sucrose intake with some diseases could not be established.[12,13] It was, however, recommended that sucrose intake in the diet should be reduced.[13]

LD_{50} (mouse, IP): 14 g/kg[14]
LD_{50} (rat, oral): 29.7 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. In the UK, the occupational exposure limit for sucrose is 10 mg/m^3 long-term (8-hour TWA) and 20 mg/m^3 short-term.[15]

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (injections; oral capsules, solutions, syrups, and tablets; topical preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Compressible sugar; confectioner's sugar; invert sugar; sugar spheres.

Invert sugar

Empirical formula: $C_6H_{12}O_6$
Molecular weight: 180.16
CAS number: [8013-17-0]
Comments: an equimolecular mixture of dextrose and fructose prepared by the hydrolysis of sucrose with a suitable mineral acid such as hydrochloric acid. Invert sugar may be used as a stabilizing agent to help prevent crystallization of sucrose syrups and graining in confectionery. A 10% aqueous solution is also used in parenteral nutrition.

18 Comments

For typical boiling points of sucrose syrups, without inversion of the sugar, *see* Table V. A specification for sucrose is contained in the Food Chemicals Codex (FCC).

The EINECS number for sucrose is 200-334-9.

Table V: Boiling points of sucrose syrups.

Sucrose concentration (% w/v)	Boiling point (°C)
50	101.5
60	103
64	104
72	105.5
75	107
77.5	108.5
80	110.5

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21 Authors

NA Armstrong.

22 Date of Revision

17 August 2005.

Sugar, Compressible

1 Nonproprietary Names

USPNF: Compressible sugar

2 Synonyms

Di-Pac; direct compacting sucrose.

3 Chemical name and CAS Registry Number

See Sections 4 and 18.

4 Empirical Formula and Molecular Weight

The USPNF 23 states that compressible sugar contains not less than 95.0% and not more than 98.0% of sucrose ($C_{12}H_{22}O_{11}$). It may contain starch, maltodextrin, or invert sugar, and may contain a suitable lubricant.

5 Structural Formula

See Section 4.

6 Functional Category

Sweetening agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Compressible sugar is used primarily in the preparation of direct-compression chewable tablets. Its tableting properties can be influenced by small changes in moisture level;[1,2] *see* Table I.

Table I: Uses of compressible sugar.

Use	Concentration (%)
Dry binder in tablet formulations	5–20
Filler in chewable tablets	20–60
Filler in tablets	20–60
Sweetener in chewable tablets	10–50

8 Description

Compressible sugar is a sweet-tasting, white, crystalline powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for compressible sugar.

Test	USPNF 23
Identification	+
Calcium	+
Chloride	⩽0.014%
Heavy metals	⩽5 ppm
Loss on drying	0.25–1.0%
Residue on ignition	⩽0.1%
Microbial limits	+
Organic volatile impurities	+
Sulfate	⩽0.010%
Assay	95.0–98.0%

10 Typical Properties

Density (bulk): 0.492 g/cm^3
Density (tapped): 0.6 g/cm^3
Moisture content: 0.57%
Particle size distribution: for *Di-Pac*, 3% maximum retained on a #40 (425 μm) mesh; 75% minimum through a #100 (150 μm) mesh; 5% maximum through #200 (75 μm) mesh.
Solubility: the sucrose portion is water-soluble.
Specific surface area: 0.13–0.14 m^2/g

11 Stability and Storage Conditions

Compressible sugar is stable in air under normal storage conditions of room temperature and low relative humidity. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with dilute acids, which cause hydrolysis of sucrose to invert sugar, and with alkaline earth hydroxides, which react with sucrose to form sucrates.

13 Method of Manufacture

Compressible sugar is prepared by cocrystallization of sucrose with other excipients such as maltodextrin.[1] Compressible sugar may also be prepared using a dry granulation process.

14 Safety

Compressible sugar is generally regarded as a relatively nontoxic and nonirritant material. *See also* Sucrose.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. *See also* Sucrose.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Confectioner's sugar; sucrose; sugar spheres; *Sugartab*.

Sugartab

Appearance: *Sugartab* (JRS Pharma LC) is a compressible sugar that does not conform to the USPNF 23 specification. It is an agglomerated sugar product containing approximately 90–93% sucrose, the balance being invert sugar.
Density (bulk): 0.60 g/cm^3
Density (tapped): 0.69 g/cm^3
EINECS number: [64333-34-2]
Flowability: 42.7 g/s
Moisture content: 0.20–0.57%.
Particle size distribution: 30% through a #20 (850 μm) mesh; 3% through a #30 (600 μm) mesh.

18 Comments

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19 Specific References

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2 Tabibi SE, Hollenbeck RG. Interaction of water vapor and compressible sugar. *Int J Pharm* 1984; **18**: 169–183.

20 General References

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Mendes RW, Gupta MR, Katz IA, O'Neil JA. Nu-tab as a chewable direct compression carrier. *Drug Cosmet Ind* 1974; **115**(6): 42–46, 130–133.
Ondari CO, Kean CE, Rhodes CT. Comparative evaluation of several direct compression sugars. *Drug Dev Ind Pharm* 1983; **9**: 1555–1572.
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21 Authors

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22 Date of Revision

17 August 2005.