Chitosan

1 Nonproprietary Names

BP: Chitosan hydrochloride
PhEur: Chitosani hydrochloridum

2 Synonyms

2-Amino-2-deoxy-(1,4)-β-D-glucopyranan; deacetylated chitin; deacetylchitin; β-1,4-poly-D-glucosamine; poly-D-glucosamine; poly-(1,4-β-D-glucopyranosamine).

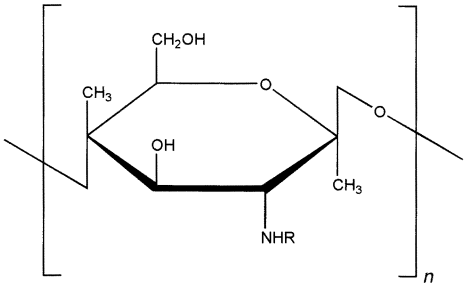
3 Chemical Name and CAS Registry Number

Poly-β-(1,4)-2-Amino-2-deoxy-D-glucose [9012-76-4]

4 Empirical Formula Molecular Weight

Partial deacetylation of chitin results in the production of chitosan, which is a polysaccharide comprising copolymers of glucosamine and *N*-acetylglucosamine. Chitosan is the term applied to deacetylated chitins in various stages of deacetylation and depolymerization and it is therefore not easily defined in terms of its exact chemical composition. A clear nomenclature with respect to the different degrees of *N*-deacetylation between chitin and chitosan has not been defined[1–3] and chitosan is not one chemical entity but varies in composition depending on the manufacturer. In essence, chitosan is chitin sufficiently deacetylated to form soluble amine salts. The degree of deacetylation necessary to obtain a soluble product must be greater than 80–85%. Chitosan is commercially available in several types and grades that vary in molecular weight between 10 000 and 1 000 000, and vary in degree of deacetylation and viscosity.[4]

5 Structural Formula



R = H or $COCH_3$

6 Functional Category

Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Chitosan is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations. The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery applications has been investigated in numerous studies.[3,5–8] These include controlled drug delivery applications,[9–14] use as a component of mucoadhesive dosage forms,[15,16] rapid release dosage forms,[17,18] improved peptide delivery,[19,20] colonic drug delivery systems,[21,22] and use for gene delivery.[23] Chitosan has been processed into several pharmaceutical forms including gels,[24,25] films,[11,12,26,27] beads,[28,29] microspheres,[30,31] tablets,[32,33] and coatings for liposomes.[34] Furthermore, chitosan may be processed into drug delivery systems using several techniques including spray-drying,[15,16] coacervation,[35] direct compression,[32] and conventional granulation processes.[36]

8 Description

Chitosan occurs as odorless, white or creamy-white powder or flakes. Fibre formation is quite common during precipitation and the chitosan may look 'cottonlike.'

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for chitosan.

Test	PhEur 2002
Identification	+
Characters	+
Appearance of solution	+
Matter insoluble in water	≤0.5%
pH (1% w/v solution)	4.0–6.0
Viscosity	+
Degree of deacetylation	+
Chlorides	10.0–20.0%
Heavy metals	≤40 ppm
Loss on drying	≤10%
Sulfated ash	≤1.0%

10 Typical Properties

Chitosan is a cationic polyamine with a high charge density at pH <6.5 (and so adheres to negatively charged surfaces and chelates metal ions). It is a linear polyelectrolyte with reactive hydroxyl and amino groups (available for chemical reaction and salt formation).[7] The properties of chitosan relate to its polyelectrolyte and polymeric carbohydrate character. The presence of a number of amino groups allows chitosan to react chemically with anionic systems, which results in alteration of physicochemical characteristics of such combinations.

The nitrogen in chitosan is mostly in the form of primary aliphatic amino groups. Chitosan therefore undergoes reactions typical of amines: for example, *N*-acylation and Schiff reactions.[3] Almost all functional properties of chitosan depend on the chain length, charge density, and charge distribution.[8] Numerous studies have demonstrated that the salt form, molecular weight, and degree of deacetylation as well as pH at which the chitosan is used all influence how this polymer is utilized in pharmaceutical applications.[7]

Acidity/alkalinity: pH = 4.0–6.0 (1% w/v aqueous solution)

Density: 1.35–1.40 g/cm^3

Glass transition temperature: 203°C[37]

Moisture content: chitosan adsorbs moisture from the atmosphere, the amount of water adsorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air.[38]

Particle size distribution: < 30 μm

Solubility: sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5. Chitosan dissolves readily in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids (except phosphoric and sulfuric acids). Upon dissolution, amine groups of the polymer become protonated, resulting in a positively charged polysaccharide (RNH_3^+) and chitosan salts (chloride, glutamate, etc.) that are soluble in water; the solubility is affected by the degree of deacetylation.[7] Solubility is also greatly influenced by the addition of salt to the solution. The higher the ionic strength, the lower the solubility as a result of a salting-out effect, which leads to the precipitation of chitosan in solution.[39] When chitosan is in solution, the repulsions between the deacetylated units and their neighboring glucosamine units cause it to exist in an extended conformation. Addition of an electrolyte reduces this effect and the molecule possesses a more random, coil-like conformation.[40]

Viscosity (dynamic): a wide range of viscosity types is commercially available. Owing to its high molecular weight and linear, unbranched structure, chitosan is an excellent viscosity-enhancing agent in an acidic environment. It acts as a pseudo-plastic material, exhibiting a decrease in viscosity with increasing rates of shear.[7] The viscosity of chitosan solutions increases with increasing chitosan concentration, decreasing temperature, and increasing degree of deacetylation; *see* Table II.[40]

Table II: Typical viscosity (dynamic) values for chitosan 1% w/v solutions in different acids.

Acid	1% acid concentration		5% acid concentration		10% acid concentration	
	Viscosity (mPa s)	pH	Viscosity (mPa s)	pH	Viscosity (mPa s)	pH
Acetic	260	4.1	260	3.3	260	2.9
Adipic	190	4.1	—	—	—	—
Citric	35	3.0	195	2.3	215	2.0
Formic	240	2.6	185	2.0	185	1.7
Lactic	235	3.3	235	2.7	270	2.1
Malic	180	3.3	205	2.3	220	2.1
Malonic	195	2.5	—	—	—	—
Oxalic	12	1.8	100	1.1	100	0.8
Tartaric	52	2.8	135	2.0	160	1.7

11 Stability and Storage Conditions

Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying. Chitosan should be stored in a tightly closed container in a cool, dry place. The PhEur 2002 specifies that chitosan should be stored at a temperature of 2–8°C.

12 Incompatibilities

Chitosan is incompatible with strong oxidizing agents.

13 Method of Manufacture

Chitosan is manufactured commercially by chemically treating the shells of crustaceans such as shrimps and crabs. The basic manufacturing process involves the removal of proteins by treatment with alkali and of minerals such as calcium carbonate and calcium phosphate by treatment with acid.[3,40] Before these treatments, the shells are ground to make them more accessible. The shells are initially deproteinized by treatment with an aqueous sodium hydroxide 3–5% solution. The resulting product is neutralized and calcium is removed by treatment with an aqueous hydrochloric acid 3–5% solution at room temperature to precipitate chitin. The chitin is dried so that it can be stored as a stable intermediate for deacetylation to chitosan at a later stage. *N*-deacetylation of chitin is achieved by treatment with an aqueous sodium hydroxide 40–45% solution at elevated temperature (110°C), and the precipitate is washed with water. The crude sample is dissolved in acetic acid 2% and the insoluble material is removed. The resulting clear supernatant solution is neutralized with aqueous sodium hydroxide solution to give a purified white precipitate of chitosan. The product can then be further purified and ground to a fine uniform powder or granules.[1] The animals from which chitosan is derived must fulfil the requirements for the health of animals suitable for human consumption to the satisfaction of the competent authority. The method of production must consider inactivation or removal of any contamination by viruses or other infectious agents.

14 Safety

Chitosan is being investigated widely for use as an excipient in oral and other pharmaceutical formulations. It is also used in cosmetics. Chitosan is generally regarded as a nontoxic and nonirritant material. It is biocompatible[41] with both healthy and infected skin.[42] Chitosan has been shown to be biodegradable.[3,41]

LD_{50} (mouse, oral): >16 g/kg[43]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Chitosan is combustible; open flames should be avoided. Chitosan is temperature-sensitive and should not be heated above 200°C. Airborne chitosan dust may explode in the presence of a source of ignition, depending on its moisture content and particle size. Water, dry chemicals, carbon dioxide, sand, or foam fire-fighting media should be used.

Chitosan may cause skin or eye irritation. It may be harmful if absorbed through the skin or if inhaled and may be irritating to mucous membranes and the upper respiratory tract. Eye and

skin protection and protective clothing are recommended; wash thoroughly after handling. Prolonged or repeated exposure (inhalation) should be avoided by handling in a well-ventilated area and wearing a respirator.

16 Regulatory Status

Chitosan is registered as a food supplement in some countries.

17 Related Substances

See Section 18.

18 Comments

Chitosan derivatives are easily obtained under mild conditions and can be considered as substituted glucens.[3]

19 Specific References

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