Fructose

1 Nonproprietary Names

BP: Fructose
JP: Fructose
PhEur: Fructosum
USP: Fructose

2 Synonyms

Advantose FS 95; *Fructamyl*; *Fructofin*; D-(–)-fructopyranose; β-D-fructose; fruit sugar; *Krystar*; laevulose; levulose.

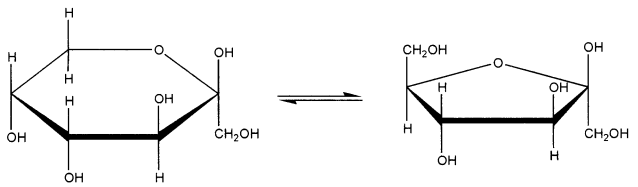
3 Chemical Name and CAS Registry Number

D-Fructose [57-48-7]

4 Empirical Formula and Molecular Weight

$C_6H_{12}O_6$ 180.16

5 Structural Formula



Pyranose form Furanose form

See Section 18.

6 Functional Category

Dissolution enhancer; flavor enhancer; sweetening agent; tablet diluent.

7 Applications in Pharmaceutical Formulation or Technology

Fructose is used in tablets, syrups, and solutions as a flavoring and sweetening agent.

The sweetness-response profile of fructose is perceived in the mouth more rapidly than that of sucrose and dextrose, which may account for the ability of fructose to enhance syrup or tablet fruit flavors and mask certain unpleasant vitamin or mineral 'off-flavors'.

The increased solubility of fructose in comparison to sucrose is advantageous in syrup or solution formulations that must be refrigerated, since settling or crystallization of ingredients is retarded. Similarly, the greater solubility and hygroscopicity of fructose over sucrose and dextrose helps to avoid 'cap-locking' (sugar crystallization around the bottle cap) in elixir preparations. Fructose also has greater solubility in ethanol (95%) and is therefore used to sweeten alcoholic formulations.

The water activity of a sweetener influences product microbial stability and freshness. Fructose has a lower water activity and a higher osmotic pressure than sucrose. Syrup formulations may be made at lower dry-substance levels than sugar syrups without compromising shelf-life stability. It may be necessary to include a thickener or gelling agent to match the texture or viscosity of the sugar-equivalent formulation.

Fructose is sweeter than the sugar alcohols mannitol and sorbitol, which are commonly used as tableting excipients. Although fructose is effective at masking unpleasant flavors in tablet formulations, tablets of satisfactory hardness and friability can only be produced by direct compression if tablet presses are operated at relatively slow speeds. However, by the combination of crystalline fructose with tablet-grade sorbitol in a 3 : 1 ratio, satisfactory direct-compression characteristics can be achieved. A directly compressible grade of fructose, containing a small amount of starch (*Advantose FS 95*, SPI Pharma) is also commercially available. Pregranulation of fructose with 3.5% povidone also produces a satisfactory tablet excipient.[1] The added sweetness of fructose may also be used to advantage by coating the surface of chewable tablets, lozenges, or medicinal gums with powdered fructose.

The coprecipitation of fructose with hydrophobic drugs such as digoxin has been shown to enhance the dissolution profile of such drugs. Fructose apparently acts as a water-soluble carrier upon coprecipitation, thereby allowing hydrophobic drugs to be more readily wetted.[2]

8 Description

Fructose occurs as odorless, colorless crystals or a white crystalline powder with a very sweet taste.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.35 (9% w/v aqueous solution)
Angle of repose: 38.8° for *Advantose FS 95*
Density: 1.58 g/cm^3. *See also* Table II.
Heat of combustion: 15.3 kJ/g (3.66 kcal/g)
Heat of solution: 50.2 kJ/g (12 kcal/g)
Hygroscopicity: at 25°C and relative humidities above approximately 60%, fructose absorbs significant amounts of moisture; *see* Figure 1.
Melting point: ≈102–105°C (with decomposition)
Osmolarity: a 5.05% w/v aqueous solution is isoosmotic with serum.
Particle size distribution: the average particle size of standard-grade crystalline fructose is 400 µm (*Fructofin C*, Xyrofin). Other grades are available that have an average particle size of 170 µm (*Fructofin CM*, Xyrofin). The average particle size of powdered fructose is 25–40 µm (*Krystar*, AE Staley Mfg Co). Other grades are available: e.g., *Krystar 300* and *Krystar 450* with average particle sizes of 300 µm and 450 µm, respectively.
Refractive index: *see* Table II.

Solubility: *see* Table III.

Specific rotation $[\alpha]_D^{20}$: $-132°$ to $-92°$ (2% w/v aqueous solution). Note that fructose shows rapid and anomalous mutarotation involving pyranose–furanose interconversion. The final value may be obtained in the presence of hydroxide ions. *See also* Section 18.

Viscosity (dynamic): *see* Table II.

Table I: Pharmacopeial specifications for fructose.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Characters	—	+	—
Color of solution	+	+	+
Acidity	+	+	+
pH	4.0–6.5	—	—
Specific optical rotation	—	–91.0° to –93.5°	—
Foreign sugars	—	+	—
Loss on drying	≤0.5%	≤0.5%	≤0.5%
Residue on ignition	≤0.1%	≤0.1%	≤0.5%
Chloride	≤0.018%	—	≤0.018%
Sulfate	≤0.024%	—	≤0.025%
Sulfite	+	—	—
Arsenic	≤1.3 ppm	—	≤1 ppm
Barium	—	+	—
Calcium and magnesium (as calcium)	+	—	≤0.005%
Lead	—	≤0.5 ppm	—
Heavy metals	≤4 ppm	—	≤5 ppm
Hydroxymethylfurfural	+	+	+
Assay (dried basis)	≥98.0%	—	98.0–102.0%

Table II: Physical properties of aqueous fructose solutions at 20°C.

Concentration of aqueous fructose solution (% w/w)	Density (g/cm^3)	Refractive index	Viscosity, dynamic (mPa s)
10	1.04	1.3477	1.35
20	1.08	1.3633	1.80
30	1.13	1.3804	2.90
40	1.18	1.3986	5.60
50	1.23	1.4393	34.0
60	1.29	1.4853	309.2

Table III: Solubility of fructose.

Solvent	Solubility at 20°C
Ethanol (95%)	1 in 15
Methanol	1 in 14
Water	1 in 0.3

11 Stability and Storage Conditions

Fructose is hygroscopic and absorbs significant amounts of moisture at relative humidities greater than 60%. Goods stored in the original sealed packaging at temperatures below 25°C and a relative humidity of less than 60% can be expected to retain stability for at least 12 months.

Aqueous solutions are most stable at pH 3–4 and temperatures of 4–70°C; they may be sterilized by autoclaving.

12 Incompatibilities

Incompatible with strong acids or alkalis, forming a brown coloration. In the aldehyde form, fructose can react with amines, amino acids, peptides, and proteins. Fructose may cause browning of tablets containing amines.

13 Method of Manufacture

Fructose, a monosaccharide sugar, occurs naturally in honey and a large number of fruits. It may be prepared from inulin, dextrose, or sucrose by a number of methods. Commercially, fructose is mainly manufactured by crystallization from high-fructose syrup derived from hydrolyzed and isomerized cereal starch or cane and beet sugar.

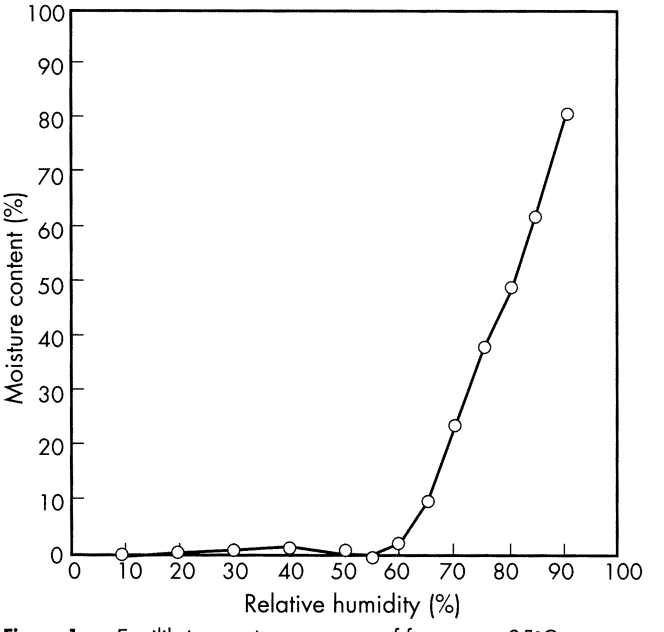


Figure 1: Equilibrium moisture content of fructose at 25°C.

14 Safety

Although it is absorbed more slowly than dextrose from the gastrointestinal tract, fructose is metabolized more rapidly. Metabolism of fructose occurs mainly in the liver, where it is converted partially to dextrose and the metabolites lactic acid and pyruvic acid. Entry into the liver and subsequent phosphorylation is insulin-independent. Further metabolism occurs by way of a variety of metabolic pathways. In healthy and well regulated diabetics, glycogenesis (glucose stored as glycogen) predominates.

Excessive oral fructose consumption (>75 g daily) in the absence of dietary dextrose in any form (e.g., sucrose, starch, dextrin, etc.) may cause malabsorption in susceptible individuals, which may result in flatulence, abdominal pain, and diarrhea. Except in patients with hereditary fructose intolerance,[3,4] there is no evidence to indicate that oral fructose intake at current levels is a risk factor in any particular disease, other than dental caries.[5]

See also Section 18.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Fructose may be irritant to the eyes. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral solutions and suspensions).

17 Related Substances

Dextrose; high-fructose syrup; liquid fructose; milled fructose; powdered fructose; pyrogen-free fructose; sucrose.

High-fructose syrup

Comments: a syrup most commonly containing 42% or 55% fructose, with the remainder consisting of dextrose and small amounts of oligosaccharides. It is a colorless, odorless, highly viscous syrup with a sweet taste.

Liquid fructose

Comments: a syrup containing ⩾99.5% fructose, made by solubilizing crystalline fructose in water. It is a colorless, odorless, highly viscous syrup with a sweet taste (*Frucotofin L*, Xyrofin).

Milled fructose

Comments: a milled fructose material that has an average particle size of 170 µm and is free of glidants (*Frucotofin CM*, Xyrofin).

Powdered fructose

Comments: finely ground crystalline fructose containing ⩽2% silicon dioxide as a glidant.

Pyrogen-free fructose

Comments: a pyrogen-free grade of crystalline fructose (*Frucotofin CFP*, Xyrofin).

18 Comments

Fructose can occur in both the furanose and pyranose forms. Fructose present in natural products occurs in the furanose form, while that produced by crystallization occurs in the pyranose form. An aqueous solution at 20°C contains about 20% of the furanose form.

Although fructose has been proposed for use in the diabetic diet, it is not regarded as a suitable source of carbohydrate, although it does have value as a sweetening agent.[6] The British Diabetic Association has recommended that intake of fructose be limited to 25 g daily.[7]

Fructose has been used as an alternative to dextrose in parenteral nutrition, but its use is not recommended by some because of the risk of lactic acidosis. Although popular in many countries, it has therefore been suggested that the use of intravenous infusions containing fructose and sorbitol should be abandoned.[4,8]

Fructose is the sweetest of all sugars; *see* Table IV.

The EINECS number for fructose is 200-333-3.

Table IV: Relative sweetness of fructose and other sugars.

Sugar	Relative sweetness at 25°C (10% solids)
Fructose	117
Sucrose	100
High fructose syrup-55	99
High fructose syrup-42	92
Dextrose	65

19 Specific References

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4 Collins J. Metabolic disease. Time for fructose solutions to go. *Lancet* 1993; **341**(8845): 600.

5 Glinsman WH, Irausquin H, Park YK. *Evaluation of Health Aspects of Sugars Contained in Carbohydrate Sweeteners: Report of Sugars Task Force.* Washington, DC: Health and Human Services Center for Food Safety and Applied Nutrition, Food and Drug Administration, 1986.

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7 Clarke BP. Is it harmful to a juvenile diabetic to substitute sorbitol and fructose for ordinary sugar? *Br Med J* 1987; **294**: 422.

8 Sweetman SC, ed. *Martindale: The Complete Drug Reference,* 33rd edn. London: Pharmaceutical Press, 2002: 1363–1364.

20 General References

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21 Author

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22 Date of Revision

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