Vanillin

1 Nonproprietary Names

BP: Vanillin
PhEur: Vanillinum
USPNF: Vanillin

2 Synonyms

4-Hydroxy-*m*-anisaldehyde; *p*-hydroxy-*m*-methoxybenzaldehyde; 3-methoxy-4-hydroxybenzaldehyde; methylprotocatechuic aldehyde; *Rhovanil*; vanillic aldehyde.

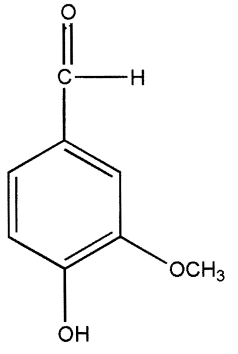
3 Chemical Name and CAS Registry Number

4-Hydroxy-3-methoxybenzaldehyde [121-33-5]

4 Empirical Formula and Molecular Weight

$C_8H_8O_3$ 152.15

5 Structural Formula



6 Functional Category

Flavoring agent.

7 Applications in Pharmaceutical Formulation or Technology

Vanillin is widely used as a flavor in pharmaceuticals, foods, beverages, and confectionery products, to which it imparts a characteristic taste and odor of natural vanilla. It is also used in perfumes, as an analytical reagent and as an intermediate in the synthesis of a number of pharmaceuticals, particularly methyldopa. Additionally, it has been investigated as a potential therapeutic agent in sickle cell anemia[1] and is claimed to have some antifungal properties.[2]

As a pharmaceutical excipient, vanillin is used in tablets, solutions (0.01–0.02% w/v), syrups, and powders to mask the unpleasant taste and odor characteristics of certain formulations, such as caffeine tablets and polythiazide tablets. It is similarly used in film coatings to mask the taste and odor of vitamin tablets.

Vanillin has also been investigated as a photostabilizer in furosemide 1% w/v injection, haloperidol 0.5% w/v injection, and thiothixene 0.2% w/v injection.[3]

8 Description

White or cream, crystalline needles or powder with characteristic vanilla odor and sweet taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for vanillin.

Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Melting range	81–84 °C	81–83 °C
Loss on drying	⩽1.0%	⩽1.0%
Sulfated ash	⩽0.05%	—
Residue on ignition	—	⩽0.05%
Related substances	+	—
Reaction with sulfuric acid	+	—
Organic volatile impurities	—	+
Assay (dried basis)	99.0–101.0%	97.0–103.0%

10 Typical Properties

Acidity/alkalinity: aqueous solutions are acid to litmus.
Boiling point: 284–285 °C (with decomposition)
Density (bulk): 0.6 g/cm^3
Flash point: 153 °C (closed cup)
Melting point: 81–83 °C
Solubility: *see* Table II.

Table II: Solubility of vanillin.

Solvent	Solubility at 20 °C unless otherwise stated
Acetone	Soluble
Alkali hydroxide solutions	Soluble
Chloroform	Soluble
Ethanol (95%)	1 in 2
Ethanol (70%)	1 in 3
Ether	Soluble
Glycerin	1 in 20
Methanol	Soluble
Oils	Soluble
Water	1 in 100 1 in 16 at 80 °C

Specific gravity: 1.056 (liquid)

11 Stability and Storage Conditions

Vanillin oxidizes slowly in moist air and is affected by light.

Solutions of vanillin in ethanol decompose rapidly in light to give a yellow-colored, slightly bitter tasting solution of 6,6′-dihydroxy-5,5′-dimethoxy-1,1′-biphenyl-3,3′-dicarbaldehyde. Alkaline solutions also decompose rapidly to give a brown-colored solution. However, solutions stable for several months may be produced by adding sodium metabisulfite 0.2% w/v as an antioxidant.[4]

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

12 Incompatibilities

Incompatible with acetone, forming a brightly colored compound.[5] A compound practically insoluble in ethanol is formed with glycerin.

13 Method of Manufacture

Vanillin occurs naturally in many essential oils and particularly in the pods of *Vanilla planifolia* and *Vanilla tahitensis*. Industrially, vanillin is prepared from lignin, which is obtained from the sulfite wastes produced during paper manufacture. Lignin is treated with alkali at elevated temperature and pressure, in the presence of a catalyst, to form a complex mixture of products from which vanillin is isolated. Vanillin is then purified by successive recrystallizations.

Vanillin may also be prepared synthetically by condensation, in weak alkali, of a slight excess of guaiacol with glyoxylic acid at room temperature. The resultant alkaline solution, containing 4-hydroxy-3-methoxymandelic acid is oxidized in air, in the presence of a catalyst, and vanillin is obtained by acidification and simultaneous decarboxylation. Vanillin is then purified by successive recrystallizations.

14 Safety

There have been few reports of adverse reactions to vanillin, although it has been speculated that cross-sensitization with other structurally similar molecules, such as benzoic acid, may occur.[6] Adverse reactions that have been reported include contact dermatitis[7] and bronchospasm caused by hypersensitivity.[8]

The WHO has allocated an estimated acceptable daily intake for vanillin of up to 10 mg/kg body-weight.[9]

LD_{50} (guinea pig, IP): 1.19 g/kg[10]
LD_{50} (guinea pig, oral): 1.4 g/kg
LD_{50} (mouse, IP): 0.48 g/kg
LD_{50} (rat, IP): 1.16 g/kg
LD_{50} (rat, oral): 1.58 g/kg
LD_{50} (rat, SC): 1.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the quantity of material handled. Eye protection is recommended. Heavy airborne concentrations of dust may present an explosion hazard.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral solutions, suspensions, syrups, and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Ethyl vanillin.

18 Comments

One part of synthetic vanillin is equivalent to 400 parts of vanilla pods. The EINECS number for vanillin is 204-465-2.

19 Specific References

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20 General References

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21 Author

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22 Date of Revision

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