Handbook of Pharmaceutical Excipients

FOURTH EDITION

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Publisher – Science and Practice

Royal Pharmaceutical Society of Great Britain

London, UK

London • Chicago

Pharmaceutical Press

APhA

American Pharmaceutical Association

Published by the Pharmaceutical Press
Publications division of the Royal Pharmaceutical Society of Great Britain

1 Lambeth High Street, London SE1 7JN, UK
100 South Atkinson Road, Suite 206, Grayslake, IL 60030-7820, USA

and the American Pharmaceutical Association
2215 Constitution Avenue NW, Washington, DC 20037-2985, USA

First edition published 1986
Second edition published 1994
Third edition published 2000
Fourth edition published 2003

Text design by Barker Hilsdon, Lyme Regis
Typeset by Bibliocraft Ltd, Dundee
Printed in Great Britain by The Bath Press, Bath

ISBN 0 85369 472 9 (UK)
ISBN 1 58212 022 6 (USA)

A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
Handbook of pharmaceutical excipients.– 4th ed. / edited by Raymond C. Rowe, Paul J. Sheskey, Paul J. Weller.
p. ; cm.
Includes bibliographical references and index.
ISBN 1-58212-022-6 (alk. paper) – ISBN 0-85369-472-9 (alk. paper)
1. Excipients–Handbooks, manuals, etc.
[DNLM: 1. Excipients–Handbooks. QV 735 H236 2003] I. Rowe, Raymond C. II. Sheskey, Paul J. III. Weller, Paul J.

RS201.E87H36 2003
615'.19–dc21

2003002641

Crospovidone

1 Nonproprietary Names

BP: Crospovidone
PhEur: Crospovidonum
USPNF: Crospovidone

2 Synonyms

Crosslinked povidone; E1202; *Kollidon CL*; *Kollidon CL-M*; *Polyplasdone XL*; *Polyplasdone XL-10*; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

3 Chemical Name and CAS Registry Number

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

4 Empirical Formula Molecular Weight

$(C_6H_9NO)_n$ >1 000 000

Crospovidone is a water-insoluble synthetic crosslinked homopolymer of *N*-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

5 Structural Formula

See Povidone.

6 Functional Category

Tablet disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods.[1–4] It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets.[5] Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

8 Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for crospovidone.

Test	PhEur 2002	USPNF 20 (Suppl 1)
Identification	+	+
Characters	+	—
pH (1% suspension)	—	5.0–8.0
Water	—	≤5.0%
Residue on ignition	≤0.1%	≤0.4%
Water-soluble substances	≤1.0%	≤1.5%
Peroxides	≤400 ppm	—
Heavy metals	≤10 ppm	≤0.001%
Vinylpyrrolidinone	—	≤0.1%
Loss on drying	≤5.0%	—
Nitrogen content (anhydrous basis)	11.0–12.8%	11.0–12.8%

10 Typical Properties

Acidity/alkalinity: pH = 5.0–8.0 (1% w/v aqueous slurry)
Density: 1.22 g/cm^3
Density (bulk): *see* Table II.
Density (tapped): *see* Table II.

Table II: Density values of commercial grades of crospovidone.

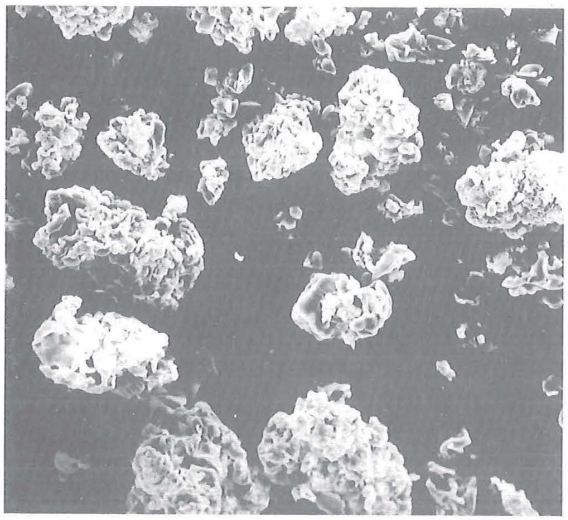
Commercial grade	Density (bulk) g/cm^3	Density (tapped) g/cm^3
Kollidon CL	0.3–0.4	0.4–0.5
Kollidon CL-M	0.15–0.25	0.3–0.5
Polyplasdone XL	0.213	0.273
Polyplasdone XL-10	0.323	0.461

Moisture content: maximum moisture sorption is approximately 60%.
Particle size distribution: less than 400 µm for *Polyplasdone XL*; less than 74 µm for *Polyplasdone XL-10*. Approximately 50% greater than 50 µm and maximum of 3% greater than 250 µm in size for *Kollidon CL*. Minimum of 90% of particles are below 15 µm for *Kollidon CL-M*.
Solubility: practically insoluble in water and most common organic solvents.
Specific surface area: *see* Table III.

Table III: Specific surface areas for commercial grades of crospovidone.

Commercial grade	Surface area (m^2/g)
Kollidon CL	1.0
Kollidon CL-M	3.0–6.0
Polyplasdone XL	0.6–0.8
Polyplasdone XL-10	1.2–1.4

SEM 1
Excipient: Crospovidone (*Polyplasdone XL-10*)
Manufacturer: ISP Corp.
Lot No.: S81031
Magnification: 400×
Voltage: 10 kV



11 Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials; *see* Povidone.

13 Method of Manufacture

Acetylene and formaldehyde are reacted in the presence of a highly active catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer vinylpyrrolidone is then polymerized in solution, using a catalyst. Crospovidone is prepared by a 'popcorn polymerization' process.

14 Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone.[6] However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.[6]

LD_{50} (mouse, IP): 12 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets; topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Povidone.

18 Comments

Crospovidone has been studied as a superdisintegrant. The ability of the compound to swell has been examined directly using scanning electron microscopy.[7] The impact of crospovidone on percolation has also been examined.[8] The impact of crospovidone on dissolution of poorly soluble drugs in tablets has also been investigated.[9]

19 Specific References

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21 Authors

X He, AH Kibbe.

22 Date of Revision

25 October 2002.

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 Molecular Weight

$(C_6H_9NO)_n$ 2500–3 000 000

The USP 25 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, ranging from 10 to 120. The *K*-value is calculated using Fikentscher's equation:[1]

$$\log z = c\left(\frac{75k^2}{1+1.5kc}\right)+k$$

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

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

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

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

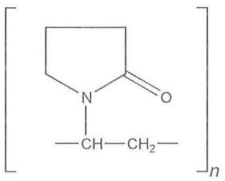
Approximate molecular weights for different povidone grades are shown in Table I.

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

K-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.

Table III: Pharmacopeial specifications for povidone.

Test	JP 2001	PhEur 2002 (Suppl 4.3)	USP 25
Identification	+	+	+
Characters	—	+	—
pH	—	—	3.0–7.0
$K \leqslant 30$	3.0–5.0	3.0–5.0	—
$K > 30$	4.0–7.0	4.0–7.0	—
Appearance of solution	+	+	—
Viscosity	—	+	—
Water	⩽5.0%	⩽5.0%	⩽5.0%
Residue on ignition	⩽0.1%	⩽0.1%	⩽0.1%
Lead	—	—	⩽10 ppm
Aldehydes	⩽500 ppm[a]	⩽500 ppm[a]	⩽0.05%
Hydrazine	⩽1 ppm	⩽1 ppm	⩽1 ppm
Vinylpyrrolidinone	⩽10 ppm	⩽10 ppm	⩽0.2%
Peroxides	⩽400 ppm[b]	⩽400 ppm[b]	—
K-value	25–90	—	10–120
⩽15	90.0–108.0%	85.0–115.0%	85.0–115.0%
>15	90.0–108.0%	90.0–108.0%	90.0–108.0%
Heavy metals	⩽10 ppm	⩽10 ppm	—
Assay (nitrogen content)	11.5–12.8%	11.5–12.8%	11.5–12.8%

[a] Expressed as acetaldehyde.

[b] Expressed as hydrogen peroxide.

10 Typical Properties

Acidity/alkalinity: pH = 3.0–7.0 (5% w/v aqueous solution).
Density (bulk): 0.29–0.39 g/cm^3 for *Plasdone*.
Density (tapped): 0.39–0.54 g/cm^3 for *Plasdone*.
Density (true): 1.180 g/cm^3
Flowability:
20 g/s for povidone K-15
16 g/s for povidone K-29/32
Melting point: softens at 150°C.
Moisture content: povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities. *See* Figures 1 and 2.

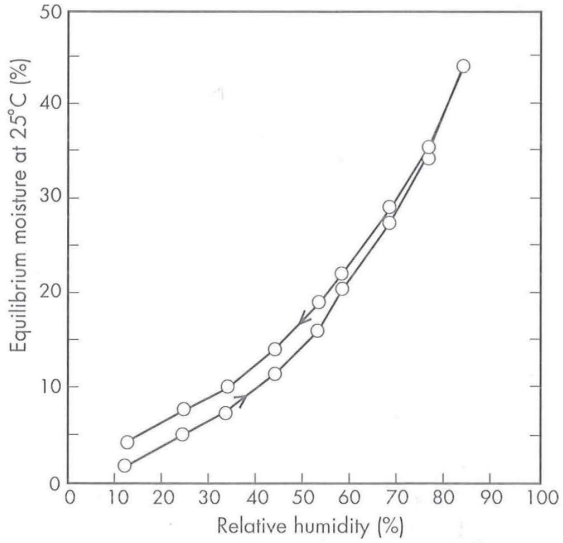


Figure 1: Sorption–desorption isotherm of povidone K-15 (*Plasdone K-15*).

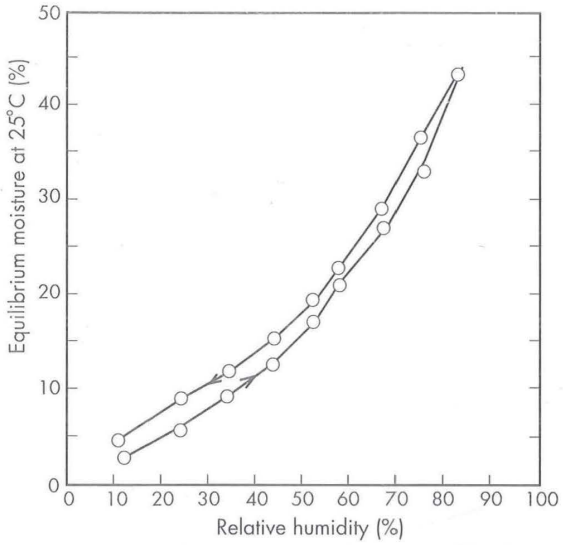


Figure 2: Sorption–desorption isotherm of povidone K-29/32 (*Plasdone K-29/32*).

Particle size distribution:
Kollidon 25/30: 90% >50 µm, 50% >100 µm, 5% >200 µm
Kollidon 90: 90% >200 µm, 95% >250 µm[7]
Solubility: freely soluble in acids, chloroform, ethanol, ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the *K*-value.
Viscosity (dynamic): the viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed. *See* Tables IV and V.[7]

Table IV: Dynamic viscosity of 10% w/v aqueous povidone (*Kollidon*) solutions at 20°C.[7]

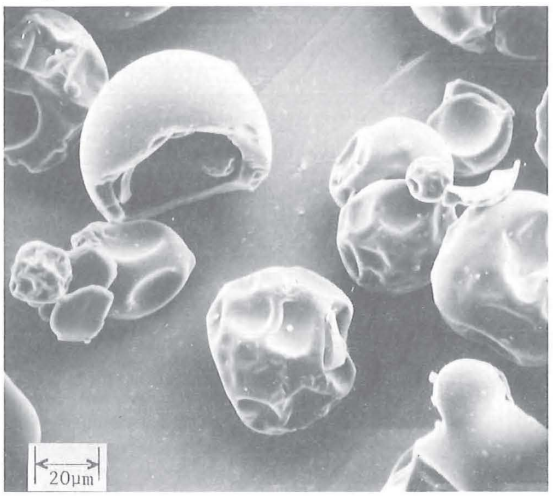
Grade	Dynamic viscosity (mPa s)
K-11/14	1.3–2.3
K-16/18	1.5–3.5
K-24/27	3.5–5.5
K-28/32	5.5–8.5
K-85/95	300–700

Table V: Dynamic viscosity of 5% w/v povidone (*Kollidon*) solutions in ethanol and propan-2-ol at 25°C.[7]

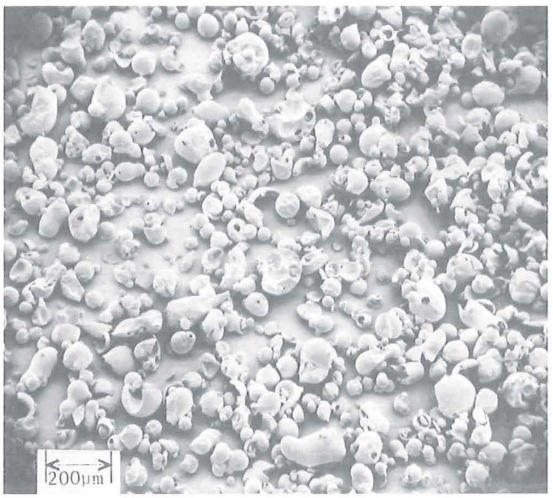
Grade	Dynamic viscosity (mPa s)	
	Ethanol	Propan-2-ol
K-12PF	1.4	2.7
K-17PF	1.9	3.1
K-25	2.7	4.7
K-30	3.4	5.8
K-90	53.0	90.0

SEM: 1
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 60×
Voltage: 5 kV

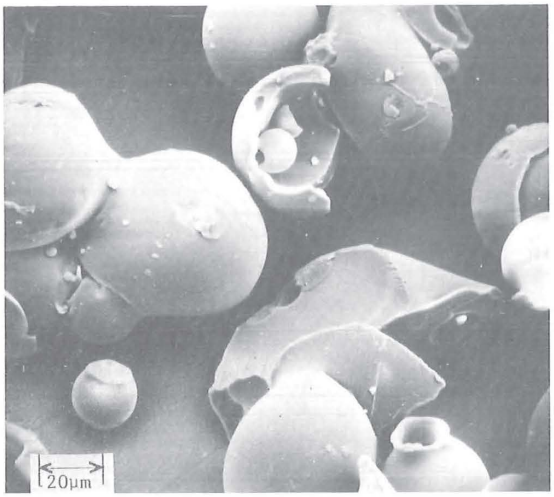
SEM: 2
Excipient: Povidone K-15 (*Plasdone K-15*)
Manufacturer: ISP
Lot No.: 82A-1
Magnification: 600×
Voltage: 5 kV



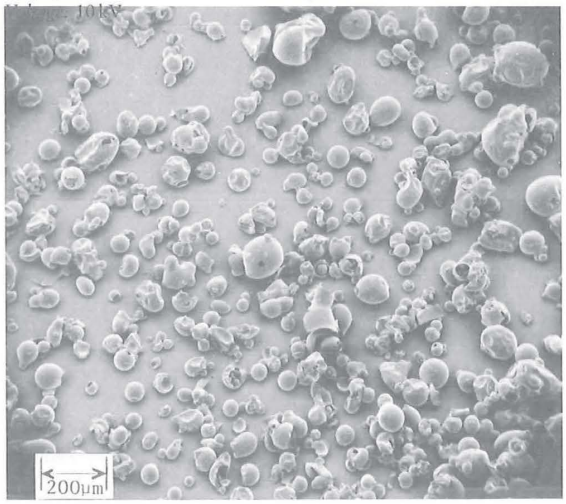
SEM: 3
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 60×
Voltage: 5 kV



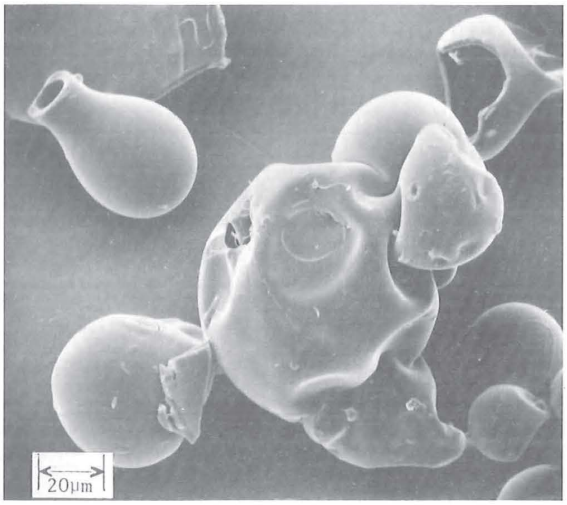
SEM: 4
Excipient: Povidone K-26/28 (*Plasdone K-26/28*)
Manufacturer: ISP
Lot No.: 82A-2
Magnification: 600×
Voltage: 10 kV



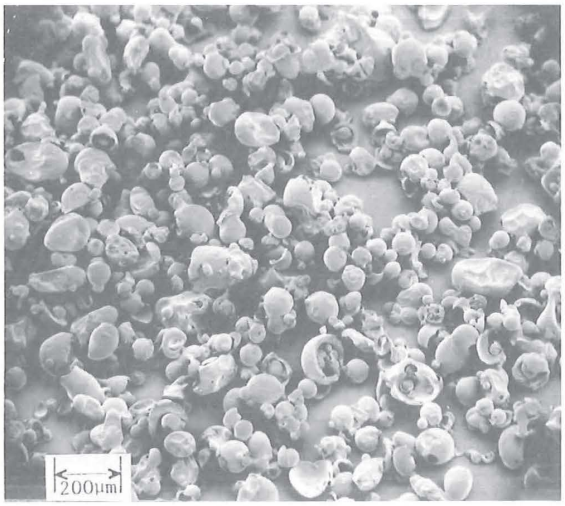
SEM: 5
Excipient: Povidone K-30 (*Plasdone K-30*)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 60×
Voltage: 10 kV



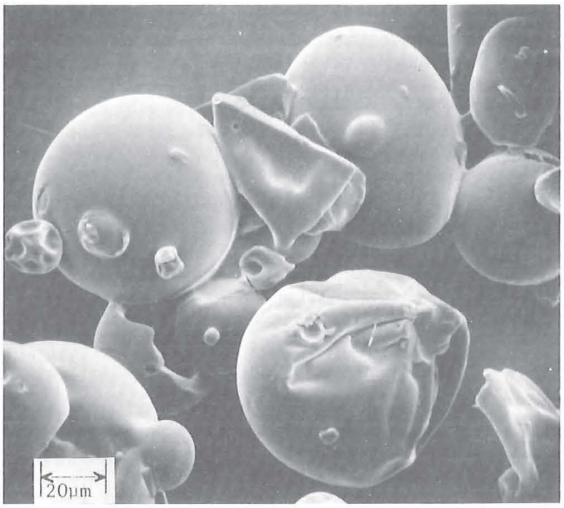
SEM: 6
Excipient: Povidone K-30 (*Plasdone K-30*)
Manufacturer: ISP
Lot No.: 82A-4
Magnification: 600×
Voltage: 10 kV



SEM: 7
Excipient: Povidone K-29/32 (*Plasdone K-29/32*)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 60×
Voltage: 5 kV



SEM: 8
Excipient: Povidone K-29/32 (*Plasdone K-29/32*)
Manufacturer: ISP
Lot No.: 82A-3
Magnification: 600×
Voltage: 10 kV



11 Stability and Storage Conditions

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous

solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds; *see* Section 18. The efficacy of some preservatives, e.g., thimerosal, may be adversely affected by the formation of complexes with povidone.

13 Method of Manufacture

Povidone is manufactured by the Reppe process. Acetylene and formaldehyde are reacted in the presence of a highly active copper acetylide catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer, vinylpyrrolidone, is then polymerized in the presence of a combination of catalysts to produce povidone.

14 Safety

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.[8]

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.[8] Povidone additionally has no irritant effect on the skin and causes no sensitization.

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone.[9] Evidence also exists that povidone may accumulate in the organs of the body following intramuscular injection.[10]

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.[11]

LD_{50} (mouse, IP): 12 g/kg[12]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Crospovidone.

18 Comments

The molecular adduct formation properties of povidone may be used advantageously in solutions, slow-release solid-dosage forms, and parenteral formulations. Perhaps the best-known example of povidone complex formation is povidone–iodine, which is used as a topical disinfectant.

For accurate standardization of solutions, the water content of the solid povidone must be determined before use and taken into account for any calculations.

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21 Author

AH Kibbe.

22 Date of Revision

30 October 2002.

Starch

1 Nonproprietary Names

BP: Maize starch
Potato starch
Rice starch
Tapioca starch
Wheat starch

JP: Corn starch
Potato starch
Rice starch
Wheat starch

PhEur: Maydis amylum (maize starch)
Solani amylum (potato starch)
Oryzae amylum (rice starch)
Tritici amylum (wheat starch)

USPNF: Starch

Note that the USPNF 20 describes starch, in a single monograph, as being obtained from either the mature grain of corn, *Zea mays*, or of wheat, *Triticum aestivum*, or from tubers of the potato, *Solanum tuberosum*, or of tapioca, *Manihot utilissima*. The PhEur 2002 has individual monographs for each of these starches, except for tapioca starch, along with an additional monograph for rice starch, *Oryza sativa*. The BP 2001 similarly describes maize, potato, rice, tapioca (cassava), and wheat starch in individual monographs, tapioca starch being obtained from the rhizomes of *Manihot utilissima* Pohl. The JP 2001 similarly describes corn (maize), rice, potato and wheat starch in separate monographs. *See also* Section 18.

2 Synonyms

Amido; amidon; amilo; amylum; *Aytex P*; *Fluftex W*; *Instant Pure-Cote*; *Melojel*; *Meritena*; *Paygel 55*; *Perfectamyl D6PH*; *Pure-Bind*; *Pure-Cote*; *Pure-Dent*; *Pure-Gel*; *Pure-Set*; *Purity 21*; *Purity 826*; *Tablet White*.

See also Sections 1 and 18.

3 Chemical Name and CAS Registry Number

Starch [9005-25-8]

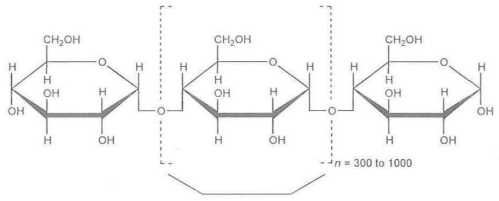
4 Empirical Formula and Molecular Weight

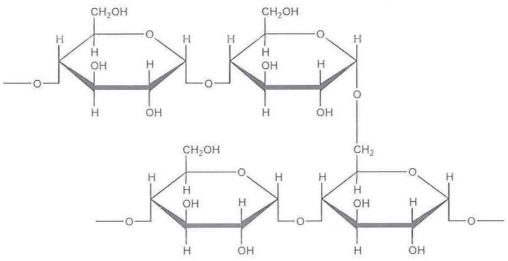
$(C_6H_{10}O_5)_n$ 50 000–160 000

where n = 300–1000.

Starch consists of amylose and amylopectin, two polysaccharides based on α-glucose. *See also* Sections 5 and 17.

5 Structural Formula





6 Functional Category

Glidant; tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Starch is used as an excipient primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix.[1]

In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–15% w/w.[2–9] However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. In

granulated formulations, about half the total starch content is included in the granulation mixture and the balance as part of the final blend with the dried granulation. Also starch when used as a disintegrant exhibits type II isotherms and has a high specific surface for water sorption.[10]

Starch has been investigated as an excipient in novel drug delivery systems for nasal,[11] oral,[12,13] peridontal,[14] and other site-specific delivery systems.[15]

Starch is also used in topical preparations; for example, it is widely used in dusting powders for its absorbency, and is used as a protective covering in ointment formulations applied to the skin. Starch mucilage has also been applied to the skin as an emollient, has formed the base of some enemas, and has been used in the treatment of iodine poisoning.

Therapeutically, rice starch-based solutions have been used in the prevention and treatment of dehydration due to acute diarrheal diseases.

8 Description

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.5–6.5 for a 2% w/v aqueous dispersion of corn starch, at 25°C.

Compressibility: *see* Figure 1.

Density (bulk): 0.462 g/cm^3 for corn starch.

Density (tapped): 0.658 g/cm^3 for corn starch.

Density (true): 1.478 g/cm^3 for corn starch.

Flowability: 10.8–11.7 g/s for corn starch;[9] 30% for corn starch (Carr compressibility index).[16] Corn starch is cohesive and has poor flow characteristics.

Gelatinization temperature: 73°C for corn starch; 72°C for potato starch; 63°C for wheat starch.

Moisture content: all starches are hygroscopic and rapidly absorb atmospheric moisture.[17,18] Approximate equilibrium moisture content values at 50% relative humidity are 11% for corn starch; 18% for potato starch; 14% for rice starch; and 13% for wheat starch. Between 30% and 80% relative humidity, corn starch is the least hygroscopic starch and potato starch is the most hygroscopic. Commercially available grades of corn starch usually contain 10–14% water. *See also* Figures 2 and 3.

Particle size distribution:
- Corn starch: 2–32 μm
- Potato starch: 10–100 μm
- Rice starch: 2–20 μm
- Tapioca starch: 5–35 μm
- Wheat starch: 2–45 μm

Median diameter for corn starch is 17 μm and for wheat starch is 23 μm.

Solubility: practically insoluble in cold ethanol (95%) and in cold water. Starch swells instantaneously in water by about 5–10% at 37°C.[2,18] Polyvalent cations produce more swelling than monovalent ions, but pH has little effect.

Specific surface area:
- 0.41–0.43 m^2/g for corn starch
- 0.12 m^2/g for potato starch
- 0.27–0.31 m^2/g for wheat starch

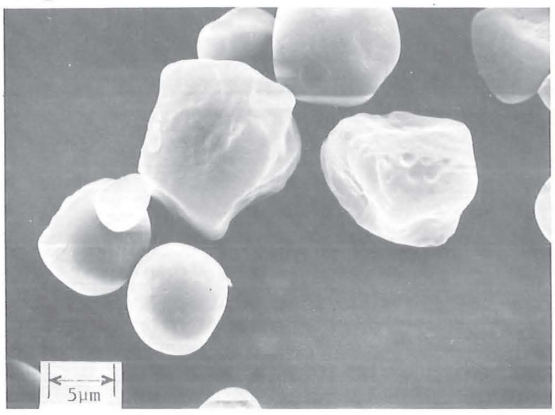
Swelling temperature:
- 65°C for corn starch
- 64°C for potato starch
- 55°C for wheat starch

Viscosity (dynamic): 13.0 mPa s (13.0 cP) for a 2% w/v aqueous dispersion of corn starch at 25°C.

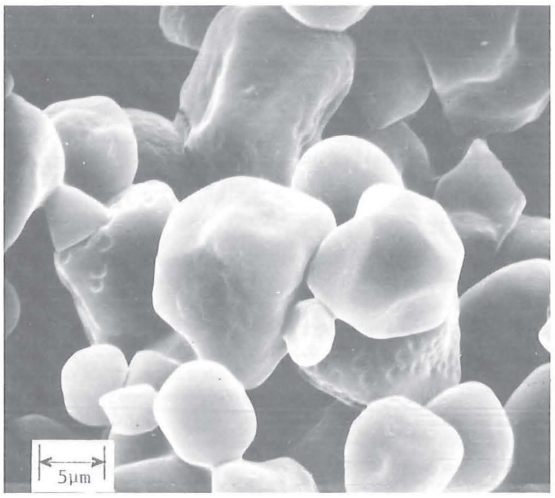
Table I: Pharmacopeial specifications for starch.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Botanic characteristics	—	+	+
Microbial limits	—	+	+
pH			
Corn starch	—	—	4.5–7.0
Potato starch	—	5.0–8.0	5.0–8.0
Tapioca	—	—	4.5–7.0
Wheat starch	—	5.0–8.0	4.5–7.0
Acidity	—	+	—
Loss on drying			
Corn starch	≤15.0%	≤15.0%	≤14.0%
Rice starch	≤15.0%	≤15.0%	—
Potato starch	≤18.0%	≤20.0%	≤14.0%
Tapioca	—	—	≤14.0%
Wheat starch	≤15.0%	≤15.0%	≤14.0%
Residue on ignition	—	—	≤0.5%
Sulfated ash			
Corn starch	≤0.5%	≤0.6%	—
Rice starch	≤1.0%	≤1.0%	—
Potato starch	≤0.5%	≤0.6%	—
Wheat starch	≤1.0%	≤0.6%	—
Iron			
Corn starch	—	—	≤0.002%
Potato starch	—	≤10 ppm	≤0.002%
Tapioca starch	—	—	≤0.002%
Wheat starch	—	≤10 ppm	≤0.002%
Organic volatile impurities	—	—	+
Oxidizing substances			
Corn starch	—	—	≤0.002%
Potato starch	—	+	≤0.002%
Tapioca starch	—	—	≤0.002%
Wheat starch	—	+	≤0.002%
Sulfur dioxide			
Corn starch	—	—	≤0.008%
Potato starch	—	≤50 ppm	≤0.008%
Wheat starch	—	≤50 ppm	≤0.008%
Total protein			
Corn starch	—	—	—
Rice starch	—	—	—
Potato starch	—	≤0.1%	—
Wheat starch	—	≤0.3%	—
Foreign matter	—	+	—

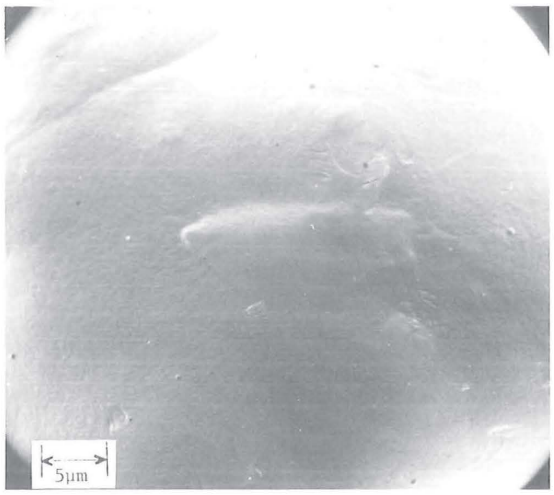
SEM: 1
Excipient: Corn starch
Manufacturer: Anheuser Busch
Lot No.: 96A-3 (67)
Magnification: 2400×
Voltage: 20 kV



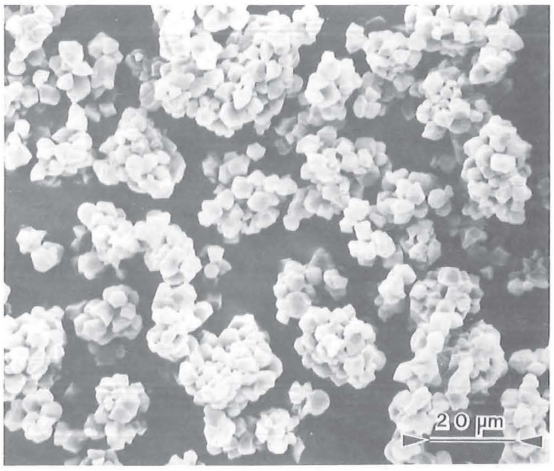
SEM: 2
Excipient: Corn starch
Manufacturer: AE Staley Mfg. Co.
Lot No.: 96A-4 (G77912)
Magnification: 2400×
Voltage: 20 kV



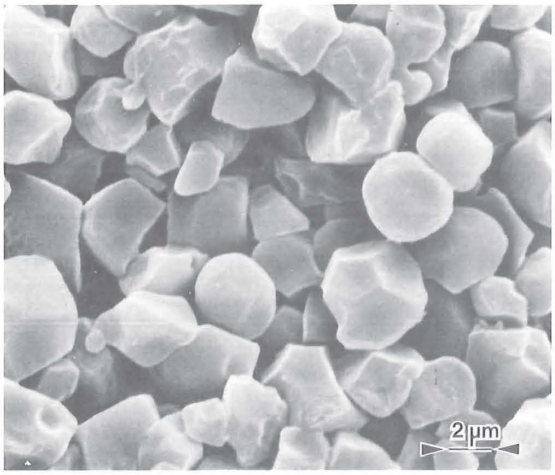
SEM: 3
Excipient: Potato starch
Manufacturer: Starchem
Lot No.: 96A-5 (1179)
Magnification: 2400×
Voltage: 20 kV



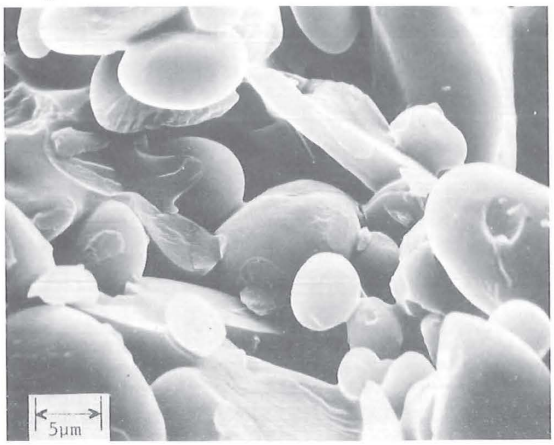
SEM: 4
Excipient: Rice starch
Supplier: Matheson, Coleman & Bell
Magnification: 600×



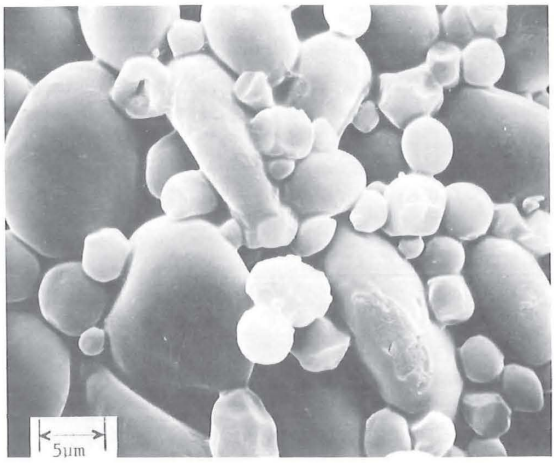
SEM: 5
Excipient: Rice starch
Supplier: Matheson, Coleman & Bell
Magnification: 3000×



SEM: 6
Excipient: Wheat starch (*Paygel 55*)
Manufacturer: Henkel Corp.
Lot No.: 96A-1 (2917D)
Magnification: 2400×
Voltage: 20 kV



SEM: 7
Excipient: Wheat starch (*Aytex P*)
Manufacturer: Henkel Corp.
Lot No.: 96A-2 (2919D)
Magnification: 2400×
Voltage: 20 kV



11 Stability and Storage Conditions

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid-dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties.

Starch should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Starch is extracted from plant sources through a sequence of processing steps involving coarse milling, repeated water washing, wet sieving, and centrifugal separation. The wet starch obtained from these processes is dried and milled before use in pharmaceutical formulations.

14 Safety

Starch is widely used as an excipient in pharmaceutical formulations, particularly oral tablets.

Starch is an edible food substance and is generally regarded as an essentially nontoxic and nonirritant material.[19] However, oral consumption of massive doses can be harmful owing the formation of starch calculi, which cause bowel obstruction.[20] Starch may also cause granulomatous reactions when applied to the peritoneum or the meninges. Contamination of surgical wounds with the starch glove powder used by surgeons has also resulted in the development of granulomatous lesions.[21]

Allergic reactions to starch are extremely rare and individuals apparently allergic to one particular starch may not experience adverse effects with a starch from a different botanical source.

LD_{50} (mouse, IP): 6.6 g/kg[22]

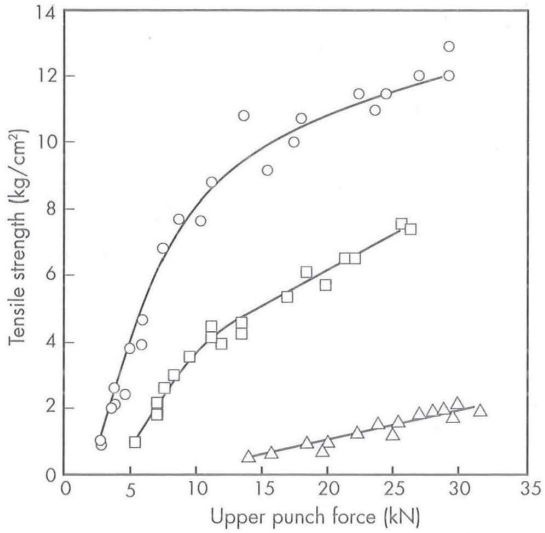


Figure 1: Compression characteristics of corn, potato and wheat starches.
□: Corn starch
○: Potato starch
△: Wheat starch
Tablet machine: Manesty F; speed: 50 per min; weight: 490–510 mg. Strength test: Diametral compression between flat-faced rams. Upper ram stationary, lower moving at 66 μm/s.

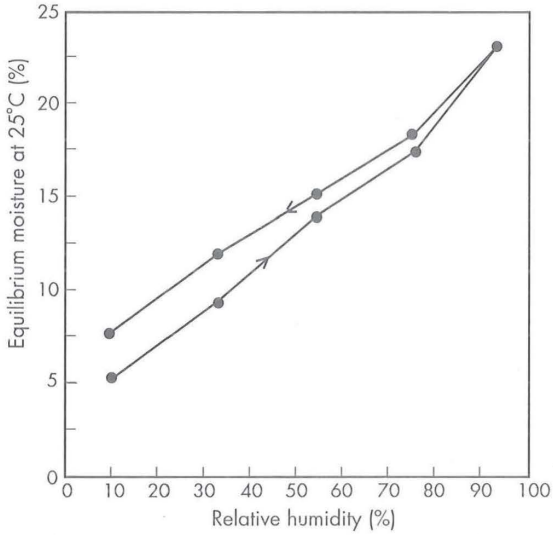


Figure 2: Sorption–desorption isotherm of corn starch. Anheuser Busch; Lot #67.

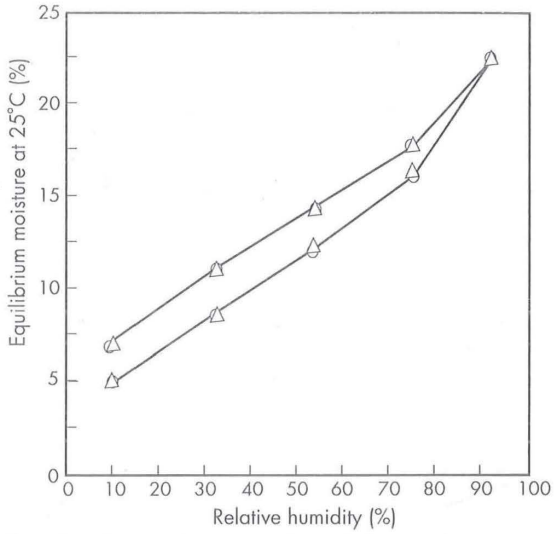


Figure 3: Sorption–desorption isotherm of wheat starch.
○: *Paygel 55* (Henkel Corp.; Lot #2917D)
△: *Aytex P* (Henkel Corp.; Lot #2919D)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosion.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.[23]

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (buccal tablets, oral capsules, powders, suspensions and tablets; topical preparations; and vaginal tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Amylopectin; α-amylose; starch, pregelatinized; starch, sterilizable maize.

Amylopectin

CAS number: [9037-22-3]
Comments: amylopectin is a branched D-glucan with mostly α-D-(1→4) and approximately 4% α-D-(1→6) linkages.
The EINECS number for amylopectin is 232-911-6.

α-Amylose

CAS number: [9005-82-7]
Comments: amylose is a linear (1→4)-α-D-glucan.

18 Comments

Note that corn starch is also known as maize starch and that tapioca starch is also known as cassava starch.

Whereas the USPNF 20 specifies that starch should be produced from corn, potato, tapioca, or wheat, the BP 2001

also permits starch to be produced from rice. In tropical and subtropical countries where these starches may not be readily available, the BP 2001 additionally permits the use of tapioca starch, subject to additional requirements.

Starches from different plant sources differ in their amylose/amylopectin ratio. For example, corn starch contains about 27% amylose, potato starch about 22%, and tapioca starch about 17%. In contrast, waxy corn starch contains almost entirely amylopectin, with no amylose. These differences modify the physical properties of the starches such that the various types may not be interchangeable in a given pharmaceutical application.

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21 Author

G Rowley.

22 Date of Revision

10 March 2002.

Starch, Pregelatinized

1 Nonproprietary Names

BP: Pregelatinised starch
PhEur: Amylum pregelificatum
USPNF: Pregelatinized starch

2 Synonyms

Compressible starch; *Instastarch*; *Lycatab C*; *Lycatab PGS*; *Merigel*; *National 78-1551*; *Pharma-Gel*; *Prejel*; *Sepistab ST 200*; *Spress B820*; *Starch 1500 G*; *Tablitz*; *Unipure LD*; *Unipure WG220*.

3 Chemical Name and CAS Registry Number

Pregelatinized starch [9005-25-8]

4 Empirical Formula Molecular Weight

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. The USPNF 20 does not specify the botanical origin of the original starch, but the PhEur 2002 (Suppl 4.1) specifies that pregelatinized starch is obtained from maize (corn), potato, or rice starch. *See also* Starch and Section 13.

5 Structural Formula

See Starch.

6 Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,[1,2] and disintegrant.[3]

In comparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression processes.[4–14] In such processes, pregelatinized starch is self-lubricating. However, when it is used with other excipients it may be necessary to add a lubricant to a formulation. Although magnesium stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinized starch.[15]

Pregelatinized starch may also be used in wet granulation processes.[16] *See* Table I.

Table I: Uses of pregelatinized starch.

Use	Concentration (%)
Diluent (hard gelatin capsules)	5–75
Tablet binder (direct compression)	5–20
Tablet binder (wet granulation)	5–10
Tablet disintegrant	5–10

8 Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Examination of fully pregelatinized starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules, i.e., no 'maltese crosses' characteristic of the starch birefringence pattern. Examination of samples suspended in glycerin show characteristic forms depending upon the method of drying used during manufacture: either irregular chunks from drum drying or thin plates. Partially pregelatinized starch (e.g., *Starch 1500G* and *Sepistab ST200*) show retention of birefringence patterns typical of unmodified starch granules.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for pregelatinized starch.

Test	PhEur 2002 (Suppl 4.1)	USPNF 20
Identification	+	+
pH (10% w/v slurry)	4.5–7.0	4.5–7.0
Iron	≤20 ppm	≤0.002%
Oxidizing substances	+	+
Sulfur dioxide	≤50 ppm	≤0.008%
Microbial limits	+	+
Loss on drying	≤15.0%	≤14.0%
Residue on ignition	—	≤0.5%
Foreign matter	+	—
Sulfated ash	≤0.6%	—
Organic volatile impurities	—	+

10 Typical Properties

Acidity/alkalinity: pH = 4.5–7.0 for a 10% w/v aqueous dispersion.
Angle of repose: 40.7° [6]
Compressibility: *see* Starch.
Density (bulk): 0.586 g/cm^3
Density (tapped): 0.879 g/cm^3
Density (true): 1.516 g/cm^3
Flowability: 18–23% (Carr compressibility index)[17]
Moisture content: pregelatinized maize starch is hygroscopic.[14,18,19] *See also* Figure 1.

Particle size distribution: 30–150 μm, median diameter 52 μm. For partially pregelatinized starch, greater than 90% through a US #100 mesh (149 μm); and less than 0.5% retained on a US #40 mesh (420 μm).

Solubility: practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Pastes can be prepared by sifting the pregelatinized starch into stirred, cold water. Cold-water-soluble matter for partially pregelatinized starch is 10–20%.

Specific surface area:
0.26 m^2/g (Colorcon)
0.18–0.28 m^2/g (Roquette Ltd)

Viscosity (dynamic): 8–10 mPa s (8–10 cP) for a 2% w/v aqueous dispersion at 25 °C.

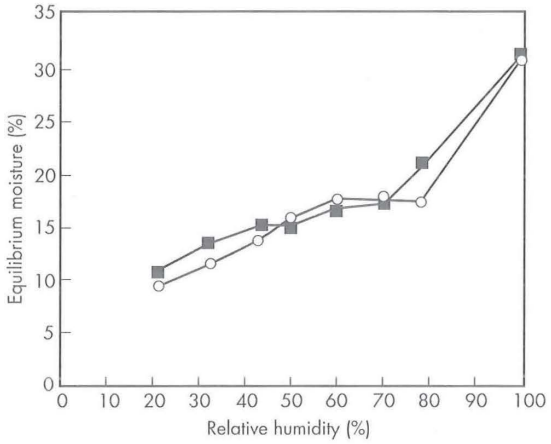

Figure 1: Pregelatinized starch sorption–desorption isotherm. ○: Sorption. ■: Desorption.

11 Stability and Storage Conditions

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

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13 Method of Manufacture

Food-grade pregelatinized starches are prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62–72 °C. Chemical additives that may be included in the slurry are gelatinization aids (salts or bases) and surfactants, added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded, or drum-dried. In the last case, the dried material may be processed to produce a desired particle size range.

Pharmaceutical grades of fully pregelatinized starch use no additives and are prepared by spreading an aqueous suspension of ungelatinized starch on hot drums where gelatinization and subsequent drying takes place. Partially pregelatinized starch is produced by subjecting moistened starch to mechanical pressure. The resultant material is ground and the moisture content is adjusted to specifications.

14 Safety

Pregelatinized starch and starch are widely used in oral solid-dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of massive amounts of pregelatinized starch may be harmful.

See Starch for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.[20]

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Starch; starch, sterilizable maize.

18 Comments

A low-moisture grade of pregelatinized starch, *Starch 1500 LM* (Colorcon), containing less than 7% of water, specifically intended for use as a diluent in capsule formulations is commercially available.[15]

Sepistab ST200 is described as an agglomerate of starch granules consisting of native and pregelatinized corn starch.[21]

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21 Author

G Rowley.

22 Date of Revision

13 June 2002.

Starch, Sterilizable Maize

1 Nonproprietary Names

USP: Absorbable dusting powder

2 Synonyms

Bio-sorb; double-dressed, white maize starch; *Fluidamid R444P*; *Keoflo ADP*; *Meritena*; modified starch dusting powder; *Pure-Dent B851*; starch-derivative dusting powder; sterilizable corn starch.

3 Chemical Name and CAS Registry Number

Sterilizable maize starch

4 Empirical Formula Molecular Weight

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Sterilizable maize starch is a modified corn (maize) starch that may also contain up to 2.0% of magnesium oxide.

See also Starch.

5 Structural Formula

See Starch.

6 Functional Category

Lubricant for surgeons' and examination gloves; vehicle for medicated dusting powders.

7 Applications in Pharmaceutical Formulation or Technology

Sterilizable maize starch is a chemically or physically modified corn (maize) starch that does not gelatinize on exposure to moisture or steam sterilization. Sterilizable maize starch is primarily used as a lubricant for examination and surgeons' gloves. It is also used as a vehicle for medicated dusting powders.

8 Description

Sterilizable maize starch occurs as an odorless, white, free-flowing powder. Particles may be rounded or polyhedral in shape.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sterilizable maize starch.

Test	USP 25
Identification	+
Stability to autoclaving	+
Sedimentation	+
pH (1 in 10 suspension)	10.0–10.8
Loss on drying	≤12%
Residue on ignition	≤3%
Magnesium oxide	≤2.0%
Heavy metals	≤0.001%

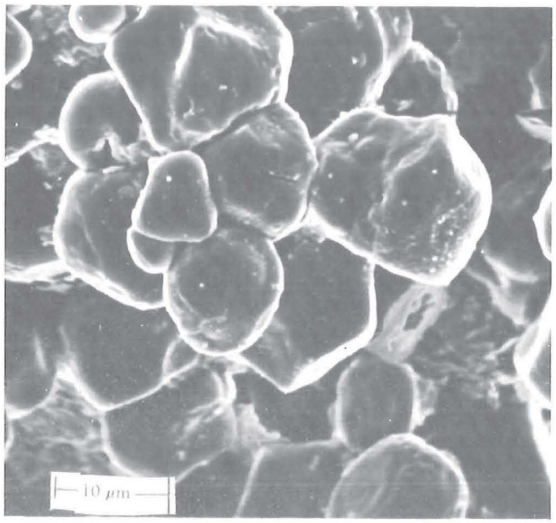
10 Typical Properties

Acidity/alkalinity: pH = 9.5–10.8 for a 10% w/v suspension at 25 °C.
Density: 1.48 g/cm^3
Density (bulk): 0.47–0.59 g/cm^3
Density (tapped): 0.64–0.83 g/cm^3
Flowability: 24–30% (Carr compressibility index)[1]
Moisture content: 10–15%
Particle size distribution: 6–25 µm; median diameter is 16 µm.
Solubility: very slightly soluble in chloroform and ethanol (95%); practically insoluble in water.
Specific surface area: 0.50–1.15 m^2/g

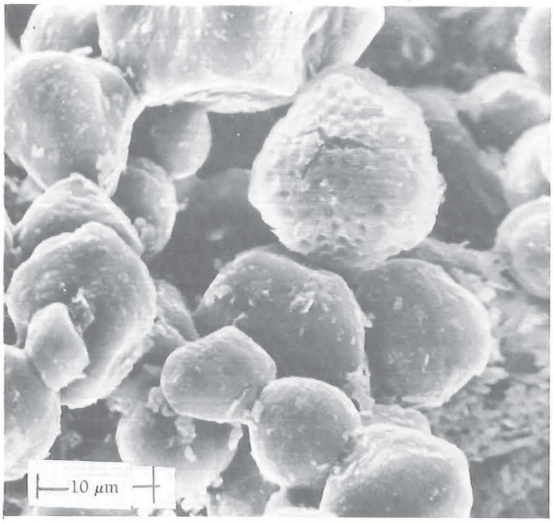
11 Stability and Storage Conditions

Sterilizable maize starch may be sterilized by autoclaving at 121 °C for 20 minutes, by ethylene oxide, or by irradiation.[2]

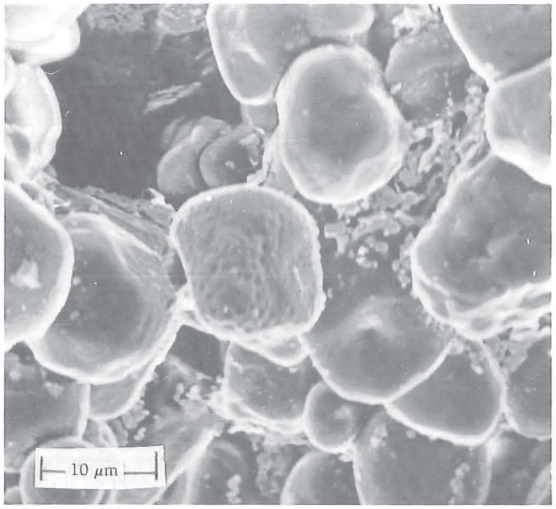
SEM: 1
Excipient: Sterilizable maize starch
Manufacturer: Corn Products
Magnification: 2000×



SEM: 2
Excipient: Sterilizable maize starch
Manufacturer: Biosorb
Magnification: 2000×



SEM: 3
Excipient: Sterilizable maize starch
Manufacturer: J & W Starches Ltd
Magnification: 2000×



Sterilizable maize starch should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

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13 Method of Manufacture

Corn starch (maize starch) is physically or chemically modified by treatment with either phosphorus oxychloride or epichlorhydrin so that the branched-chain and straight-chain starch polymers crosslink. Up to 2.0% of magnesium oxide may also be added to the starch.

See also Starch.

14 Safety

Sterilizable maize starch is primarily used as a lubricant for surgeons' gloves and as a vehicle for topically applied dusting powders.

Granulomatous reactions and peritonitis at operation sites have been attributed to contamination with surgical glove powders containing sterilizable maize starch.[3,4] The use of excessive quantities of sterilizable maize starch on surgeons' gloves should therefore be avoided.

See also Starch.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.[5]

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral tablets and topical preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Starch; starch, pregelatinized.

18 Comments

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19 Specific References

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21 Author

G Rowley.

22 Date of Revision

13 June 2002.

Sugar Spheres

1 Nonproprietary Names

BP: Sugar spheres
PhEur: Sacchari spheri
USPNF: Sugar spheres

2 Synonyms

Non-pareil; non-pareil seeds; *NPTAB*; *Nu-Core*; *Nu-Pareil PG*; sugar seeds; *Suglets*.

3 Chemical Name and CAS Registry Number

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4 Empirical Formula Molecular Weight

See Section 8.

5 Structural Formula

See Section 8.

6 Functional Category

Tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Sugar spheres are mainly used as inert cores in capsule and tablet formulations, particularly multiparticulate sustained-release formulations.[1–4] They form the base upon which a drug is coated, usually followed by a release-modifying polymer coating.

Alternatively, a drug and matrix polymer may be coated onto the cores simultaneously. The active drug is released over an extended period either via diffusion through the polymer or through to the controlled erosion of the polymer coating.

Complex drug mixtures contained within a single-dosage form may be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer coatings.

Sugar spheres are also used in confectionery products.

8 Description

The USPNF 20 describes sugar spheres as approximately spherical granules of a labeled nominal-size range with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch.

The PhEur 2002 states that sugar spheres contain not more than 92% of sucrose calculated on the dried basis. The remainder consists of corn (maize) starch and may also contain starch hydrolysates and color additives. The diameter of sugar spheres varies from 200 to 2000 µm and the upper and lower limits of the size of the sugar spheres are stated on the label.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sugar spheres.

Test	PhEur 2002	USPNF 20
Identification	+	+
Heavy metals	≤5 ppm	≤5 ppm
Loss on drying	≤5.0%	≤4.0%
Microbial limits	+	+
Organic volatile impurities	—	+
Particle size distribution	+	+
Residue on ignition	≤0.2%	≤0.25%
Specific rotation	—	+41° to +61°
Sucrose (dried basis)	≤92%	62.5–91.5%

10 Typical properties

Density:
1.57–1.59 g/cm^3 for *Suglets* less than 500 µm in size
1.55–1.58 g/cm^3 for *Suglets* more than 500 µm in size

Flowability: <10 seconds, free flowing.

Particle size distribution: sugar spheres are of a uniform diameter. The following sizes are commercially available from various suppliers (US standard sieves):

45–60 mesh (250–355 µm)
40–50 mesh (300–425 µm)
35–45 mesh (355–500 µm)
35–40 mesh (420–500 µm)
30–35 mesh (500–600 µm)
25–30 mesh (610–710 µm)
20–25 mesh (710–850 µm)
18–20 mesh (850–1000 µm)
16–20 mesh (850–1180 µm)
14–18 mesh (1000–1400 µm)

Solubility: solubility in water varies according to the sucrose-to-starch ratio. The sucrose component is freely soluble in water, whereas the starch component is practically insoluble in cold water.

Specific surface area:
0.1–0.2 m^2/g for *Suglets* less than 500 µm in size
>0.2 m^2/g for *Suglets* more than 500 µm in size

11 Stability and Storage Conditions

Sugar spheres are stable when stored in a well-closed container in a cool, dry place.

12 Incompatibilities

See Starch and Sucrose for information concerning the incompatibilities of the component materials of sugar spheres.

13 Method of Manufacture

Sugar spheres are prepared from crystalline sucrose, which is coated using sugar syrup and a starch dusting powder.

14 Safety

Sugar spheres are used in oral pharmaceutical formulations. The sucrose and starch components of sugar spheres are widely used in edible food products and oral pharmaceutical formulations.

The adverse reactions and precautions necessary with the starch and sucrose components should be considered in any product containing sugar spheres. For example, sucrose is generally regarded as more cariogenic than other carbohydrates, and in higher doses is also contraindicated in diabetic patients.

See Starch and Sucrose for further information.

15 Handling Precautions

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

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK and Europe. The sucrose and starch components of sugar spheres are individually approved for use as food additives in Europe and the USA.

17 Related Substances

Compressible sugar; confectioner's sugar; starch; sucrose.

18 Comments

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19 Specific References

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RC Moreton.

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7 October 2002.

Index

Note:

Greek characters (α, β, γ etc.), numerical prefixes (5′-, 1,2- etc.) and prefixes such as *para*, *ortho*, *O*-, *N*-, D-, L- etc. are excluded from alphabetization; page numbers in **bold** refer to monograph titles.