CHAPTER III

DRUG AND POLYMER PROFILE

3.1 ZIDOVUDINE PROFILE (Martindale Extrapharmacopoeia, 2007)

Chemical name: Azidodeoxythymidine; Azidothymidine; AZT; Compound-S; Zidovudinum, 3’-Azido-3’-deoxythymidine.

Molecular formula: C_{10}H_{13}N_{5}O_{4}

Molecular Weight: 267.2

Excretion: Renal

pKa: 9.68

History (En.wikipedia.org/wiki//Zidovudine)

Zidovudine was the first drug approved for the treatment of AIDS and HIV infection. Jerome Horwitz first synthesized AZT in 1964, under a US National Institutes of Health (NIH) grant. It was originally intended to treat cancer, but failed to show efficacy and had an unacceptably high side effect profile. The drug then faded from view until February 1985, when Samuel Broder, Hiroaki Mitsuya, and Robert Yarchoan, three scientists in the National Cancer Institute (NCI), collaborating with Janet Rideout and several other scientists in Burroughs Wellcome Co., started working on it as an AIDS drug. After showing that this drug was an effective agent against HIV in vitro, the team conducted the initial clinical trial that provided evidence that it could increase CD4 counts in AIDS patients.
A placebo-controlled randomized trial of AZT was subsequently conducted by Burroughs-Wellcome (now GlaxoSmithKline), in which it was shown that it could prolong the life of patients with AIDS. Burroughs Wellcome Co. filed for a patent on AZT in 1986. The Food and Drug Administration (FDA) approved the drug (via the then-new FDA accelerated approval system) for use against HIV, AIDS, and AIDS Related Complex (ARC, a now-defunct medical term for pre-AIDS illness) on March 20, 1987, and then as a preventive treatment in 1990. It was initially administered in much higher dosages than today, typically one 400 mg dose every four hours (even at night). However, the unavailability at that time of alternatives to treat AIDS affected the risk/benefit ratio, with the certain toxicity of HIV infection outweighing the risk of drug toxicity. One of AZT’s side-effects includes anemia, a common complaint in early trials.

Modern treatment regimens typically use lower dosages two to three times a day in order to improve the overall quality of life. Like other antiretroviral drugs, AZT is also almost always used in highly active antiretroviral therapy (HAART). That is, it is combined with other drugs in order to prevent mutation of the HIV into an AZT-resistant form.

The crystal structure of AZT was reported by Alan Howie (Aberdeen University) in 1988. In the solid state AZT forms a hydrogen bond network. AZT is based upon a sugar.

**Pharmacopoeial Description** (I.P., 2007; B.P., 2007; U.S.P., 2007)

- Indian Pharmacopoeia: A white or almost white powder

Adverse Effects

The commonest serious adverse effects reported with zidovudine are anaemia and leucopenia, mainly neutropenia, occurring within a few weeks of starting treatment. This haematological toxicity occurs most commonly in those with pre-existing haematological abnormalities and is usually reversed by interrupting treatment or reducing dosage but it can be severe enough to require blood transfusion.

Other frequently reported adverse effects include asthenia, fever and malaise; dizziness, headache, insomnia, myopathy and paraesthesia; abdominal pain, anorexia, dyspepsia, diarrhoea, nausea, and vomiting; myalgia and rashes. Lactic acidosis have been reported as rare, but potentially fatal, occurrences in patients taking zidovudine, Pancreatitis, convulsions, and pigmentation of nails, skin, and oral mucosa have occurred.

Precautions

Zidovudine should be used with care in patients with anaemia or bone-marrow suppression. The incidence of neutropenia is greater in patients with low vitamin B₁₂ concentrations. Dosage adjustments may be necessary and it has been recommended that it should not be used if the neutrophil count or haemoglobin value is abnormally low. Care is also required in the elderly and in patients with reduced kidney or liver function who may require reductions in dose. Patients with risk factors for liver disease should be monitored during treatment. Zidovudine treatment should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly, or metabolic or lactic acidosis of unknown aetiology. It should not be given to neonates with hyperbilirubinaemia requiring treatment other than phototherapy or with markedly increased aminotransferase concentrations.
Because of the haematological toxicity of zidovudine it is recommended that, in patients with advanced symptomatic HIV disease taking oral zidovudine, blood tests should be carried out at least every 2 weeks for the first 3 months of treatment and at least monthly thereafter; blood tests should be performed at least every week in those receiving intravenous zidovudine. In patients with early HIV infection blood tests may be performed less frequently (e.g. every 1 to 3 months).

**Interactions**

**Analgesics**

There may be an increased risk of haematoxicity during concomitant use of zidovudine and NSAIDs.

**Antibacterials**

Studies have indicated that the absorption of zidovudine could be reduced by concurrent administration of clarithromycin.

Trimethoprim has been reported to decrease the renal clearance of zidovudine by up to 60% with a consequent increase in plasma concentrations.

**Antiepileptics**

Administration of valproic acid to 6 patients receiving zidovudine produced increases in plasma zidovudine.

**Antifungals**

Administration of fluconazole in combination with zidovudine produced higher serum-zidovudine concentrations, increase in the area under the serum concentration-time curve and prolonged terminal half-life compared with zidovudine alone in a study in 12 patients.

**Antivirals**

Studies in vitro showed that ribavirin and zidovudine inhibited each other's anti-HIV activity and the manufacturer recommends that this combination should be avoided.
With Atovaquone

Administration of atovaquone in combination with zidovudine produced moderate increase in the zidovudine plasma concentration and area under the plasma concentration-time curve, probably by inhibition of glucuronidation.

With Probenecid

Administration of probenecid with zidovudine results in increased plasma concentrations and area under the plasma concentration time curve of zidovudine, probably due to inhibition of glucuronidation.

Antiviral Action

Zidovudine is converted intracellularly in stages to the triphosphate via thymidine kinase and other kinases. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. It has also been shown to possess activity against Epstein - Barr virus and Gram-negative bacteria in vitro.

Pharmacokinetics (www.gsk.com)

Zidovudine is rapidly absorbed from the gastrointestinal tract and undergoes first-pass hepatic metabolism with a bioavailability of about 60 to 70%. Peak plasma concentrations occur after about 1 hour. Absorption is delayed by administration with food, but bioavailability is probably unaffected. Zidovudine crosses the blood-brain barrier producing CSF to plasma ratios of about 0.5. It crosses the placenta and is distributed into breast milk. Plasma protein binding is reported to be 34 to 38%. The plasma half-life is about 1 hour.

Zidovudine is metabolized intracellularly to the antiviral triphosphate. It is also metabolized in the liver mainly to the inactive glucuronide and is excreted in the urine as unchanged drug and metabolite.
Bioavailability
Absorption of oral zidovudine was delayed or reduced when the dose was taken with a meal compared when taken after an overnight fast. It was suggested that zidovudine must be taken with empty stomach to have a high plasma concentration.

Mechanism of Action
Zidovudine is a nucleoside reverse transcriptase inhibitor structurally related to thymidine. It has activity against retro viruses including HIV.

Indications
1. It is used in the general management of HIV infection.
2. Also for a prophylactic treatment for HIV.

Dose
1. It is given by orally in adult doses of 500 to 600 mg, daily in divided dosages. Higher dosages may be required for neurological diseases.
2. The oral dose for children over three months of age is 360 to 480 mg per m$^2$ body surface daily.

Dosage forms existing in market:
Zidovudine Capsules, Zidovudine Injection, Zidovudine Oral Solution.

3.2 POLYETHYLENE SORBAN FATTY ACID ESTERS
(Rowe, et al., 2003)

Functional Category
Emulsifying agent; nonionic surfactant; solubilizing agent; wetting, dispersing/suspending agent.
Applications in Pharmaceutical Formulation

Polyoxyethylene sorbitan fatty acid esters (polysorbates) are a series of partial fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20, 5 or 4 moles of ethylene oxide for each mole of sorbitol and its anhydrides. The resulting product is therefore a mixture of molecules of varying sizes rather than a single uniform compound. Polysorbates containing 20 units of oxyethylene are hydrophilic nonionic surfactants that are used widely as emulsifying agents in the preparation of stable oil-in-water pharmaceutical emulsions. They may also be used as solubilizing agents for a variety of substances including essential oils and oil-soluble vitamins, and as wetting agents in the formulation of oral and parenteral suspensions. They have been found to be useful in improving the oral bioavailability of drug molecules that are substrates for p-glycoprotein. Polysorbates are also widely used in cosmetics and food products.

Stability and Storage Conditions

Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. The oleic acid esters are sensitive to oxidation. Polysorbates are hygroscopic and should be examined for water content prior to use and dried if necessary. Also, in common with other polyoxyethylene surfactants, prolonged storage can lead to the formation of peroxides.

Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place.
Table 1: Uses of polysorbates

<table>
<thead>
<tr>
<th>Uses</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsifying agent</td>
<td>-</td>
</tr>
<tr>
<td>Used alone in oil-in-water emulsions</td>
<td>1–15</td>
</tr>
<tr>
<td>Used in combination with hydrophilic emulsifiers in oil-in-water emulsions</td>
<td>1–10</td>
</tr>
<tr>
<td>Used to increase the water-holding properties of ointments</td>
<td>1–10</td>
</tr>
<tr>
<td>Solubilizing agent</td>
<td>-</td>
</tr>
<tr>
<td>For poorly soluble active constituents in lipophilic bases</td>
<td>1–10</td>
</tr>
<tr>
<td>Wetting agent</td>
<td>-</td>
</tr>
<tr>
<td>For insoluble active constituents in lipophilic bases</td>
<td>0.1–3</td>
</tr>
</tbody>
</table>

Incompatibilities
Discoloration and/or precipitation occur with various substances, especially phenols, tannins, tars, and tar-like materials. The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.

Regulatory Status
Polysorbates 60, 65, and 80 are GRAS listed. Polysorbates 20, 40, 60, 65, and 80 are accepted as food additives in Europe. Polysorbates 20, 40, 60, and 80 are included in the FDA Inactive Ingredients Guide (IM, IV, oral, rectal, topical, and vaginal preparations). Polysorbates are included in parenteral and non-parenteral medicines licensed in the UK. Polysorbates 20, 21, 40, 60, 61, 65, 80, 81, 85, and 120 are included in the Canadian List of Acceptable Non-medicinal Ingredients.
3.2.1 **Tween 20** (Raymond C. Rowe, *et al.*, 2003).

**Nonproprietary Names**
Polysorbate 20

**Synonym**
Armotan PML 20; Capmul POE-L; Campul POE-L Low PV; Crillet 1; Drewmulse; E432; Durfax 20; E432; Eumulgin SML; Glycosperse L-20; Hodag PSML-20; Lamesorb SML-20; Liposorb L-20; Liposorb L-20K; Montanox 20; Nissan Nonion LT-221; Norfox Sorbo T-20; POE-SML; Ritabate 20; Sorbax PML-20; sorbitan monododecanoate; Sorgen TW-20; T-Maz 20; TMaz 20K; poly(oxy-1,2-ethanediyl) derivatives; polyoxyethylene 20 laurate; Protasorb L-20; Tego SML 20; Tween 20.

**Chemical name**
Polyoxyethylene 20 sorbitan monolaurate

**Structure**

![Structure diagram]

**Empirical formula and molecular weight**
\[ C_{18}H_{34}O_6(C_2H_4O)_n \]

**Colour and form**
Yellow oily liquid.

**Solubility**
Soluble in water and ethanol. Insoluble in mineral oils.
Safety

Moderate toxicity by IP and IV routes. Moderately toxic by ingestion. Human skin irritant.

- \( \text{LD}_{50} \) (hamster, oral): 18 g/kg
- \( \text{LD}_{50} \) (mouse, IV): 1.42 g/kg
- \( \text{LD}_{50} \) (rat, oral): 37 g/kg

3.2.2 Tween 40 (Rowe, et al., 2003)

*Nonproprietary Names*
Polysorbate 40

*Synonym*
Crillet 2; E434; Eumulgin SMP; Glycosperse S-20; Hodag PSMP-20; Lamesorb SMP-20; Liposorb P-20; Lonzest SMP-20; Montanox 40; poly(oxy-1,2-ethanediyl) derivatives; Protasorb P-20; Ritabate 40; sorbitan monohexadecanoate; Sorbax PMP-20; Tween 40.

*Chemical name*
Polyoxyethylene 20 sorbitan monopalmitate

*Structure*

\[
\text{Empirical formula and molecular weight}
\]

\[ C_{22}H_{42}O_6(C_2H_4O)_n \]
Colour and form

Yellow oily liquid

Solubility

Soluble in water and ethanol. Insoluble in mineral oils

Safety

LD$_{50}$ (rat, IV): 1.58 g/kg.
Moderately toxic by IV route.

Toxicological Information

Acute Toxicity

\[
\begin{array}{ll}
\text{LD}_50 & \text{Oral, Rat} > 38400 \text{ mg/kg} \\
\text{LD}_50 & \text{Intravenous, Rat, 1580 mg/kg} \\
\text{LD}_50 & \text{Intravenous, Mouse, 50 gm/kg}
\end{array}
\]

3.2.3 Tween 60 (Raymond C. Rowe, et al., 2003)

Nonproprietary Names

Polysorbate 60

Synonym

Atlas 70K; Atlas Armaton PMS 20; Capmul POE-S; Cremophor PS 60; Crillett3; Drewpone 60K; Durfax 60; Durfax 60K; E435; Emrite 6125; Eumulgin SMS; Glycosperse S-20; Glycosperse S-20FG; Glycosperse S-20FKG; Hodag PSMS-20; Hodag SVS-18; Lamsorb SMS-20; Liposorb S-20; Liposorb S-20K; Lonzest SMS-20; Nikkol TS-10; Norfox SorboT-60 Montanox 60; Polycon T 60 K; polyoxyethylene 20 stearate; Ritabate 60; Protasorb S-20; Sorbax PMS-20; sorbitan mono-octadecanoate poly(oxy-1,2-ethanediyl) derivatives; T-Maz 60; T-Max 60KHS; Tween 60; Tween 60K; Tween 60 VS.
Chemical name
Polyoxyethylene 20 sorbitan monostearate

Structure

\[
\text{HO}\biggl[\underbrace{\text{O}}_a\biggr]\biggl[\underbrace{\text{OH}}_b\biggr]^{n = a + b + c + d}\biggl[\underbrace{\text{O}}_c\biggr]\biggl[\underbrace{\text{OH}}_d\biggr]^{\text{O}}\biggl[\text{O}_2\biggr]\biggl[\text{H}_4\biggr]\biggl[\text{O}_6\biggr].
\]

Empirical formula and molecular weight
\[C_{24}H_{46}O_6 \cdot (C_2H_4O)_n\]

Colour and form
Yellow oily liquid

Solubility
Soluble in water and ethanol. Insoluble in mineral oils

Safety
LD_{50} (rat, IV): 1.22 g/kg.
Moderately toxic by IV route. Experimental tumorigen, reproductive effects.

3.2.4 Tween 80 (Raymond C. Rowe, et al., 2003)

Nonproprietary Names
Polysorbate 80

Synonym
Atlas E; Armotan PMO 20; Capmul POE-O; Cremophor PS 80; Crillet 4; Crillet 50; Drewmulse POE-5MO; Drewpone 80K; Durfax 80; Durfax 80K; E433; Emrite 6120; Eumulgin SMO; Glycosperse O-20; Hodag PSMO-20; Liposorb O-20; Liposorb O-20K; Montanox 80; polyoxyethylene 20 olate; Protasorb O-20; Ritabate 80; (Z)-sorbitan mono-9-octadecenoate poly(oxy1,2-ethanediyl) derivatives; Tego SMO 80; Tego SMO 80V; Tween 80.
Chemical name
Polyoxyethylene 20 sorbitan monooleate

Structure

![Chemical structure](image)

Empirical formula and molecular weight
C_{64}H_{124}O_{26}
M.W.: 1310

Colour and form
Yellow oily liquid

Solubility
Soluble in water and ethanol. Insoluble in mineral oils

Safety
Moderately toxic by IV route. Mildly toxic by ingestion. Eye irritation. Experimental tumorigen, reproductive effects. Mutagenic data.

- LD_{50} (mouse, IP): 7.6 g/kg
- LD_{50} (mouse, IV): 4.5 g/kg
- LD_{50} (mouse, oral): 25 g/kg
- LD_{50} (rat, IP): 6.8 g/kg
- LD_{50} (rat, IV): 1.8 g/kg
3.3 **SORBITAN ESTERS** *(Sorbitan Fatty Acid Esters (Rowe, *et al.*, 2003)*

**Functional Category**

Emulsifying agent; nonionic surfactant; solubilizing agent; wetting and dispersing/suspending agent.

**Applications in Pharmaceutical Formulation**

Sorbitan monoesters are a series of mixtures of partial esters of sorbitol and its mono- and dianhydrides with fatty acids. Sorbitan diesters are a series of mixtures of partial esters of sorbitol and its monoanhydride with fatty acids.

Sorbitan esters are widely used in cosmetics, food products, and pharmaceutical formulations as lipophilic nonionic surfactants. They are mainly used in pharmaceutical formulations as emulsifying agents in the preparation of creams, emulsions, and ointments for topical application. When used alone, sorbitan esters produce stable water-in-oil emulsions and microemulsions but are frequently used in combination with varying proportions of a polysorbate to produce water-in-oil or oil-in-water emulsions or creams of varying consistencies.

Sorbitan monolaurate, sorbitan monopalmitate and sorbitan trioleate have also been used at concentrations of 0.01–0.05% w/v in the preparation of an emulsion for intramuscular administration.

**Stability and Storage Conditions**

Gradual soap formation occurs with strong acids or bases; sorbitan esters are stable in weak acids or bases. Sorbitan esters should be stored in a well-closed container in a cool, dry place.

**Solubility**

Sorbitan esters are generally soluble or dispersible in oils; they are also soluble in most organic solvents. In water, although insoluble, they are generally dispersible.
Safety

Sorbitan esters are widely used in cosmetics, food products, and oral and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. However, there have been occasional reports of hypersensitive skin reactions following the topical application of products containing sorbitan esters. When heated to decomposition, the sorbitan esters emit acrid smoke and irritating fumes. The WHO has set an estimated acceptable daily intake of sorbitan monopalmitate, monostearate and tristearate and of sorbitan monolaurate and monooleate at up to 25 mg/kg body-weight calculated as total sorbitan esters.

Regulatory Status

Certain sorbitan esters are accepted as food additives in the UK. Sorbitan esters are included in the FDA Inactive Ingredients Guide (inhalations; IM injections; ophthalmic, oral, topical and vaginal preparations). Sorbitan esters are used in nonparenteral medicines licensed in the UK. Sorbitan esters are included in the Canadian List of Acceptable Non-medicinal Ingredients.

Table 2: Uses of Sorbitan Esters

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<td>For insoluble active constituents in lipophilic bases</td>
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</tr>
</tbody>
</table>
3.3.1 Span 20 (Rowe, et al., 2003)

*Nonproprietary Names*
Sorbitan monolaurate

*Synonym*
Arlacel 20; Armotan ML; Crill 1; Dehymuls SML; E493; Glycomul L; Hodag SML; Liposorb L; Montane 20; Protachem SML; Sorbester P12; Sorbirol L; sorbitan laurate; Span 20; Tego SML.

*Chemical name*
Sorbitan monododecanoate

*Structure*

![Structure of Span 20](image)

*Empirical formula and molecular weight*
\[ C_{18}H_{34}O_6 \]
M.W: 346

*Colour and form*
Yellow viscous liquid

*Safety*
LD_{50} (rat, oral): 33.6 g/kg.
Experimental neoplasitigen.

3.3.2 Span 40 (Rowe, et al., 2003)

*Nonproprietary Names*
Sorbitan monopalmitate

*Formulation Development and In vivo Evaluation of Zidovudine Niosomes*
Chapter III

Drug & Polymer Profile

**Synonym**

1,4-Anhydro-D-glucitol, 6-hexadecanoate; Ablunol S-40; Arlacel 40; Armotan MP; Crill 2; Dehmuls SMP; E495; Glycomul P; Hodag SMP; Lamesorb SMP; Liposorb P; Montane 40; Nikkol SP-10; Nissan Nonion PP-40R; Protachem SMP; Proto-sorb SMP; Sorbester P16; Sorbirol P; sorbitan palmitate; Span 40.

**Chemical name**

Sorbitan monohexadecanoate

**Structure**

![Structure of Sorbitan monohexadecanoate]

**Empirical formula and molecular weight**

C\(_{22}\)H\(_{42}\)O\(_6\); M.W: 403

**Colour and form**

Cream solid

**3.3.3 Span 60** (Rowe, *et al.*, 2003)

*Nonproprietary Names*

Sorbitan monostearate

**Synonym**

Ablunol S-60; Alkamuls SMS; 1,4-Anhydro-D-glucitol, 6-octadecanoate; anhydroisorbitol monostearate; Arlacel 60; Armotan MS; Atlas 110K; Capmul S; Crill 3; Dehmuls SMS; Drewmulse SMS; Drewsorb 60K; Durban 60; Durtan 60K; E491; Fandom MS Kosher; Glycomul S FG; Glycomul S KFG; Hodag SMS; Lamesorb SMS; Liposorb S; Liposorb SC; Liposorb S-K; Montane 60; Nissan Nonion SP-60R; Norfox Sorbo S-60FG; Polycon S60K; Protachem SMS; Protosorb SMS; S-Maz 60K; SMaz 60KHS; Sorbester P18; Sorbirol S; sorbitan stearate; Sorgen 50; Span 60; Span 60K; Span 60 VS; Tego SMS.
Chapter I

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Formulation Development and In vivo Evaluation of Zidovudine Niosomes

Chemical name

Sorbitan mono-octadecanoate

Structure

Empirical formula and molecular weight

\[ C_{24}H_{46}O_6 \]

M.W: 431

Colour and form

Cream solid

Safety

LD50 (rat, oral): 31 g/kg.

Very mildly toxic by ingestion. Experimental reproductive effects.

3.3.4 Span 80 (Rowe, et al., 2003)

Nonproprietary Names

Sorbitan monooleate

Synonym

Ablunol S-80; Arlacel 80; Armotan MO; Capmul O; Crill 4; Crill 50; Dehymuls SMO; Drewmulse SMO; Drewsorb 80K; E494; Glycomul O; Hodag SMO; Lamesorb SMO; Liposorb O; Montane 80; Nikkol SO-10; Nissan Nonion OP-80R; Norfox Sorbo S-80; Polycon S80 K; Proto-sorb SMO; Protachem SMO; S-Maz 80K; Sorbester P17; Sorbirol O; sorbitan oleate; Sorgen 40; Sorgon S-40-H; Span 80; Tego SMO.
Chemical name

(Z)-Sorbitan mono-9-octadecenoate

Structure

Empirical formula and molecular weight

\[ C_{24}H_{44}O_6 \]; M.W: 429

Colour and form:

Yellow viscous liquid

3.4 OTHER FORMULATION ADDITIVES

3.4.1 Dicetyl phosphate (Rowe, et al., 2003)

Synonym: Dihexadecyl phosphate

Formula: \[ C_{32}H_{67}O_4P \]

Molecular Weight: 546.85 g/mol

Appearance

Form solid

Structure

Linear Formula:

\[ [\text{CH}_3(\text{CH}_2)_{15}\text{O}]_2\text{P(O)}\text{OH} \]
TOXICOLOGICAL INFORMATION

Chronic exposure
IARC: No component of this product presents at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

Potential Health Effects
Inhalation May be harmful if inhaled. May cause respiratory tract irritation.
Skin May be harmful if absorbed through skin. May cause skin irritation.
Eyes May cause eye irritation.
Ingestion May be harmful if swallowed

3.4.2 Cholesterol (Rowe, et al., 2003)

Nonproprietary Names
Cholesterol

Synonyms
Cholesterin; cholesterolum.

Chemical Name
Cholest-5-en-β-ol [57-88-5]

Empirical Formula and Molecular Weight
C_{27}H_{46}O
386.67

Structure

Formulation Development and In vivo Evaluation of Zidovudine Niosomes
Functional Category

Emollient; emulsifying agent.

Applications in Pharmaceutical Formulation

Cholesterol is used in cosmetics and topical pharmaceutical formulations at concentrations of 0.3–5.0% w/w as an emulsifying agent. It imparts water-absorbing power to an ointment and has emollient activity. Cholesterol also has a physiological role. It is the major sterol of the higher animals, and it is found in all body tissues, especially in the brain and spinal cord. It is also the main constituent of gallstones.

Description

Cholesterol occurs as white or faintly yellow, almost odorless, pearly leaflets, needles, powder or granules. On prolonged exposure to light and air, cholesterol acquires a yellow to tan color.

Stability and Storage Conditions

Cholesterol is stable and should be stored in a well-closed container, protected from light.

Table 3: Solubility of cholesterol in different solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>Soluble</td>
</tr>
<tr>
<td>Benzene</td>
<td>1 in 7</td>
</tr>
<tr>
<td>Chloroform</td>
<td>1 in 4.5</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1 in 147 at 0°C</td>
</tr>
<tr>
<td></td>
<td>1 in 78 at 20°C</td>
</tr>
<tr>
<td></td>
<td>1 in 29 at 40°C</td>
</tr>
<tr>
<td></td>
<td>1 in 19 at 50°C</td>
</tr>
<tr>
<td></td>
<td>1 in 13 at 60°C</td>
</tr>
<tr>
<td>Ethanol (95%)</td>
<td>1 in 78 (slowly)</td>
</tr>
<tr>
<td></td>
<td>1 in 3.6 at 80°C</td>
</tr>
<tr>
<td>Ether</td>
<td>1 in 2.8</td>
</tr>
<tr>
<td>Isopropyl myristate</td>
<td>1 in 19</td>
</tr>
<tr>
<td>Methanol</td>
<td>1 in 294 at 0°C</td>
</tr>
<tr>
<td>Vegetable oils</td>
<td>Soluble</td>
</tr>
<tr>
<td>Water</td>
<td>Practically insoluble</td>
</tr>
</tbody>
</table>
Safety

Cholesterol is generally regarded as an essentially nontoxic and nonirritant material at the levels employed as an excipient. It has, however, exhibited experimental teratogenic and reproductive effects, and mutation data have been reported. Cholesterol is often derived from animal sources and this must be done in accordance with the regulations for human consumption. The risk of bovine spongiform encephalopathy (BSE) contamination has caused some concern over the use of animal-derived cholesterol in pharmaceutical products. However, synthetic methods of cholesterol manufacture have been developed.

Regulatory Status

Included in the FDA Inactive Ingredients Guide (injections, ophthalmic, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

3.4.3 β-Cyclodextrin (Rowe, et al., 2003)

Formula : C_{42}H_{70}O_{35}·H_{2}O
Molecular weight : 1134.99
Synonyms : β-Dextrin; beta-Cycloamylose; beta-Cycloheptaamylose; Cycloheptaamylose; Cycloheptaglucan; Cycloheptaglucosan; Schardinger beta-dextrin; Cyclomaltoheptaose
β-Cyclodextrin is a compendial substance and is considered for a (generally recognized as safe) status. This absorption optimizer has a lot of potential as it shows the promise for good absorption enhancement without significant toxicity potential.

**PHYSICAL AND CHEMICAL PROPERTIES**

**Physical State**: White, practically odorless, fine crystalline powder, having a slightly sweet taste.

**Melting Point**: 255-265°C

**Bulk density**: 0.523 g/cm³.

**Tapped density**: 0.754 g/cm³.

**Specific Rotation**: +162.0°

**Surface tension**: 71 m Nm (71 dynes/cm)

**Solubility In Water**: Soluble

<table>
<thead>
<tr>
<th>Temperature °C</th>
<th>*Grams in 100ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 C</td>
<td>1.8</td>
</tr>
<tr>
<td>45 C</td>
<td>4.5</td>
</tr>
<tr>
<td>60 C</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Other solvents: Soluble in 1 in 200 parts of propylene glycol, practically insoluble in acetone, ethanol (95 %) and methylene chloride.

**Stability**

β-cyclodextrin are stable in the solid state if protected from high humidity. It should be stored in a tightly sealed container in a cool, dry place.
Safety

LD$_{50}$ (mouse, IP) : 0.33 g/kg
LD$_{50}$ (mouse, SC) : 0.41 g/kg
LD$_{50}$ (Rat, IP) : 0.36 g/kg
LD$_{50}$ (Rat, IV) : 1.0 g/kg
LD$_{50}$ (Rat, Oral) : 18.8 g/kg
LD$_{50}$ (Rat, SC) : 3.7 g/kg

3.4.4 Lactose Monohydrate (Rowe et al., 2003)

Synonyms: (alpha)-Lactose; Milk Sugar; Lactose Monohydrate

Lactose occurs as white to off white crystalline particles or powder.
Lactose is odorless
Molecular formula : C$_{12}$H$_{22}$O$_{11}$
Molecular weight : 360.31

Properties
Bulk density : 0.62g/cm$^3$
Tapped density : 0.94g/cm$^3$
True density : 1.552
Melting point : 201-202°C
Specific rotation : + 52° to 52.6°

Stability and storage conditions
Lactose should be stored in a well-closed container in a cool, dry place.
1. **Solubility**

   **Table 5: Solubility of lactose in water**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility at 20°C unless otherwise stated</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloroform</td>
<td>Practically soluble</td>
</tr>
<tr>
<td>ethanol</td>
<td>Practically soluble</td>
</tr>
<tr>
<td>ether</td>
<td>Practically soluble</td>
</tr>
<tr>
<td>water</td>
<td>1 in 4.63</td>
</tr>
<tr>
<td></td>
<td>1 in 3.14 at 40°C</td>
</tr>
<tr>
<td></td>
<td>1 in 2.04 at 50°C</td>
</tr>
<tr>
<td></td>
<td>1 in 1.68 at 60°C</td>
</tr>
<tr>
<td></td>
<td>1 in 1.07 at 80°C</td>
</tr>
</tbody>
</table>

**Regulatory status**

Included in the FDA inactive ingredients guide (IV injections: oral capsules and tablets) included in non-parenteral and parenteral medicines licensed in the UK.