Coloring Agents

1 Nonproprietary Names

See Section 17 and Tables I, II, III, and IV.

2 Synonyms

See Section 17 for specific, selected coloring agents.

3 Chemical Name and CAS Registry Number

See Tables I, II, III, and IV.

4 Empirical Formula Molecular Weight

See Section 17 for specific selected coloring agents.

Table I: European Union list of coloring materials authorized for coloring medicinal products up to January 2002. *See also* Section 16.

E number	Common name	CAS number	Alternate name
E100	Curcumin	[458-37-7]	Turmeric
E101	Riboflavin	[83-88-5]	Lactoflavin
E102	Tartrazine	[1934-21-0]	
E104	Quinoline yellow	[8004-92-0]	
E110	Sunset yellow FCF	[2783-94-0]	
E120	Carmine	[1260-17-9]	Cochineal, carminic acid
E122	Carmoisine	[3567-69-9]	
E123	Amaranth	[915-67-3]	
E124	Ponceau 4R	[2611-82-7]	
E127	Erythrosine	[16423-68-0]	
E129	Allura red AC	[25956-17-6]	
E131	Patent blue V	[3536-49-0]	
E132	Indigo carmine	[860-22-0]	Indigotine
E133	Brilliant blue FCF	[2650-18-2]	
E140	Chlorophylls	[479-61-8] for (i) [519-62-0] for (ii)	Magnesium chlorophyll
E141	Copper complexes of chlorophylls and chlorophyllins	—	
E142	Green S	[3087-16-9]	Brilliant green BS
E150	Caramel	[8028-89-5]	
E151	Brilliant black BN	[2519-30-4]	Black PN
E153	Vegetable carbon	[7440-44-0]	Carbo medicinalis vegetabilis
E160	Carotenoids		
	(a) Alpha-, beta-, gamma-carotene	[7235-40-7]	
	(b) Capsanthin	[465-42-9]	Paprika oleoresin
	(c) Capsorubin	[470-38-2]	Paprika oleoresin
	(d) Lycopene	[502-65-8]	
	(e) Beta-apo-8′ carotenal	[1107-26-2]	
	(f) Ethyl ester of beta-apo-8′ carotenoic acid	—	
E161	Xanthophylls		
	(b) Lutein	[127-40-2]	
	(g) Canthaxanthin	[514-78-3]	
E162	Beetroot red	[7659-95-2]	Betanin
E163	Anthocyanins		
	Cyanidin	[528-58-5]	
	Delphidin	[528-53-0]	
	Malvidin	[643-84-5]	
	Pelargonidin	[134-04-3]	
	Peonidin	[134-01-0]	
	Petunidin	[1429-30-7]	
E170[a]	Calcium carbonate	[471-34-1]	
E171	Titanium dioxide	[13463-67-7]	
E172	Iron oxides and hydroxides	[977053-38-5]	
E173	Aluminum	[7429-90-5]	

[a] For surface coloring only.

Note: List of colors taken from Directive 94/34/EC, Annex I and IV. (*Official Journal EC* 1994; L237/13).

5 Structural Formula

See Section 17 for specific selected coloring agents.

6 Functional Category

Colorants; opacifiers.

7 Applications in Pharmaceutical Formulation or Technology

Coloring agents are used mainly to impart a distinctive appearance to a pharmaceutical dosage form. The main categories of dosage form that are colored are:

- Tablets: either the core itself or the coating.
- Hard or soft gelatin capsules: the capsule shell or coated beads.
- Oral liquids.
- Topical creams and ointments.

Color is a useful tool to help identify a product in its manufacturing and distribution stages. Patients, especially those using multiple products, often rely on color to be able to recognize the prescribed medication.[1] The use of different colors for different strengths of the same drug can also help eliminate errors.

Many drug products look similar; hence color in combination with shape and/or an embossed or printed logo can help with identification. Also, this combination can assist in the prevention of counterfeiting.

Unattractive medication can be made more acceptable to the patient by the use of color, and color can also be used to make a preparation more uniform when an ingredient in the formulation has itself a variable appearance from batch to batch.[2]

Some of the insoluble colors or pigments have the additional benefit when used in tablet coatings or gelatin shells of providing useful opacity, which can contribute to the stability of light-sensitive active materials in the tablet or capsule formulation. Pigments such as the iron oxides, titanium dioxide, and some of the aluminum lakes are especially useful for this purpose.[3]

Table II: Permanently listed color additives subject to US certification in 2002, excluding those approved exclusively for use in medical devices.

Color	Common name	CAS number	21 CFR references to drug use
FD&C blue #1	Brilliant blue FCF	[2650-18-2]	74.1101
FD&C blue #2	Indigotine	[860-22-0]	74.1102
D&C blue #4	Alphazurine FG	[6371-85-3]	74.1104
D&C blue #9	Indanthrene blue	[130-20-1]	74.1109
FD&C green #3	Fast green FCF	[2353-45-9]	74.1203
D&C green #5	Alizarin cyanine green F	[4403-90-1]	74.1205
D&C green #6	Quinizarine green SS	[128-80-3]	74.1206
D&C green #8	Pyranine concentrated	[6358-69-6]	74.1208
D&C orange #4	Orange II	[633-96-5]	74.1254
D&C orange #5	Dibromofluorescein	[596-03-2]	74.1255
D&C orange #10	Diiodofluorescein	[38577-97-8]	74.1260
D&C orange #11	Erythrosine yellowish Na	[38577-97-8]	74.1261
FD&C red #3[a]	Erythrosine	[16423-68-0]	74.1303
FD&C red #4	Ponceau SX	[4548-53-2]	74.1304
D&C red #6	Lithol rubin B	[5858-81-1]	74.1306
D&C red #7	Lithol rubin B Ca	[5281-04-9]	74.1307
D&C red #17	Toney red	[85-86-9]	74.1317
D&C red #21	Tetrabromofluorescein	[15086-94-9]	74.1321
D&C red #22	Eosine	[17372-87-1]	74.1322
D&C red #27	Tetrachlorotetrabromofluorescein	[13473-26-2]	74.1327
D&C red #28	Phloxine B	[18472-87-2]	74.1328
D&C red #30	Helindone pink CN	[2379-74-0]	74.1330
D&C red #31	Brilliant lake red R	[6371-76-2]	74.1331
D&C red #33	Acid fuchsine	[3567-66-6]	74.1333
D&C red #34	Lake bordeaux B	[6417-83-0]	74.1334
D&C red #36	Flaming red	[2814-77-9]	74.1336
D&C red #39	Alba red	[6371-55-7]	74.1339
FD&C red #40	Allura red AC	[25956-17-6]	74.1340
FD&C red #40 lake	Allura Red AC	[68583-95-9]	74.1340
D&C violet #2	Alizurol purple SS	[81-48-1]	74.1602
FD&C yellow #5	Tartrazine	[1934-21-0]	74.1705
FD&C yellow #6	Sunset yellow FCF	[2783-94-0]	74.1706
D&C yellow #7	Fluorescein	[2321-07-5]	74.1707
Ext. D&C yellow #7	Naphthol yellow S	[846-70-8]	74.1707[a]
D&C yellow #8	Uranine	[518-47-8]	74.1708
D&C yellow #10	Quinoline yellow WS	[8004-92-0]	74.1710
D&C yellow #11	Quinoline yellow SS	[8003-22-3]	74.1711

[a] Dye is permanently listed. The lake is not permitted in medicinal products (*see* Table III).

Table III: Provisionally listed color additives subject to US certification in 2002.

Color	Common name	CAS number	21 CFR references to drug use
FD&C lakes	General	*See* individual color	82.51
D&C lakes	General	*See* individual color	82.1051
Ext. D&C lakes	General	*See* individual color	82.2051
FD&C blue #1 lake	Brilliant blue FCF	[53026-57-6]	82.101
FD&C blue #2 lake	Indigotine	[16521-38-3]	82.102
D&C blue #4 lake	Alphazurine FG	[6371-85-3]	82.1104
FD&C green #3 lake	Fast green FCF	[2353-45-9]	82.1203
D&C green #5 lake	Alizarin cyanine green F	[4403-90-1]	82.1205
D&C green #6 lake	Quinizarine green SS	[128-80-3]	82.1206
D&C orange #4 lake	Orange II	[633-56-5]	82.1254
D&C orange #5 lake	Dibromofluorescein	[596-03-2]	74.1255
D&C orange #10 lake	Diiodofluorescein	[38577-97-8]	82.1260
D&C orange #11 lake	Erythosine yellowish Na	[38577-97-8]	82.1261
FD&C red #4 lake	Ponceau SX	[4548-53-2]	82.1304
D&C red #6 lake	Lithol rubin B	[17852-98-1]	82.1306
D&C red #7 lake	Lithol rubin B Ca	[5281-04-9]	82.1307
D&C red #17 lake	Toney red	[85-86-9]	82.1317
D&C red #21 lake	Tetrabromofluorescein	[15086-94-9]	82.1321
D&C red #22 lake	Eosine	[17372-87-1]	82.1322
D&C red #27 lake	Tetrachlorotetrabromofluorescein	[13473-26-2]	82.1327
D&C red #28 lake	Phloxine B	[18472-87-2]	82.1328
D&C red #30 lake	Helindone pink CN	[2379-74-0]	82.1330
D&C red #31 lake	Brilliant lake red R	[6371-76-2]	82.1331
D&C red #33 lake	Acid fuchsine	[3567-66-6]	82.1333
D&C red #34 lake	Lake bordeaux B	[6417-83-0]	82.1334
D&C red #36 lake	Flaming red	[2814-77-9]	82.1336
D&C violet #2 lake	Alizurol purple SS	[81-48-1]	82.1602
FD&C yellow #5 lake	Tartrazine	[12225-21-7]	82.1705
FD&C yellow #6 lake	Sunset yellow FCF	[15790-07-5]	82.1706
D&C yellow #7 lake	Fluorescein	[2321-07-5]	82.1707
Ext. D&C yellow #7 lake	Naphthol yellow S	[846-70-8]	82.2707
D&C yellow #8 lake	Uranine	[518-47-8]	82.1708
D&C yellow #10 lake	Quinoline yellow WS	[68814-04-0]	82.1710

Of the many classifications possible for pharmaceutical coloring agents, one of the most useful is to simply divide the colors into those that are soluble in water (dyes) and those that are insoluble in water (pigments).

Colors for clear liquid preparations are limited to the dyes;[4] e.g., *see* Section 17.

For surface coloration, which includes coated tablets, the choice of color is usually restricted to insoluble pigments. The reasons for this include their lack of color migration, greater opacity, and enhanced color stability over water-soluble colors.[5]

Lakes are largely water-insoluble forms of the common synthetic water-soluble dyes. They are prepared by adsorbing a sodium or potassium salt of a dye onto a very fine substrate of hydrated alumina, followed by treatment with a further soluble aluminum salt. The lake is then purified and dried.[6]

Lakes are frequently used in coloring tablet coatings since, for this purpose, they have the general advantages of pigments over water-soluble colors. *See* Table V.

8 Description

The physical appearances of coloring agents vary widely. *See* Section 17 for specific selected coloring agents.

9 Pharmacopeial Specifications

Some materials used as pharmaceutical coloring agents are included in various pharmacopeias; for example, titanium dioxide is included in the PhEur 2002. However, if titanium dioxide is being used exclusively as a colorant, then the specific purity criteria from Directive 95/45/EC apply.[7]

10 Typical Properties

Typical properties of specific selected coloring agents are shown in Section 17. Selected properties are shown in Tables V, VI, and VII.

11 Stability and Storage Conditions

Pharmaceutical coloring agents form a chemically diverse group of materials that have widely varying stability properties. Specific information for selected colors is shown in Table VII and can be found in Woznicki and Schoneker.[4] *See also* Section 17.

While some colors, notably the inorganic pigments, show excellent stability, other coloring agents, such as some organic colors, have poor stability properties but are used in formulations because of their low toxicity.[8]

Table IV: List of color additives exempt from certification permitted for drug use in the USA in 2002.

Color	CAS number	21 CFR references to drug use
Alumina	[1332-73-6]	73.1010
Aluminum powder	[7429-90-5]	73.1645
Annatto extract	[8015-67-6]	73.1030
Beta-carotene	[7235-40-7]	73.1095
Bismuth oxychloride	[7787-59-9]	73.1162
Bronze powder	[7440-66-6]	73.1646
Calcium carbonate	[471-34-1]	73.1070
Canthaxanthin	[514-78-3]	73.1075
Caramel	[8028-89-5]	73.1085
Chromium–cobalt–aluminum oxide	[68187-11-1]	73.1015
Chromium hydroxide green	[12182-82-0]	73.1326
Chromium oxide green	[1308-38-9]	73.1327
Cochineal extract; carmine	[1260-17-9] [1390-65-4]	73.1100
Copper powder	[7440-50-6]	73.1647
Dihydroxyacetone	[62147-49-3]	73.1150
Ferric ammonium citrate	[1185-57-5]	73.1025
Ferric ammonium ferrocyanide	[25869-00-5]	73.1298
Ferric ferrocyanide	[14038-43-8]	73.1299
Guanine	[68-94-0] [73-40-5]	73.1329
Iron oxides synthetic	[977053-38-5]	73.1200
Logwood extract	[8005-33-2]	73.1410
Mica	[12001-26-2]	73.1496
Potassium sodium copper chlorophyllin	—	73.1125
Pyrogallol	[87-66-1]	73.1375
Pyrophyllite	[8047-76-5]	73.1400
Talc	[14807-96-6]	73.1550
Titanium dioxide	[13463-67-7]	73.1575
Zinc oxide	[1314-13-2]	73.1991

Table V: Typical characteristic properties of aluminum lakes.

Average particle size	5–10 μm
Moisture content	12–15%
Oil absorption	40–45[a]
Specific gravity	1.7–2.0 g/cm^3
pH stability range	4.0–8.0

[a] ASTM D281-31, expressed as grams of oil per 100 g of color.

Some natural and synthetic organic colors are particularly unstable in light. However, with appropriate manufacturing procedures, combined with effective product packaging, these colors may be used successfully in formulations, thus making a wide choice of colors practically available.

Lakes, inorganic dyes, and synthetic dyes should be stored in well-closed, light-resistant containers at a temperature below 30°C.

For most natural and nature-identical colors, the storage conditions are more stringent and a manufacturer's recommendations for a particular coloring agent should be followed.

To extend their shelf-life, some natural colors are supplied as gelatin-encapsulated or similarly encapsulated powders and may be sealed in containers under nitrogen.

12 Incompatibilities

See Section 17 for incompatibilities of specific selected coloring agents; see also Woznicki and Schoneker,[4] and Walford.[9,10]

Table VI: Approximate solubilities for selected colors at 25°C (g/100 mL)[a]

Color	Water	Glycerin	Propylene glycol	Ethanol (95%)	Ethanol (50%)
Brilliant blue FCF	18	20	20	1.5	20
Indigo carmine	1.5	1	0.1	Trace	0.2
FD&C green #3	17	15	15	0.2	7
Erythrosine	12	22	22	2	4
Allura red AC	20	3	1.5	Trace	1
Tartrazine	15	18	8	Trace	4
Sunset yellow	18	15	2	Trace	2

[a] The solubility of individual batches of commercial product will differ widely depending on the amounts of salt, pure dye, moisture and subsidiary dyes present.

13 Method of Manufacture

See Section 17 and Walford[9,10] for information on specific selected coloring agents.

14 Safety

Coloring agents are used in a variety of oral and topical pharmaceutical formulations, in addition to their extensive use in foodstuffs and cosmetic products.

Toxicology studies are routinely conducted on an ongoing basis by organizations such as the World Health Organization (WHO), the US Food and Drug Administration (FDA), and the European Commission (EC). The outcome of this continuous review is that the various regulatory bodies around the world have developed lists of permitted colors that are generally regarded as being free from serious adverse toxicological effects. However, owing to the widespread and relatively large use of colors in food, a number of coloring agents in current use have been associated with adverse effects, although in a relatively small number of people.[11,12] Restrictions or bans on the use of some coloring agents have been imposed in some countries, while the same colors may be permitted for use in a different country. As a result the same color may have a different regulatory status in different territories of the world.

The lake of erythrosine (FD&C red #3), for example, has been delisted (*see* Section 16) in the USA since 1990, following studies in rats that suggested that it was carcinogenic. This delisting was as a result of the Delaney Clause, which restricts the use of any color shown to induce cancer in humans or animals in any amount. However, erythrosine was not regarded as being an immediate hazard to health and products containing it were permitted to be used until supplies were exhausted.[13]

Tartrazine (FD&C yellow #5) has also been the subject of controversy over its safety, and restrictions are imposed on its use in some countries; *see* Section 17.

In general, concerns over the safety of coloring agents in pharmaceuticals and foods are associated with reports of hypersensitivity[14–16] and hyperkinetic activity, especially among children.[17]

In the USA, specific labeling requirements are in place for prescription drugs that contain tartrazine (*see* Section 18) as this color was found to be the potential cause of hives in fewer than one in 10 000 people. In the EU medicinal products containing tartrazine, sunset yellow, carmoisine, amaranth, ponceau 4R or brilliant black BN must carry a warning on the label concerning possible allergic reactions.

Table VII: Stability properties of selected colors.

Color	Heat	Light	Acid	Base	Oxidizing agents	Reducing agents
Brilliant blue FCF	Good	Moderate	Very good	Moderate	Moderate	Poor
Indigo carmine	Good	Very poor	Moderate	Poor	Poor	Good
FD&C green #3	Good	Fair	Good	Poor	Poor	Very poor
Erythrosine	Good	Poor	Insoluble	Good	Fair	Very poor
Allura red AC	Good	Moderate	Good	Moderate	Fair	Fair
Tartrazine	Good	Good	Good	Moderate	Fair	Fair
Sunset yellow	Good	Moderate	Good	Moderate	Fair	Fair
D&C yellow #10	Good	Fair	Good	Moderate	Poor	Good

15 Handling Precautions

Pharmaceutical coloring agents form a diverse group of materials and manufacturers' data sheets should be consulted for safety and handling data for specific colors.

In general, inorganic pigments and lakes are of low hazard and standard chemical handling precautions should be observed depending upon the circumstances and quantity of material handled. Special care should be taken to prevent excessive dust generation and inhalation of dust.

The organic dyes, natural colors, and nature-identical colors present a greater hazard and appropriate precautions should accordingly be taken.

16 Regulatory Status

Coloring agents have an almost unique status as pharmaceutical excipients in that most regulatory agencies of the world hold positive lists of colors that may be used in medicinal products. Only colors on these lists may be used and some colors may be restricted quantitatively. The legislation also defines purity criteria for the individual coloring agents. In many regions around the world there is a distinction between colors that may be used in drugs and those for food use.

European Union legislation:
The primary legislation that governs coloring matters that may be added to medicinal products is Council Directive 78/25/EEC of 12 December 1977.[18] This Directive links the pharmaceutical requirements with those for foods in the EU. Unfortunately, the Directive makes some specific references to food legislation from 1962 that has subsequently been repealed. However the European Commission has provided guidance on cross references to the current food color legislation as contained in Council Directive 94/36/EC.[19] In addition, the Scientific Committee on Medicinal Products and Medical Devices has delivered opinions on the suitability and safety of amaranth,[20] erythrosine,[21] canthaxanthin,[22] aluminum,[23] and silver[24] as colors for medicines. Silver was considered unsuitable. Table I gives the current position taking the above information into account.

Directive 95/45/EC[7] lays down specific purity criteria for food colors and essentially replaces the provisions of the 1962 Directive.

United States legislation:
The 1960 Color Additive Amendment to the Food Drug and Cosmetic Act defines the responsibility of the Food and Drug Administration in the area of pharmaceutical colorants. Tables II, III, and IV provide lists of permitted colors.[25] The list is superficially long, but many of the coloring agents have restricted use.

For the so-called certified colors, the FDA operates a scheme whereby each batch of color produced is certified as analytically correct by the FDA prior to the issuing of a certification number and document that will permit sale of the batch in question. Colors requiring certification are described as FD&C (Food Drug and Cosmetic); D&C (Drug and Cosmetic) or External D&C. The remaining colors are described as uncertified colors and are mainly of natural origin.

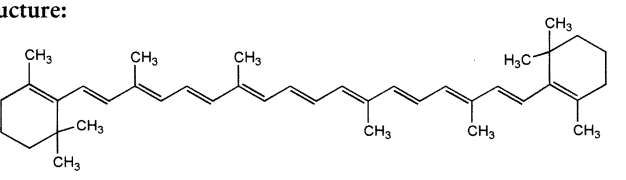
The USA also operates a system of division of certified colors into permanently and provisionally listed colors. Provisionally listed colors require the regular intervention of the FDA Commissioner to provide continued listing of these colors. Should the need arise, the legislative process for removal of these colors from use is comparatively easy.

Licensing authority approval:
In addition to national approvals and lists, a pharmaceutical licensing authority can impose additional restrictions at the time of application review. Within the EU this generally takes the form of restricting colors, such as tartrazine and other azo colors, in medicinal products for chronic administration, and especially in medicines for allergic conditions.

17 Related Substances

Beta-carotene; indigo carmine; iron oxides; sunset yellow FCF; tartrazine; titanium dioxide.

Beta-carotene
Empirical formula: $C_{40}H_{56}$
Molecular weight: 536.85
CAS number: [7235-40-7]
Synonyms: betacarotene; β-carotene; β,β-carotene; E160a.
Structure:



Appearance: occurs in the pure state as red crystals when recrystallized from light petroleum.
Color Index No.:
CI 75130 (natural)
CI 40800 (synthetic)
Melting point: 183°C
Purity (EU):
Arsenic: ≤3 ppm
Lead: ≤10 ppm
Mercury: ≤1 ppm
Cadmium: ≤1 ppm
Heavy metals: ≤40 ppm

Assay: ⩾96% total coloring matters expressed as beta-carotene
Identification: maximum in cyclohexane at 453–456 nm
Sulfated ash: ⩽0.2%
Subsidiary coloring matters: carotenoids other than beta-carotene, ⩽3.0% of total coloring matters.

Purity (US):
Arsenic: ⩽3 ppm
Assay: 96–101%
Lead: ⩽10 ppm
Residue on ignition: ⩽0.2%
Loss on drying: ⩽0.2%

Solubility: soluble 1 in 30 parts of chloroform; practically insoluble in ethanol, glycerin, and water.

Incompatibilities: generally incompatible with oxidizing agents; decolorization will take place.

Stability: beta-carotene is very susceptible to oxidation and antioxidants such as ascorbic acid, sodium ascorbate, or tocopherols should be added. Store protected from light at a low temperature (–20°C) in containers sealed under nitrogen.

Method of manufacture: all industrial processes for preparing carotenoids are based on β-ionone. This material can be obtained by total synthesis from acetone and acetylene via dehydrolinalol. The commercially available material is usually 'extended' on a matrix such as acacia or maltodextrin. These extended forms of beta-carotene are dispersible in aqueous systems. Beta-carotene is also available as micronized crystals suspended in an edible oil such as peanut oil.

Comments: beta-carotene is capable of producing colors varying from pale yellow to dark orange. It can be used as a color for sugar-coated tablets prepared by the ladle process. However, beta-carotene is very unstable to light and air, and products containing this material should be securely packaged to minimize degradation. Beta-carotene is particularly unstable when used in spray-coating processes, probably owing to atmospheric oxygen attacking the finely dispersed spray droplets.

Because of its poor water solubility, beta-carotene cannot be used to color clear aqueous systems, and cosolvents such as ethanol must be used.

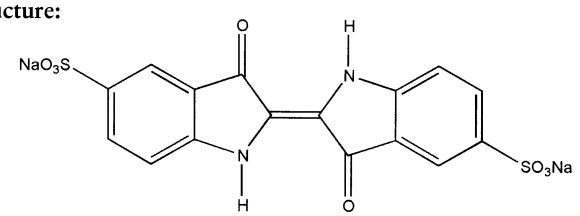
Suppositories have been successfully colored with beta-carotene in approximately 0.1% concentration.

The EINECS number for beta-carotene is 230-636-6.

Indigo carmine

Empirical formula: $C_{16}H_8N_2Na_2O_8S_2$
Molecular weight: 466.37
CAS number: [860-22-0]
Synonyms: 2-(1,3-dihydro-3-oxo-5-sulfo-2*H*-indol-2-ylidene)-2,3-dihydro-3-oxo-1*H*-indole-5-sulfonic acid disodium salt; disodium 5,5′-indigotin disulfonate; E132; FD&C blue #2; indigotine; sodium indigotin disulfonate; soluble indigo blue.

Structure:



Appearance: dark blue powder. Aqueous solutions are blue or bluish-purple.

Absorption maximum: 604 nm
Color Index No.: CI 73015

Purity (EU):
Arsenic: ⩽3 ppm
Lead: ⩽10 ppm
Mercury: ⩽1 ppm
Cadmium: ⩽1 ppm
Heavy metals: ⩽40 ppm
Ether-extractable matter: ⩽0.2% under neutral conditions
Accessory colorings: ⩽1.0%
Isatin-5-sulfonic acid: ⩽1.0%
Water-insoluble matter: ⩽0.2%
Assay: ⩾85% total coloring matters, calculated as the sodium salt
Disodium 3,3′-dioxo-2,2′-biindoylidene-5,7′-disulfonate: ⩽18%.
Water-insoluble matter: ⩽0.2%.
Subsidiary coloring matters: excluding provision above, ⩽1.0%
Organic compounds other than coloring matters: ⩽0.5%
Unsulfonated primary aromatic amines: ⩽0.01%, as aniline

Purity (US):
Arsenic: ⩽3 ppm
2-(1,3-Dihydro-3-oxo-2*H*-indol-2-ylidene)-2,3-dihydro-3-oxo-1*H*-indole-5-sulfonic acid sodium salt: ⩽2%
2-(1,3-Dihydro-3-oxo-7-sulfo-2*H*-indol-2-ylidene)-2,3-dihydro-3-oxo-1*H*-indole-5-sulfonic acid disodium salt: ⩽18%
Isatin-5-sulfonic acid: ⩽0.4%
Lead: ⩽10 ppm
Mercury: ⩽1 ppm
5-Sulfoanthranilic acid: ⩽0.2%
Total color: ⩾85%
Volatile matter, chlorides and sulfates (calculated as the sodium salts): ⩽15.0% at 135°C
Water-insoluble matter: ⩽0.4%

Solubility: *see* Table VIII.

Table VIII: Solubility of indigo carmine.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Practically insoluble
Ethanol (75%)	1 in 1430
Glycerin	1 in 100
Propylene glycol	1 in 1000
Propylene glycol (50%)	1 in 167
Water	1 in 125 at 2°C 1 in 63 at 25°C 1 in 45 at 60°C

Incompatibilities: poorly compatible with citric acid and saccharose solutions. Incompatible with ascorbic acid, gelatin, glucose, lactose, oxidizing agents, and saturated sodium bicarbonate solution.

Stability: sensitive to light.

Method of manufacture: indigo is sulfonated with concentrated or fuming sulfuric acid.

Safety: LD_{50} (rat, IV): 93 mg/kg

Comments: Indigo carmine is an indigoid dye used to color oral and topical pharmaceutical preparations. It is used

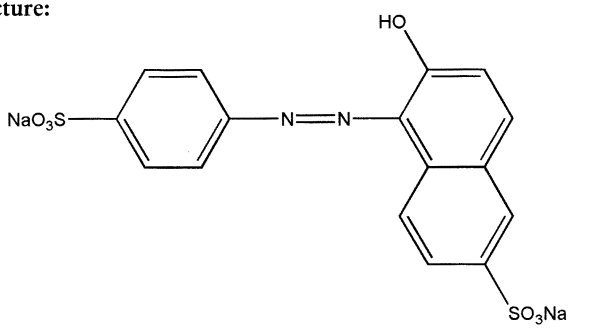
with yellow colors to produce green colors. Indigo carmine is also used to color nylon surgical sutures and is used diagnostically as a 0.8% w/v injection.

Iron oxides

Empirical formula:
$Fe_2O_3 \cdot H_2O$ (yellow, 97–98% monohydrate)
Fe_2O_3 (red)
$FeO \cdot Fe_2O_3$ (black or brown)
CAS number: [977053-38-5]
Synonyms: E172
Appearance: yellow, red, black, or brown powder. The color depends on the particle size and shape and the amount of combined water.
Color Index No.:
CI 77491 (red, brown)
CI 77492 (yellow)
CI 77499 (black)
Purity (EU):
Assay: yellow ⩾60% total iron; red and black ⩾68% total iron
Arsenic: ⩽5ppm
Barium: ⩽50 ppm
Cadmium: ⩽5 ppm
Chromium: ⩽100 ppm
Copper: ⩽50 ppm
Lead: ⩽20 ppm
Mercury: ⩽1 ppm
Nickel: ⩽200 ppm
Zinc: ⩽100 ppm
Water-soluble matter: ⩽1%
Purity (US):
Arsenic: ⩽3 ppm
Lead: ⩽10 ppm
Mercury: ⩽3 ppm
Solubility: practically insoluble in water; partially soluble in strong mineral acids.
Incompatibilities: it has been reported that iron oxides make hard gelatin capsules brittle at higher temperatures when the residual moisture is 11–12%. This factor affects the use of iron oxides for coloring hard gelatin capsules and will limit the amount to be incorporated into the gelatin material.
Method of manufacture: Fe^{2+} salt solutions are precipitated and oxidized to black (or brown) iron oxide.
Comments: iron oxides are gaining importance as mineral colorants as a result of the limitations affecting some synthetic organic dyestuffs. Nevertheless, the use of iron oxide colorants is limited in the USA to a maximum ingestion of 5 mg of elemental iron per day. There are also some technical restrictions affecting the use of iron oxides, e.g., dullness and limitation of shade, and abrasiveness.

Sunset yellow FCF

Empirical formula: $C_{16}H_{10}N_2Na_2O_7S_2$
Molecular weight: 452.37
CAS number: [2783-94-0]
Synonyms: E110; FD&C yellow #6; 6-hydroxy-5-[(4-sulfophenyl)azo]-2-naphthalenesulfonic acid disodium salt; 1-*p*-sulfophenylazo-2-naphthol-6-sulfonic acid disodium salt; yellow orange S.
Structure:



Appearance: reddish yellow powder. Aqueous solutions are bright orange colored.
Absorption maximum: 482 nm
Color Index No.: CI 15985
Purity (EU):
Arsenic: ⩽3 ppm
Lead: ⩽10 ppm
Mercury: ⩽1 ppm
Cadmium: ⩽1 ppm
Heavy metals: ⩽40 ppm
Ether-extractable matter: ⩽0.2% under neutral conditions
Assay: ⩾85% total coloring matters as the sodium salt
Subsidiary colors: ⩽5%
Water-insoluble matter: ⩽0.2%
Organic compounds other than coloring matters: ⩽0.5%
Unsulfonated primary aromatic amines: ⩽0.01% as aniline
Ether-extractable matter: ⩽0.2% under neutral conditions
Purity (US):
Arsenic: ⩽3 ppm
Lead: ⩽10ppm
Mercury: ⩽1ppm
4-Aminobenzenesulfonic acid: ⩽0.2% as the sodium salt
6-Hydroxy-2-naphthalenesulfonic acid: ⩽0.3% as the sodium salt
6,6′-Oxybis[2-naphthalenesulfonic acid]: ⩽1% as the disodium salt
4,4′-(1-Triazene-1,3-diyl)bis[benzenesulfonic acid]: ⩽0.1% as the disodium salt
4-Aminobenzene: ⩽50 ppb
4-Aminobiphenyl: ⩽15 ppb
Aniline: ⩽250 ppb
Azobenzene: ⩽200 ppb
Benzidine: ⩽1 ppb
1,3-Diphenyltriazene: ⩽40 ppb
1-(Phenylazo)-2-naphthalenol: ⩽10 ppm
Total color: ⩾87%
Sum of volatile matter at 135°C, chlorides and sulfates: ⩽13.0%
Water-insoluble matter: ⩽0.2%
Solubility: *see* Table IX.
Incompatibilities: poorly compatible with citric acid, saccharose solutions, and saturated sodium bicarbonate solutions. Incompatible with ascorbic acid, gelatin, and glucose.
Method of manufacture: diazotized sulfanilic acid is coupled with Schaeffer's salt (sodium salt of β-naphthol-6-sulfonic acid).
Safety:
LD_{50} (mouse, IP): 4.6 g/kg
LD_{50} (mouse, oral): >6 g/kg
LD_{50} (rat, IP): 3.8 g/kg
LD_{50} (rat, oral): >10 g/kg
Comments: sunset yellow FCF is a monoazo dye.

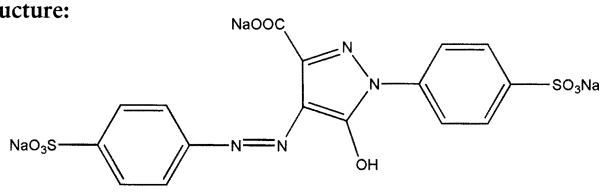
The EINECS number for sunset yellow FCF is 220-491-7.

Table IX: Solubility of Sunset yellow FCF.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	1 in 38.5
Ethanol (75%)	1 in 333
Glycerin	1 in 5
Propylene glycol	1 in 45.5
Propylene glycol (50%)	1 in 5
Water	1 in 5.3 at 2°C 1 in 5.3 at 25°C 1 in 5 at 60°C

Tartrazine

Empirical formula: $C_{16}H_9N_4Na_3O_9S_2$
Molecular weight: 534.39
CAS number: [1934-21-0]
Synonyms: 4,5-dihydro-5-oxo-1-(4-sulfophenyl)-4-[(4-sulfophenyl)azo]-1*H*-pyrazole-3-carboxylic acid trisodium salt; E102; FD&C yellow #5; hydrazine yellow.
Structure:



Appearance: yellow or orange-yellow powder. Aqueous solutions are yellow-colored; the color is retained upon addition of hydrochloric acid solution, but with sodium hydroxide solution a reddish color is formed.
Absorption maximum: 425 nm
Color Index No.: CI 19140
Purity (EU):
Arsenic: ≤3 ppm
Lead: ≤10 ppm
Mercury: ≤1 ppm
Cadmium: ≤1 ppm
Heavy metals: ≤40 ppm
Assay: ≥85% total coloring matters as the sodium salt
Organic compounds other than coloring matters: ≤0.5%
Unsulfonated primary aromatic amines: ≤0.01% as aniline
Ether-extractable matter: ≤0.2% under neutral conditions
Accessory colorings: ≤1.0%
Water-insoluble matter: ≤0.2%
Purity (US):
Arsenic: ≤3 ppm
Lead: ≤10 ppm
Mercury: ≤1ppm
Total color: ≥87.0%
Volatile matter, chlorides and sulfates (calculated as the sodium salts): ≤13.0% at 135°C
Water-insoluble matter: ≤0.2%
4,4′-[4,5-Dihydro-5-oxo-4-[(4-sulfophenyl)hydrazono]-1*H*- pyrazol-1,3-diyl]bis[benzenesulfonic acid]: ≤0.1% as the trisodium salt
4-Aminobenzenesulfonic acid: ≤0.2% as the sodium salt
4,5-Dihydro-5-oxo-1-(4-sulfophenyl)-1*H*-pyrazole-3-carboxylic acid: ≤0.2% as the disodium salt
Ethyl or methyl 4,5-dihydro-5-oxo-1-(4-sulfophenyl)-1*H*-pyrazole-3-carboxylate: ≤0.1% as the sodium salt
4,4′-(1-Triazene-1,3-diyl)bis[benzenesulfonic acid]: ≤0.05% as the disodium salt
4-Aminobenzene: ≤75 ppb
4-Aminobiphenyl: ≤5 ppb
Aniline: ≤100 ppb
Azobenzene: ≤40 ppb
Benzidine: ≤1 ppb
1,3-Diphenyltriazene: ≤40 ppb
Solubility: *see* Table X.

Table X: Solubility of tartrazine.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Practically insoluble
Ethanol (75%)	1 in 91
Glycerin	1 in 5.6
Propylene glycol	1 in 14.3
Propylene glycol (50%)	1 in 5
Water	1 in 26 at 2°C 1 in 5 at 25°C 1 in 5 at 60°C

Incompatibilities: poorly compatible with citric acid solutions. Incompatible with ascorbic acid, lactose, 10% glucose solution, and saturated aqueous sodium bicarbonate solution. Gelatin accelerates the fading of the color.
Method of manufacture: phenylhydrazine *p*-sulfonic acid is condensed with sodium ethyl oxalacetate; the product obtained from this reaction is then coupled with diazotized sulfanilic acid.
Safety:
LD_{50} (mouse, oral): >6 g/kg
LD_{50} (mouse, IP): 4.6 g/kg
LD_{50} (rat, oral): 10 g/kg
LD_{50} (rat, IP): 3.8 g/kg
Comments: tartrazine is a monoazo, or pyrazolone, dye. It is used to improve the appearance of a product and to impart a distinctive coloring for identification purposes.

US regulations require that prescription drugs for human use containing tartrazine bear the warning statement:

> This product contains FD&C yellow #5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons.

Although the overall incidence of sensitivity to FD&C yellow #5 (tartrazine) in the general population is low, it is frequently seen in patients who are also hypersensitive to aspirin.

18 Comments

Titanium dioxide is used extensively to impart a white color to film-coated tablets, sugar-coated tablets, and gelatin capsules. It is also used in lakes as an opacifier, to 'extend' the color. *See* Titanium dioxide for further information.

In the EU, colors used in pharmaceutical formulations and colors used in cosmetics are controlled by separate regulations. Cosmetic colors are also classified according to their use, e.g., those that may be used in external products that are washed off after use.

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