CHAPTER – V

MATERIALS AND METHODS

PART A:

5.1 Drug Profile: Tenofovir Disoproxil Fumarate (TDF)

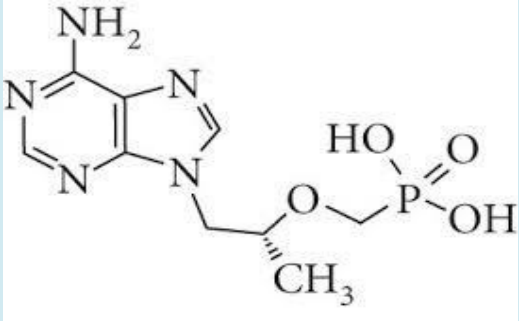
Tenofovir Disoproxil Fumarate is a tenofovir prodrug that is the fumaric acid salt of tenofovir's bis-isopropoxycarbonyloxymethyl ester derivative. In vivo, TDF is transformed into tenofovir, an acyclic nucleoside phosphonate (nucleotide) analogue of adenosine 5'-monophosphate. Tenofovir has action against HIV-1 reverse transcriptase. It is used in conjunction with other antiretroviral medications to treat human immunodeficiency virus type 1 infection in adults and paediatric patients aged two years and up who weigh at least ten kilogrammes. It is used to treat chronic hepatitis B virus (HBV) in adults and children aged two and above who weigh at least ten kilogrammes.[1]

Category: Nucleoside Reverse Transcriptase Inhibitor (NRTIs) namely HIV-1 reverse transcriptase inhibitor and an HBV reverse transcriptase inhibitor (HBV RTI)

Mechanism of Action: It is an acyclic nucleoside phosphonate diester, similar to adenosine monophosphate. It requires diester hydrolysis to become tenofovir, which is subsequently phosphorylated by cellular enzymes to become tenofovir diphosphate (TFV-DP), an essential chain terminator. Tenofovir diphosphate inhibits HIV-1 and HBV reverse transcriptase (RT) activity by competing with the natural substrate deoxyadenosine 5'-triphosphate and, if incorporated into DNA, ending the chain. Tenofovir diphosphate is a mild inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.[2]

Table 5.1 : Characteristics of Tenofovir Disoproxil Fumarate

Parameter	Tenofovir Disoproxil Fumarate
CAS No.	202138-50-9
Chemical Name	Tenofovir disoproxil fumarate is 9-[(R)-2[bis[[(isopropoxycarbonyl)oxy]-methoxy] phosphinyl] methoxy] propyl] adenine fumarate (1:1}
Empirical Formula	$C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$
Molecular Weight	635.52
Description	White to off-white bitter crystalline powder with

Parameter	Tenofovir Disoproxil Fumarate
	characteristic odor
Melting point	114-118°C
Structure	
Solubility	About 13.4 mg/mL in distilled water at 25 °C. In ethanol and DMSO solubility is about 100 mg/ml. Solubility in 0.1N hydrochloric acid is about 78.2 mg/ml and in methanol is about 96.3 mg/ml.
(log P)	1.25 at 25 °C
Peak plasma time (T_{max}):	1-1.4 hours
Metabolism	Metabolized by CYP enzymes.
Excretion	About 70-80% tenofovir is recovered in urine unchanged in 72 hours
Half-life	Approximately 17 hours
Dosage forms & Strengths	Tablets, Oral Powder 300 mg
Storage	Store tenofovir tablets or tenofovir powder dosage form at 20 to 25°C. The bulk powder of tenofovir should be below 4°C. Store in tightly closed container. Keep away the tenofovir tablets or tenofovir powder dosage form from the reach of children.

5.1.1 Determination of Organoleptic Properties (TDF)

The organoleptic properties of Tenofovir disoproxil fumarate were determined by sensory evaluation like color, odor, and taste.

Table 5.2 : Organoleptic Properties of Tenofovir Disoproxil Fumarate

Parameter	Observed
Color	White to off-white
Odor	Characteristic
Taste	Bitter

Inference: The taste of Tenofovir Disoproxil Fumarate was found to have bitter characteristics.

5.1.2 Particle Size Distribution (TDF):

The particle size distribution of Drug substance referred from Vendor COA. The method of testing is Malvern Master sizer.[3]

Inference: The Particle size distribution of Tenofovir disoproxil fumarate API: d (0.9) – 190 µm.

5.1.3 Density and Flow Properties (TDF):

Bulk density is the ratio of bulk weight to bulk volume. Fifty g of API was precisely weighed and carefully poured via a glass funnel into a 100 ml calibrated measuring cylinder. The surface was carefully levelled with no pressure.[4] The volume occupied by pellets was utilised to calculate the bulk density (g/ml) using the equation,

Bulk density = Weight of powder ÷ $Bulk\ volume\ of\ pellets$…….(5.1)

Tapped density is ratio of bulk weight and tapped volume. Tapped density was estimated in a similar way to that of bulk density. However, final volume was measured after tapping the cylinder from 3 inches until constant volume was obtained using Electrolab tapped density apparatus.[4] The volume occupied by pellets after tapping was noted and tapped density (g/ml) was calculated using the equation,

Tapped density = Weight of powder ÷ Tapped $volume\ of\ pellets$…….(5.2)

Carrs's Index is calculated using bulk density and tapped density data.[5]

$Carr's\ Index = (Tapped\ density - Bulk\ density) \div Tapped\ density \times 100$ …….(5.3)

Density and flow properties of Tenofovir disoproxil fumarate API was evaluated and the results are given in the following table,

Table 5.3 : Density and Flow Properties of TDF

Bulk density (g/mL)	Tapped density (g/mL)	Carr's Index (%)
0.35	0.51	30.85

Inference: Tenofovir disoproxil fumarate API showed poor to very poor flow characteristic.

5.1.4 Solubility of Tenofovir Disoproxil Fumarate

The aqueous solubility of the drug is significant in drug absorption. When the drug is administered orally, the composition of GI fluid changes with the position of the dosage form. Therefore, to simulate the conditions, the solubility of the drug in 0.1N HCl, distilled water, and phosphate buffer pH 6.8 was determined. Also, the solubility was determined in ethanol, methanol, and DMSO.[6]

Technique: Equilibrium solubility method was used.

Procedure: It is determined by placing 1 g of TDS in 100 ml of distilled water on a rotatory shaker for 24 hr at 37°C.After 24 hours the solution was filtered using 0.45 µ member filter. The amount dissolved in the filtrate was determined using UV- Visible spectrophotometer at 260 nm.[6,7]

Table 5.4 : Solubility of TDF

Solvent	Solubility (mg/ml)
0.1 N HCl	77.86 ± 2.06
Distilled water	13.27 ± 0.45
pH 6.8 phosphate buffer	68.33 ± 1.96
Ethanol	97.42 ± 3.57
Methanol	80.09 ± 2.81
DMSO	101.55 ± 3.32

Inference: The highest solubility among aqueous media is in 0.1 N acid and the lowest in distilled water. Among the organic solvents, highest solubility is found in DMSO.

5.1.5 Melting point of TDF:

The melting point of Tenofovir disoproxil fumarate API was evaluated using two different methods, Capillary technique using mineral oil and Differential Scanning Calorimetry (DSC)[8]

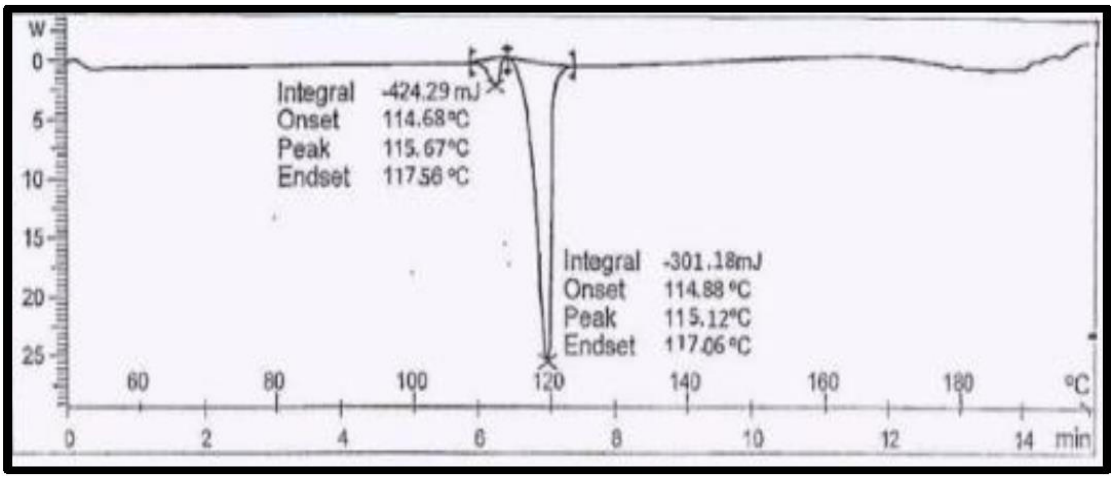


Fig. 5.1 : DSC Thermogram of Tenofovir Disoproxil Fumarate

Inference: Melting point of Tenofovir disoproxil fumarate API found to be between 115-118°C (by Capillary technique) and 115.67°C (by DSC).

5.1.6 Loss on Drying of TDF

The Loss on drying is determined using Hot air oven technique. The 1 g of TDF at 105±2°C was kept in hot air oven till constant weight was observed.

Inference: The % Loss on Drying for TDF sample was found to be 1.23%.

5.2 Risk Assessment for Drug Substance Attributes of TDF

A risk evaluation of the drug substance attributes was conducted to determine the potential influence of each attribute on the drug product Critical Quality Attributes. The assessment results and related reasoning are summarised here. The relative risk of each trait was rated as high, medium, or low. The high-risk features deserved additional research, but the low-risk attributes did not. According to current

understanding, a medium risk is tolerable. Further examination of medium risk may be required to lessen the danger.[9]

Table 5.5 : Overview of Relative Risk Ranking System

Low	Broadly acceptable risk. No further investigation is needed.
Medium	Risk is accepted. Investigation may be needed in order to reduce the risk.
High	Risk is unacceptable. Investigation is needed to reduce the risk.

The risk assessment of drug substance qualities that affect drug product CQAs is provided below based on the drug substance's physicochemical parameters.

Table 5.6 : Risk Assessment of the Drug Substance Attributes for TDF

Drug product CQA	Tenofovir drug substance attributes					
	Organoleptic properties	**Particle size**	**Solubility**	**Melting point**	**Loss on drying**	**Flow properties**
Taste	High	Low	Low	Low	Low	Low
Content uniformity	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	Low
Dissolution	Low	Medium	Medium	Low	Low	Low

Table 5.7

Drug Substance Attributes	Drug Product CQAs	Justification
Organoleptic Properties (Color, Odor, Taste & nature)	Taste	High risk as the taste of API is bitter, so it impacts patients' acceptance. It may induce nausea.
	Content Uniformity	Low risk as organoleptic characteristics has no direct impact on Content uniformity, assay and dissolution.
	Assay	
	Dissolution	

Particle size	Taste	Low risk as Particle size has no direct impact on taste
	Content Uniformity	Particle size may have impact on flow properties and hence, assay and content uniformity. However, API is being granulated. Hence risk is low.
	Assay	
	Dissolution	Particle size may have impact on dissolution hence risk is medium.
Melting Point	Taste	Low risk as Melting Point has no direct impact on taste, Content uniformity, assay, and dissolution
	Content Uniformity	
	Assay	
	Dissolution	
Solubility	Taste	Low risk as Solubility has no direct impact on taste, content uniformity, assay and dissolution
	Content Uniformity	
	Assay	
	Dissolution	The solubility of drug substance in dissolution medium has impact on dissolution. The risk is medium.
Loss on Drying	Taste	Low risk as Loss on drying has no direct impact on taste, content uniformity, assay, and dissolution.
	Content Uniformity	
	Assay	
	Dissolution	
Flow Properties	Taste	Low risk as Flow properties has no direct impact on taste.
	Content Uniformity	Tenofovir disoproxil fumarate has very

	Assay	poor flow property. However, the drug substance would be subjected to dry granulation process to facilitate blend flow. Hence, impact of flow of Tenofovir disoproxil fumarate on content uniformity and assay is low.
	Dissolution	Flow of Tenofovir disoproxil fumarate is unlikely to impact dissolution. The risk is low.

5.3 Excipients for TDF:

The excipients were selected based on literature search, the requirement of immediate-release tablets and pre-formulation studies. Excipients were selected based on their functionality. For development of tablet dosage form, the grades suitable for wet granulation process and hot melt coating were selected.

5.3.1 Gelucire 43/01

A glyceride with intermediate melting point used as a matrix agent for sensitive APIs and a viscosity-increasing agent in oral and topical formulations. It is composed of mono-, di- and triglyceride esters of fatty acids (C_8 to C_{18}), the triester fraction being predominant. It is available in pellet form. It is a blend of saturated triglycerides of different fatty acids, viz., C8 - 3%, C10 - 2%, C12 - 29%, C14 - 2%, C16 - 17%, and C18 - 36%. Gelucire® 43/01 is ideal for API protection and capsule filling. Matrix-former for protection of APIs sensitive to oxidation, humidity, or light. It is composed of PEG-esters, a small glyceride fraction and free PEG. It is a solid at ambient temperature making it suitable for capsule filling, melt granulation and extrusion. It is available in pellet form.[10]

Synonyms (USP/NF/JPE/EP): Hard fats

Preferred FDA Name: Fat, Hard

CAS Number: 157710-38-8

Melting point: 42-46°C

Category: Protective, Lubricant, 3D printing drug carrier, emulsifier, viscosity modifier, solubilizes.

HLB: 1-2

Drop point: 53-57°C

Mean particle size: 50 μ

Formulations & Processes: Melt processes: granulation and capsule molding. Topical lotions, emulsion and ointment.

Pharmacopoeial compliance: Yes

Solubility: It is hydrophobic grades and insoluble in water.

Applications: Diltiazem hydrochloride (melt granulation) as matrix carrier in multi-unit floating drug delivery system, Metoprolol succinate (melt granulation) in sustained release floating drug delivery system, Cefuroxime axetile (melt granulation filled in capsule) in enhancement of bioavailability, Famotidine in floating tablet, Metformin hydrochloride (melt granulation) in enhancement of bioavailability, Tramadol HCL mouth dissolving tablets for taste masking, and increase drug release on aging from matrices using Gelucire® 43/01. It is used as a lipid binder in melt techniques so that the physicochemical properties and plasticity of the lipid agglomerate offers high resistance to fracture, useful for flash melt and chewable tablets.[10]

Safety: Safety of use is supported by toxicological data and food additive status.

Storage: Store in cool and dry place in moisture resistant plastic containers.

5.3.2 Precirol ATO 5

A glyceride with an intermediate melting point that is utilised as a lubricant and flow aid in powder mixes for capsule filling, as well as a coating agent for flavour masking. It is an organic molecule classified as long-chain fatty acid. These are fatty acids having an aliphatic tail that comprises 13 to 21 carbon atoms. Stearic acid is also commonly used as a solid lipid in the manufacture of NLCs. Aadhunik Industries is India's leading manufacturer of Glyceryl Palmitostearate or Glycerol Palmitostearate, Speciality Chemicals, Pharmaceutical Excipients, Food Fragrance and Flavour chemicals. It is made via direct esterification of stearic and palmitic acids with glycerine in the absence of a catalyst. FDA recommended as excipient in non-parenteral formulations.[11,12]

Synonym: Glycerin Palmitostearate; Glycerol Palmitostearate; 2-[(1-oxo-hexadecyl)-oxyl]-pxy]-1,3-Propanediyl Dicotadecanoate and 1,2,3-Propane Triol; Glyceryl Distearate; Glyceryl Distearate (Type I); Precirol® ATO 5

CAS Number: 8067-32-1

CAS name: Precirol ATO 5

Pharmacopoeial Compliance: USP-NF; Ph.Eur

IUPAC Name: Hexadecanoic acid; octadecanoic acid; propane-1,2,3-triol

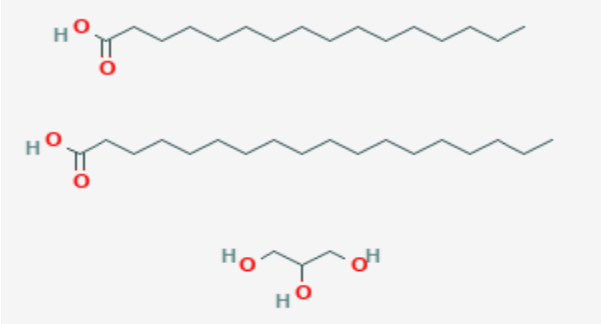


Fig. 5.2: Structure of Precirol ATO 5

Appearance: Fine white waxy powder.

Solubility: Freely soluble in chloroform and dichloromethane but practically insoluble in water, mineral oil and alcohol.

Category: Lubricant and flowing aid for capsules, coating for protection and taste masking, lipid matrix for sustained release and SLN/NLC, viscosity modification. It works as stabilizer, non-ionic emulsifier, emollient, gelling agent and as plasticizer in pharmaceutical formulations.

Molecular formula: $C_{37}H_{76}O_7$

Molecular weight: 633.0 g/mol

Melting point: 50-60 °C

Boiling point: 200°C

Drop point: 53-57°C

Flash point: 162 °C

Heavy metal: 10 ppm maximum.

Dosage forms: Oral and topical formulation

Particle size: About 50-60 µ

Hydrogen bond donor: 5

Hydrogen bond acceptor: 7

Covalently bonded unit: 3

Acid value: < 6

Iodine value: < 3

Peroxide value: < 3

Hydroxy value: 60-115

Saponification value: 175-195

Water content: < 1%

Free glycerine content: < 3%

1- Monoglyceride content: < 8-11%

Unsaponified matter: < 1%

Sulphated ash: < 0.1%

HLB: 1-2

Median lethal dose, LD_{50} (Rat oral dose): > 6 g/kg

GHS Hazards: Not classified. Food and Drug Administration (FDA) added to food substances (Document 184.1329)

Applications: In solid dosage forms as lubricant, matrix former in sustained release dosage forms using melt granulation or hot melt coating technique. It is used in immediate release formulation. It is used as polymer in microcapsules preparations and converting into tablet or capsule unit dosage form. It is used as biodegradable injectable gel.

Storage: It should be stored at temperature not exceeding 35 °C.

Containers: Air tight container, protected from light and moisture.

Incompatibilities: Ketoprofen and naproxen

5.3.3 Microcrystalline Cellulose (Avicel PH 101)

Synonyms: Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

Molecular Formula: $(C_6H_{10}O_5)_n$, $n \approx 200$

Molecular weight: 36000g/mol

CAS Number: 9004-34-6

Structural Formula:

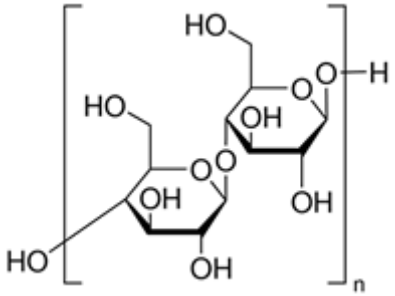


Fig. 5.3 : Structure of Microcrystalline Cellulose

Functional Category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrates.

Description: It is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

pH: pH 5.0-7.5

Melting point: Chars at 260–270°C.

Angle of repose: 33-49°

Bulk density: 0.337 g/ml

Tapped density: 0.478 g/ml

True density: 1.512- 1.668 g/ml

Moisture content: < 5%

Particle size: 20-200µ

Specific surface area: 0.78- 1.30 m^2/g

Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agents.

Stability & Storage condition: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Applications: Microcrystalline cellulose is widely utilised in medicines, particularly as a binder/diluent in oral tablet and capsule formulations using both wet-granulation and direct-compression processes. In addition to its function as a binder/diluent, microcrystalline cellulose possesses lubricating and disintegrating qualities that make

it valuable in tableting. Microcrystalline cellulose is also utilised in cosmetics and culinary goods.[13]

Incompatibilities: It is incompatible with strong oxidizing agents.

Handling precaution: It may be irritant to the eyes. Use of gloves, eye protection aid, and dust mask is recommended.

Stability: Stable although it is hygroscopic material.

Storage: Store in well closed container in cool and dry place.

5.3.4 Spray Dried Lactose (DCL 11)[14]

Synonyms: Lactopress Spray-Dried, FlowLac 100, NF Lactose–316 Fast Flo, Pharmatose DCL 11, Pharmatose DCL 14, Super-Tab Spray-Dried, NF Lactose–315, Flowlac, Granulac, Microfine, Pharmatose, Prismalac, milk sugar, HMS, Sorbolac, Super-Tab, Tabletosse, Wyndale, Zeparox, Lactochem, Inhalac, Capsulac, Fastflo.

Chemical name: It is a mixture of α-and-β-lactose, and O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate. O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose anhydrous

CAS registry number: 63-42-3 and 64044-51-5.

Molecular formula: $C_{12}H_{22}O_{11}$ and $C_{12}H_{22}O_{11}.H_2O$

Molecular weight: 342.30 (anhydrous) and 360.31 (monohydrate)

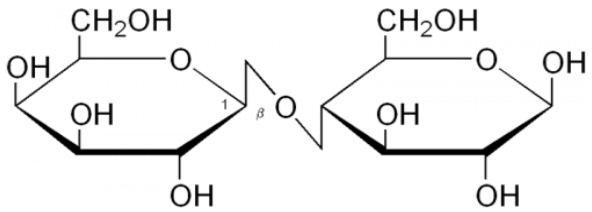


Fig. 5.4: Structure of Lactose

Category: Diluent or filler directly compressible tablet and capsule, binder. Diluent in dry powder inhaler.

Description: It is white or off-white crystalline odorless powder with sweet in taste. It is directly compressible and normally composed of 80–90% of α-lactose monohydrate and 10–20% of amorphous lactose. The α- lactose is about 15% sweet in comparison with sucrose. The β- lactose is sweeter than α- lactose.

Solubility: It is water-soluble, insoluble in ether and chloroform and having slight solubility in ethanol.

pH (10% solution): 4.5 to 7.5

Optical rotation: + 55.4 °

Melting point: 202–205 °C

Flash point: 358–360 °C

Bulk density: 0.57 – 0.62 g/ml

Tapped density: 0.67 – 0.78 g/ml

Moisture content: Maximum 6

Loss on drying: 0.3 – 0.6%

Osmolarity: 9.75% is osmolar with serum

Pharmaceutical applications: As a binder, filler-binder, spray-dried lactose is majorly preferred in direct compression of tablets.

Storage: Containers must be firmly sealed stored in a well-closed container in a cool, dry place.

Incompatibilities: Spray dried lactose is incompatible with agents with primary amino group, with amino acids, aminophylline, amphetamines, and also with lisinopril. Maillard reaction may occurs between lactose and these compounds to produce brown or yellow brown-coloured products.

Safety: Spray dried lactose is employed as diluents in oral solid medicaments. It is also preferred in parenteral. Lactose shows adverse reactions due to its intolerance, majorly in persons with deficient of enzyme lactase.

Handling precautions: Normal precautions as per the conditions and extent of material being handled need to be observed. During handling extreme creation of dust and inhalation of dust must be avoided.

5.3.5 Polyvinyl Pyrrolidone K-30[15]

Povidones are a family of water-soluble polymers based on N-vinylpyrrolidone that combine a unique set of properties for application in a wide variety of dosage forms. These are prepared by synthetic reaction. They contain linear chain of 1-vinyl 2-pyrrolidone with varying degree of polymerization. Based on polymerization molecular weight of polymer changes. The viscosity of these polymers is based on K-value, which is range from 10-120 corresponding to molecular weight range from 2,500 to 30,00,000. It manufactured by spray drying spherical form. They are commonly used as binders for the development of tablet formulations, whether

manufactured by wet granulation, dry granulation, or direct compression. The special grade pyrogen free povidone grades are available for parenteral preparation. These polymers are used in solid dispersion formulations to enhance the solubility of active pharmaceutical ingredients and increase bioavailability. Their various grades are also used to inhibit recrystallization in liquid soft gels. It was firstly used as plasma expander in 1940, now it was replaced by dextran. It is not absorbed by GIT and mucous membrane. It does not cause irritation to skin and mucous membrane and hence included in GRAS list.

Synonyms: Kollidone; Povidone; Plasdone; Poly[1-(2-oxo-1-pyrrolidinyl) ethylene];

Non-proprietary Names: BP, JP, USP: Povidone, and PhEur: Povidonum

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer

CAS Registry Number: 9003-39-8

Molecular formula: $(C_6H_9NO)_n$

Molecular weight: 50, 000

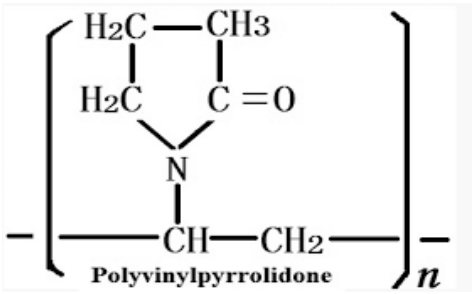


Fig. 5.5 : Structure of Polyvinyl Pyrrolidone

Description: Colourless to almost colourless, fine, white to creamy amorphous hygroscopic powder. It is pH stable and form transparent film.

Odour: Odourless

Melting point: 150° C

Residue on ignition: ≤ 0.05 %

Water content: ≤ 5.00 %

Sulphated ash: ≤ 0.10 %

pH of solution (5% at 25° C in water): 3.0-5.0

Viscosity of solution (5% at 25° C in water): 2.4 cP

K-value: 27-32.4

Residual monomer content: 0.8%

Peroxide content: ≤ 400 ppm

Hydrazine content: ≤ 1 ppm

Lead content (USP): ≤ 10 ppm

Nitrogen content: 11.5-12.8%

Bulk density: 0.29-0.39 g/ml

Tapped density: 0.39-0.54 g/ml

True density: 1.180 g/ml

Solubility: Freely soluble in acids, chloroform, ethanol Practically insoluble in ether. Soluble in water (0.5g/ 10 ml).

Functional category: Disintegrant; dissolution enhancer; emulsion stabilizer in creams & lotions, dispersant, suspending agent; tablet binder, viscosity modifier & coating agent.

Storage and Precautions: It darkens on heating at 150°C and reduce aqueous solubility. It is stable heat exposure around 110– 130°C for short cycle.

Incompatibilities: It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. Handling precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

Regulatory status: Accepted as a food additive in Europe. Listed in the FDA Inactive Ingredients Database (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspension tablets; sublingual tablets; topical and vaginal preparations).

Applications: Used in adhesives, inks, glue stick, synthetic fiber and porous membrane manufacture. Dispersant in ceramics.

Storage: Store in tightly closed in a dry, cool and well-ventilated place. The containers should be resealed immediately after use and kept upright to prevent leakage.

Incompatibilities: The efficacy of preservatives like thiomersal was affected adversely by complexation when used with povidone.

Precautions: Avoid skin, and eye contact. Avoid inhalation of vapour or mist. Normal measures to be taken for preventive fire protection. Use protective aids.

Consult a physician in any case of following-

1. If inhaled or breathed in, move person into fresh air.
2. If not breathing, give artificial respiration.
3. In case of skin contact, wash off with soap and plenty of water.
4. In case of eye contact, rinse thoroughly with plenty of water for at least 15 minutes
5. If swallowed, never give anything by mouth to an unconscious person. Rinse mouth with water.

5.3.6 Alpha- Tocopherol[16]

Alpha-Tocopherol is a naturally occurring fat-soluble fatty molecule with varied levels of powerful antioxidant action, often known as vitamin E. It is an amphipathic chemical present in plant tissues, although it may also be produced synthetically. RRR-alpha-tocopherol acetate is a relatively stable version of vitamin E that is frequently employed as a food ingredient when necessary. It has the capacity to neutralise endogenous free radicals. Vitamin E naturally occurs in eight fat-soluble isoforms: α-, β-, γ-, and δ-tocopherol, as well as α-, β-, γ-, and δ-tocotrienol. Supplementing with α-tocopherol is the only way to correct symptoms of vitamin E insufficiency, as the body preferentially utilises it. Tocopherol additionally protects the skin from the sun's damaging UV radiation. It is used in a broad range of goods, including sunscreens and moisturisers, cosmetics, hair styling products, and more. It also acts as a preservative, keeping the items fresh. It is used as a moisturising and conditioning agent. It has anti-inflammatory qualities that moisturise and heal damaged, brittle hair. Tocopherol's antioxidant capabilities encourage healthy hair.

Synonym and trade name: Tocopherol; α-Tocopherol; Vitamin E; alpha-Tocopherol; Copherol Fl300; Vitamin E; all-rac- α-Tocopherol; DL-α-Tocopherol; α-Tocopherolum; E307; RRR-α-Tocopherol; Synthetic alpha Tocopherol; all-rac-α-Tocopherol;

Molecular formula: $C_{29}H_{50}O_2$

Molecular weight: 430.71

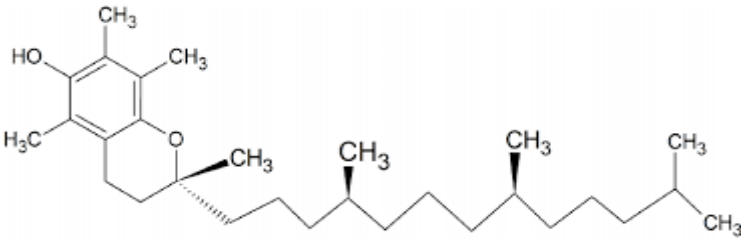


Fig. 5.6 : Structure of Alpha-tocopherol

IUPAC Name: 2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol, (±)-3,4-Dihydro-2,5,7,8-Tetramethyl-2-(4,8,12-Trimethyltridecyl)-2H-1 Benzopyran-6-ol; 5,7,8-trimethyltocol

CAS Number: 59-02-9

Category: Antioxidant; Fatting Agent; and Therapeutic Agent

Description: Alpha Tocopherol is supplied as a clear, colourless or yellowish-brown, viscous oily liquid.

Solubility: Soluble in DMSO (100 mg/ mL) and ethanol (100 mg/ mL) require ultrasonication. Practically insoluble in water. Freely soluble in ethanol, ether, acetone, and vegetable oils.

Melting point: 2.5-3.5°C

Boiling point: 200-220°C

Acid value: ≤ 2

Optical rotation: -0.01- + 0.01°

Heavy metals: < 20 ppm

Refractive index: 1.503-1.507

Specific gravity: 0.947-0.955

Density: 0.947-0.955 g/ml

Flash point: 240°C

Indications: Vitamin E, known for its antioxidant effects, has been demonstrated to protect against cardiovascular disease and some forms of cancer while also boosting the immune system. It may be of some use to persons with asthma or rheumatoid arthritis. It may help with a variety of neurological diseases, including Alzheimer's, ocular issues including cataracts, diabetes, and premenstrual syndrome. It may also help protect skin from UV rays, however claims that it reverses skin ageing, increases male fertility, and enhances exercise performance are unfounded. It may help relieve

muscle cramps. Because of vitamin E's biologic action, there is ongoing interest and study into whether its antioxidant characteristics may be used to help prevent or treat a range of conditions, including cardiovascular disease, eye issues, diabetes, cancer, and others. However, there is presently insufficient official data and evidence to suggest any novel uses for vitamin E.

Interactions: Orlistat may limit the absorption of D-alpha-Tocopherol acetate, resulting in a lower serum concentration and perhaps a reduction in effectiveness. A variety of cholesterol-lowering medicines (such as cholestyramine and colestipol), as well as orlistat, sucralfate, mineral oil, and the fat replacement olestra, which inhibit fat absorption, may theoretically reduce the absorption of fat-soluble vitamins, including vitamin E.

Storage: Below 4°C, protect from light, stored under inert environment

Shelf life: Below -20°C as powder for 3 years, below 4°C as powder, 2 years, in solvent below -80°C for 6 months, in solvent below -20°C for 1 month. Avoid freeze-thaw cycle.

Incompatibilities: Incompatible with metal ion and peroxides. It is absorbed by plastics.

5.3.7 Magnesium Stearate[17]

Molecular Formula: $[CH_3 (CH_2)_{16}COO]$ 2Mgs

Synonyms: Dibasic magnesium stearate; Magnesium Distearate

Structural formula:

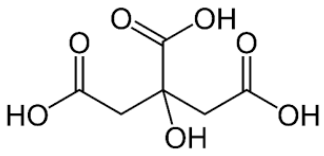


Fig. 5.7 : Structure of Magnesium Stearate

Synonyms: Dibasic magnesium stearate; Magnesium distearate; Magnesiistearas; Magnesium octadecanoate; Octadecanoic acid, magnesium salt; Stearic acid; Magnesium salt; Synpro90.

Empirical formula: $C_{36}H_{70}MgO_4$

Molecular weight: 591.24 g/mol

Description: It is a very fine, light white, precipitated or milled powder with a low bulk density, a mild stearic acid odour, and a distinct flavour. The powder feels oily to the touch and easily sticks to the skin.

Functional categories: Tablet and capsule lubricant.

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Melting point: 117–150˚C

Density: 1.092 g/cm^3

Loss on drying: 46.0%

Stability and storage conditions: Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials.

Applications: It is primarily used as a lubricant in capsule and tablet manufacture.

5.3.8 Talc[18]

Non-proprietary names:

BP: Purified talc

JP and USP: Talc

Synonyms: Magsilosmanthus; Magsil Star; Powdered talc; Purified French chalk; Purtalc.

Empirical formula: $Mg_6 (Si_2O_5)_4(OH)_4$

Molecular Formula: $Mg_6 (Si_2O_5)_4(OH)_4$

Structure:

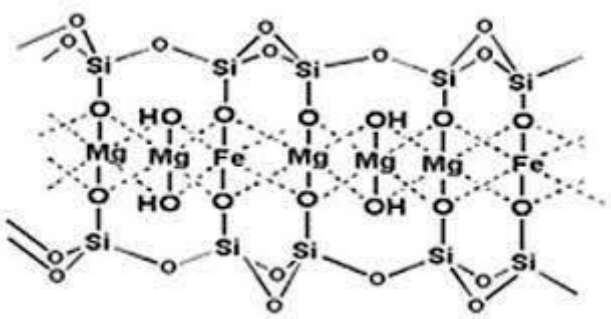


Fig. 5.8 : Structure of Talc

Description: Talc is a very fine; white to greyish-white, odourless, impalpable, unctuous, Crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Functional categories: Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Solubility: Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Melting point: 150˚C

Handling Precautions: Talc is irritant if inhaled and prolonged excessive exposure may cause Pneumoconiosis. Eye protection, gloves and respirator is recommended.

Stability and storage conditions: Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with quaternary ammonium compounds.

Applications:

1. It is used as a diluent, lubricant in tablet formulations.
2. In a novel powder coating for extended-release pellets and as an adsorbent.
3. In topical preparations, it is used as a dusting powder, used to clarify liquids.
4. It is also used in cosmetics and food products.

5.3.9 Crospovidone (CP)[19]

Non-proprietary Names

BP: Crospovidone

Ph Eur: Crospovidonum

USP/NF: Crospovidone

Synonyms: Crosslinked povidone; Kollidon CL; E1202; Kollidon CL-M; 1-vinyl-2-pyrrolidinone homopolymer; Polyplasdone XL.

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula: $(C_6H_9NO)_n$

Molecular weight: >1 000 000

Structural Formula

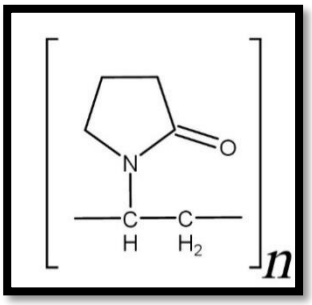


Fig. 5.9 : Structure of Crospovidone

Functional Category: Tablet disintegrant.

Description: Crospovidone is a hygroscopic powder that is white to creamy-white, free-flowing, almost tasteless, odorless or nearly odorless.

Typical properties

Acidity/alkalinity: pH 5.0–8.0 (aqueous slurry of 1% w/v)

Density: 1.22 g/cm^3

Solubility: In water and most typical organic solvents are almost insoluble.

Applications in pharmaceutical preparation or technology

Crospovidone is a water-insoluble tablet disintegrant and dissolving agent that is used at a rate of 2-5 percent in tablets manufactured by direct compression or wet and dry granulation. It has a strong capillary action and a high hydration capacity, with a low tendency to create gels. According to study, the crystal structure of crospovidone influences the breakdown of analgesic tablets. Larger molecules dissolve more quickly than smaller ones. Crospovidone can be used as a solubility enhancer. Crospovidone can be used in the co-evaporation method to increase the solubility of weakly water-soluble medications. In the presence of enough solvent, the medication is deposited on crospovidone, which is subsequently vaporised. This approach produces a faster rate of disintegration.

Storage Conditions and Stabilization: Crospovidone should be kept in a tightly sealed container in a cold, dry location since it is hygroscopic.

Incompatibilities: Most organic and inorganic medicinal compounds are compatible with crospovidone. When subjected to a specific water level, crospovidone may form molecular intermediates with some compounds.

Safety: Crospovidone is a safe and non-irritant substance that is utilised in oral medicinal formulations. Short-term animal toxicology tests have revealed no negative impacts associated with crospovidone.

Handling Precautions: Follow standard safety procedures that are suitable for the conditions and amount of material being handled. Eye protection, gloves, and a dust mask are recommended.

5.3.10 Silicified Microcrystalline Cellulose (PROSOLV)[20]

Non-proprietary Names

Synonyms: Silicified Microcrystalline Cellulose; SMCC; Microcrystalline Cellulose, Silicified; Comprecel® SMCC; PROSOLV® SMCC; Avicel® SMCC

Empirical Formula: (C6H10O5)n

Molecular weight: Approx. 36 000

Structural Formula

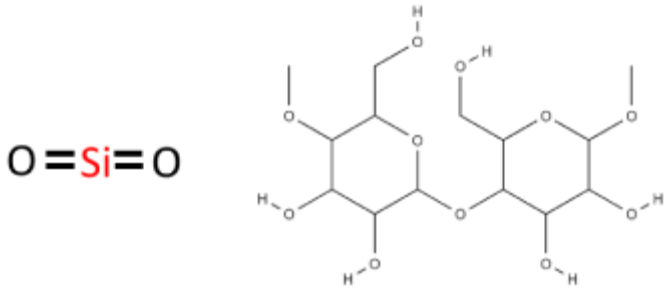


Fig. 5.10 : Structure of Silicified Microcrystalline Cellulose

Functional Category: Filler, Cushioning agent.

Description: It is a co-processed pharmaceutical excipient made up of two functional excipients: microcrystalline cellulose and colloidal silicon dioxide. The two component materials are not covalently bonded but quite stable.

Typical properties

Appearance: White fibrous powder with high flowability

pH value: 5.0-7.5 (10% w/v aqueous suspension)

Density: 1.58 g/cm

Applications in pharmaceutical preparation or technology

Silicified MCC has superior flowability and lower cohesion than non-silicified Microcrystalline cellulose grades. In pharmaceutical goods, silicified microcrystalline

cellulose is used as a filler-diluent in direct compression or capsule filling procedures. It can also be added to wet granulated powder mixtures (extra-granularly) to improve formulation compaction qualities, especially in cases when normal Microcrystalline cellulose is ineffective.

Storage Conditions and Stabilization: Should be kept in a tightly sealed container in a cold, dry location since it is hygroscopic.

Incompatibilities: Most organic and inorganic medicinal compounds are compatible

Safety: It is a safe and non-irritant substance that is utilised in oral medicinal formulations. Short-term animal toxicology tests have revealed no negative impacts associated with silicified MCC.

Handling Precautions: Follow standard safety procedures that are suitable for the conditions and amount of material being handled. Eye protection, gloves, and a dust mask are recommended.

5.3.11 Mannitol [21]

Non-proprietary Names

Synonyms: D-mannitol

Chemical Name: (2R,3R,4R,5R)-hexane-1,2,3,4,5,6-hexol

Empirical Formula: C6H14O6

Molecular weight: 182.17 g/mol

Structural Formula

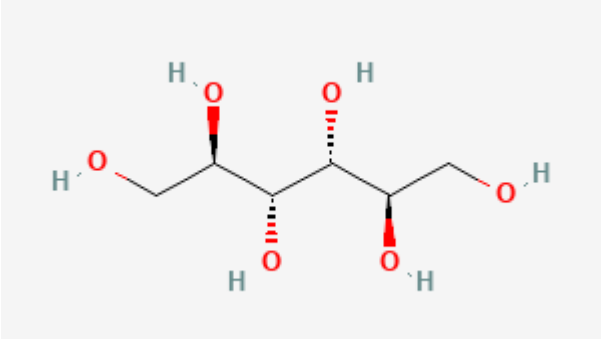


Fig. 5.11 : Structure of Mannitol

Functional Category: Filler

Description: white odourless crystalline solid having a sweet taste

Typical properties

Appearance: White powder

Flowability: Highly flowable

Density: 1.52 g/cm

Applications in pharmaceutical preparation or technology

Mannitol is generally used in pharmaceutical formulations and offers several benefits. It is known to contribute to the overall efficiency and safety of medications. Here are some key benefits of Mannitol in pharmaceutical formulations:

Enhanced Stability and Shelf Life: Mannitol is highly stable, making it an appropriate excipient for medicinal formulations. Its capacity to resist crystallisation contributes to the stability of medicinal formulations and guarantees that the product's quality remains consistent throughout time. This improved stability also helps to lengthen shelf life. As a result, it decreases the possibility of deterioration and guarantees that the drug stays effective for the prescribed storage term.

Osmotic Properties for Drug Delivery: Mannitol's osmotic qualities make it useful in medication delivery systems. It is often utilised in osmotic-controlled release formulations, which allow for regulated medication release over time. Mannitol's osmotic pressure may be modified to provide various release patterns, resulting in regulated and sustained distribution of the active pharmaceutical ingredient (API).

Compatibility with Active Ingredients: Mannitol is well-known for being compatible with a wide range of active medicinal substances. Its inert properties and lack of reactivity with diverse medicinal components make it an appealing choice as a filler or diluent in pharmaceutical formulation. This compatibility means that Mannitol does not interfere with the chemical stability or efficacy of the active components, hence contributing to the medication's overall trustworthiness.

Patient Safety and Tolerability: Mannitol is typically well tolerated by patients, with very few adverse events reported. Its safety profile makes it appropriate for use in formulations designed for a variety of patient groups. Mannitol is often used in oral dose forms including pills and capsules. Here, its sweetness improves the medication's palatability. Mannitol's low caloric content and non-cariogenic characteristics make it an ideal ingredient for sugar-free recipes. As a result, it caters to the demands of diabetics and those on a tight diet.

PART B

5.4 Drug Profile: Sitagliptin Phosphate Monohydrate[1-5]

Sitagliptin phosphate is used type II diabetes in which body cannot produce sufficient insulin or insulin produced cannot work appropriately. It is prescribed to patient who doing regular exercise and intake-controlled diet regularly. It increases the production of insulin and decrease glucagon preparation in patient body. It is available in market in tablet form alone or in combination with metformin or ertugliflozin. It is an oral dipeptidyl peptidase-4 (DPP-4) inhibitor used for the management of type 2 diabetes mellitus. It is FDA approved drug (16th October 2006).

Insulin is a molecule generated by the human body that helps remove sugar from the bloodstream and transport it to cells, where it may be utilised for energy. Incretins are hormones in the body that control insulin synthesis and release. Sitagliptin works by keeping incretin hormones from breaking down too rapidly. This improves insulin sensitivity and decreases blood sugar. Controlling high blood sugar levels helps avoid kidney disease, blindness, nerve difficulties, limb loss, and sexual dysfunction.

Category: Antidiabetic Agents

Mechanism of Action: Sitagliptin inhibits DPP-4, which delays the inactivation of incretins such as GLP-1 and GIP. Incretins are produced throughout the day and increased in response to meals to maintain glucose homeostasis. Reduced inhibition of incretins boosts insulin production and decreases glucagon release in a glucose concentration-dependent way. These effects result in improved blood glucose management, as seen by lower glycosylated haemoglobin (HbA1c).

Groups: Approved, Investigational

BCS Class: BSC Class III (low solubility and high permeability)

Mode of action: Inhibits DPP-4, increasing levels of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)

Molecular weight: 407.11

Molecular formula: $C_{16}H_{15}F_6N_5O$

CAS Number: 486460-32-6

IUPAC Name: (3R)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5H-[1,2,4] triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one

IUPAC Name: (3R)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5H-[1,2,4] triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one

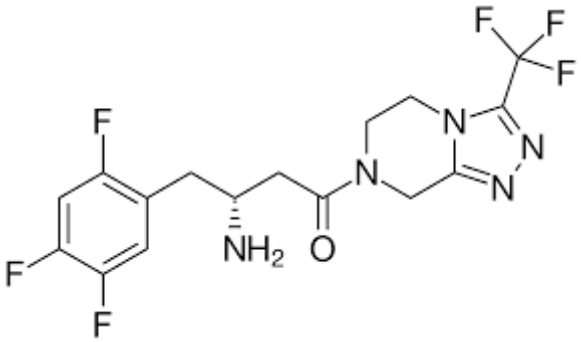


Fig. 5.12: Structure of Sitagliptin

Description: White to off-white crystalline non-hygroscopic solid with distinct odour and bitter taste

Solubility: Soluble in water and DMSO, slightly soluble in methanol and very slightly soluble in acetone, acetonitrile and ethanol. Insoluble in isopropanol and isopropyl acetate.

Water content: NMT 0.5%

Melting point: Melting point of Sitagliptin base, Sitagliptin phosphate monohydrate and Sitagliptin phosphate anhydrous are 120.29°C, 206.37°C and 214.92°C respectively.

Dissociation constant (pKa): 8.78

Nature: It is basic compound can accept H+ ion and became positively charged. Due to presence tertiary amine, it is categories under weak acid.

Partition coefficient: 1.8 for octanol/ water system

Peak time: 2 hr

Half-life: 11-12 hr

Drug absorption: Drug absorbed throughout intestine

Oral bioavailability: Before or after meal 87%

Volume of distribution: 198 L

Protein binding: 38%

Excretion: Approximately 79% of the dosage was eliminated unaltered via urine. Minor metabolites produced by CYP P450, CYP 3A4, and, to a lesser extent, CYP 2C8. Sitagliptin is a substrate for the human organic anion transporter-3 (hOAT-3),

which may play a role in its renal clearance. The clinical significance of hOAT-3 in sitagliptin transport has not been determined. Sitagliptin is also a p-glycoprotein substrate, which may play a role in sitagliptin's renal clearance. Cyclosporine, a p-glycoprotein inhibitor, did not alter sitagliptin's renal clearance.

Elimination: 87% of administered dose excreted through urine and remaining through faces.

Clearance: 350 ml/ min

Safety and efficacy: Safe to use throughout pregnancy and breastfeeding. There is no safety and efficacy data for paediatrics. There was no difference in reported safety or efficacy data when comparing to the elderly. Patient reaction did not vary significantly by gender, age, race, ethnicity, or BMI. When prescribing to a patient with renal impairment, use caution.

Side effects: Stomach upset and pain, diarrhoea, vomiting, upper respiratory infection, runny nose, sore throat, headache, lower sugar, skin rashes, swelling, hiving, etc.

Indication: Indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. It is not used to treat type 1 diabetes or patients with a history of pancreatitis.

Warning: It increases the risk of pancreatitis and joint pain. If patient with gall stone, alcoholism, kidney issues, pancreatitis, smoking and high triglyceride levels should inform the patient before starting treatment.

Dose and Dosage form: Tablets of 25, 50 and 100 mg. Typical dose 100 mg once daily.

Storage: Store at temperature between 20-25°C. Protect from light and moisture. Stable if stored as directed under conditions directed. Avoid storage with oxidizing agents.

Stability: Sitagliptin phosphate monohydrate and Sitagliptin phosphate anhydrous are stable than Sitagliptin base.

5.5 Risk Assessment for Drug Substance Attributes (SPM)

A risk assessment of the drug substance attributes was performed to evaluate the impact that each attribute could have on the drug product Critical Quality Attributes. The outcome of the assessment and the accompanying justification is provided as a summary below. The relative risk that each attribute presents was ranked as high, medium or low. The high-risk attributes warranted further investigation whereas the low-risk attributes required no further investigation. The medium risk is considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk.[6]

Based upon the physicochemical properties of the drug substance, the risk assessment of drug substance attributes that impact the drug product CQAs is given below.[7]

Table 5.8 : Risk Assessment of the Drug Substance Attributes for SPM

Drug product CQA	Sitagliptin drug substance attributes				
	Particle size	Solubility	Melting point	Water content	Flow properties
Moisture uptake	Low	Low	Low	Medium	Low
Drug Content	Low	Low	Low	Medium	Low
Dissolution	Low	Low	Low	Low	Low

Table 5.9: Justification of Risk Assessment of Drug Substance Attributes of SPM

Drug Substance Attributes	Drug Product CQAs	Justification
Particle size	Moisture uptake	Low risk as Particle size has no direct impact on Moisture uptake. The API has good flow characteristics, thus does not have any impact on drug content of final product. This is BCS class III drug thus particle size has no impact on dissolution.
	Drug Content	
	Dissolution	
Solubility	Moisture uptake	Low risk as solubility has no direct impact on

Drug Substance Attributes	Drug Product CQAs	Justification
	Drug Content	Moisture uptake and drug content. This is BCS class I drug thus particle size has no impact on dissolution.
	Dissolution	
Melting point	Moisture uptake	Low risk as Melting point has no direct impact on Moisture uptake, drug content and dissolution
	Drug Content	
	Dissolution	
Water content	Moisture uptake	Medium Risk as Sitagliptin is affected by moisture and leads to degradation at higher rate. API has controlled water content about NMT 0.5%.
	Drug Content	
	Dissolution	Low risk as Water content has no direct impact on dissolution
Flow Properties	Moisture uptake	Low risk as Melting point has no direct impact on Moisture uptake, drug content and dissolution
	Drug Content	
	Dissolution	

5.6 Coating Agent Profile:

5.6.1 Palmitic Acid[8]

The majority of animal and vegetable fats include palmitic acid (35 to 45% of palm oil). It is the most abundant fatty acid found in animals, plants, and microbes. It is the primary component of palm tree oil (palm oil, palm kernel oil, and coconut oil), although it may also be found in meat, cheese, butter, and dairy products. It is composed of sixteen carbon atoms and contains long-chain saturated fatty acids. It is biochemically safe for use in food labelling and dietary advice. Excess carbs in the body are turned into palmitic acid. It is the first fatty acid created during fatty acid synthesis and serves as a precursor for longer fatty acids. Palmitate has a negative

feedback loop with acetyl CoA carboxylase (ACC), which converts acetyl-CoA to malonyl-CoA, which is then added to the expanding acyl chain, limiting further palmitate production.

Palmitoylation is a process that involves adding a palmitoyl group to some proteins. Palmitoylation plays a key role in the membrane localisation of several proteins. Palmitic acid is produced by processing fats and oils with water at high pressure and temperature (over 200°C), resulting in the hydrolysis of triglycerides. The combined mixture is then distilled.

Synonym: n-Hexadecanoic acid, 1-Pentadecanecarboxylic acid, Cetylic acid, Hexadecylic acid, palmitate, Palmitinic acid, palmitinsaeure, cetyl acid, n-hexadecoate, pentadecane carboxylate, 1-hexyldecocanoate, n-hexadecoate, palmic acid, Acid, palmitic

Occurrence: Animals, plants and microorganisms

Dietary sources: Meat, dairy products, palm oil, coconut oil, and breast milk

Chemical name: Palmitic acid

Molecular formula: CH3 (CH2)14COOH

Molecular weight: 256.42

Description: White or off-white, odourless or slight characteristic odour and oily taste large crystalline powder

Melting point: 59 to 63°C

Boiling point: 351.5°C

Acid value: 217 to 220

Iodine value: NMT 1.5

Saponification value: 208 to 222

Refractive index (nD80) = 1.4 to 1.6

Log P: 6.4

CD ratio: 16

Specific gravity: 0.849 to 0.851

Density: 0.8527 g/ml

Specific surface area: 0.51 to 0.53 m2/g

Polar surface area: 37.3 $A^{\circ 2}$

Viscosity: 7.80 mPa.sec (cP) at 62°C

pH: 2.7

Solubility: It is insoluble in water, freely soluble in chloroform, ether, isopropyl alcohol, hot ethanol (95%). It is soluble in amyl acetate, carbon tetrachloride, ethanol, acetone, and benzene. Miscible with diethyl ether.

Distribution coefficient: log (oil/water) = 8.6

Applications: Palmitic acid is commonly utilised as a lubricant and addition in industrial processes. It is used to produce metallic stearates, medicines, soaps, cosmetics, and food packaging. It functions as a softener, accelerator, activator, and dispersion agent in rubbers. It functions as a coating agent in modified release formulations. It is utilised as an emollient and emulsifier.

Physiological role: Crucial for membrane physical properties, protein palmitoylation, and surfactant activity

Stability: Palmitic acid is stable under ordinary conditions. Anti-oxidant may be added in the container.

Storage: Store in a tightly closed container in a cool, dry and well-ventilated area.

Keep away from sources of ignition and incompatible substances.

5.6.2 Stearic Acid[8,9]

Stearic acid is an eighteen-carbon, long-chain saturated fatty acid. It is biochemically safe for use in food labelling and dietary guidelines. However, studies from over 30 years ago shows that, in terms of diet and heart disease concerns involving saturated fatty acids, stearic acid may act differently than other saturated fatty acids found in considerable quantities in the diet. The predominant long-chain saturated fatty acids in the diet include lauric (C12), myristic (C14), palmitic (C16), and stearic (C18).

Stearic acid is found in a variety of foods, including meat and fat-containing dairy products. Stearic acid, as a proportion of total fat calories, is relatively consistent in beef, hog, lamb, and veal at 9 to 12%, whereas poultry has a lower percentage at 6 to 7%. Common cooking oils contain just 2-4% stearic acid, while hydrogenation of vegetable oils for shortening and margarine can raise the percentage. Of all

commercially available fats, cocoa butter has the highest amount of stearic acid. Stearic acid accounts for around 3 to 4% of total calories in the United States diet.

Occurrence: Found in many animal and vegetable fats

Dietary sources: Meat, poultry, fish, eggs, dairy products, fats, beef tallow, lard, butterfat, cocoa butter, and shea butter

Benefits: Moisturizing and anti-inflammatory properties

Synonym: Octadecanoic acid, 1-Heptadecane carboxylic acid, Stearophanic acid, n-Octadecanoic acid

Chemical name: Stearic acid

Molecular formula: $C_{18}H_{36}O_2$

Molecular weight: 284.48

Description: White to faintly yellowish glossy crystalline solid or white to yellowish white powder with slight tallow-like taste.

Melting point: 68 to 70°C

Acid value: 200 to 212

Iodine value: Less than 4

Saponification value: 200 to 220

Refractive index (n_D^{80}) = 1.4299

Specific gravity: 0.940 to 0.941 (Water = 1)

Specific surface area: 0.51 to 0.53 m^2/g

Density: 0.847 g/cm^3 (20°C)

Boiling point: 232°C (450°F; 505 K) at 15 mmHg

Solubility: It is easily soluble in benzene, diethyl ether, acetone, chloroform, carbon disulfide, carbon tetrachloride, amyl acetate, hexane, propylene glycol and toluene. It is insoluble in cold water, hot water, and slightly soluble in ethanol.

Distribution coefficient: The product is more soluble in oil and log (oil/water) = 8.2.

Applications: Its applications include food, medicines, and cosmetics. It is widely utilised as a lubricant, binder, and coating agent. It serves as a medication carrier with prolonged release. Stearic acid is commonly employed as an emulsifying and solubilising agent. It also serves as a hardening agent in glycerin suppositories.

Precautions: Do not ingest or breathe dust

Incompatibilities: It is not compatible with most metal hydroxides or oxidising agents. Many metals react to generate insoluble stearates; when combined with calcium and zinc salts, ointment base becomes lumpy. The compatibility of stearic acid with medicines was examined using Differential Scanning Calorimetry (DSC). Stearic acid induces pitting in aqueous tablet film coating, which is determined by its melting point.

Stability: Stearic acid is stable under ordinary conditions. Anti-oxidant may be added in the container.

Storage: Store in tightly closed container in a cool, dry and well-ventilated area. Keep away from sources of ignition.

5.7 Excipient Profile:

5.7.1 Dicalcium Phosphate[10, 11,12]

Dicalcium phosphate dibasic (DP) is an inorganic, insoluble diluent used in tablet and capsule production. In pharmaceutical development, two hydration forms of dicalcium phosphate are used: anhydrous (DPA) and dihydrate. The anhydrous form is a triclinic crystal, whereas the dihydrate generates a monoclinic structure. Dicalcium phosphate dihydrate has excellent flow characteristics and minimal hygroscopicity. However, depending on temperature (40-50 °C) and humidity (32-75% relative humidity), it tends to lose water of hydration, which may induce chemical instability of APIs in dosage forms. The anhydrous version offers an option without sacrificing medication stability.

The two forms have distinct porosities due to their hydration. Because there is no water in the crystal structure, the anhydrous form has a larger porosity, allowing for better compressibility and quicker disintegration. It is chemically made up of calcium ions (Ca^{2+}) and phosphate anions in a 1:1 molar ratio. Dibasic calcium phosphate is one of a family of eleven mineral compounds known as calcium phosphate. They have considerable uses in the medical, geological, construction, and dentistry industries. The materials created vary in function, composition, structure, physical qualities, and applications depending on the manufacturing processes used.

In the pharmaceutical industry, the three most significant minerals from this family are dibasic calcium phosphate anhydrous, dibasic calcium phosphate dihydrate, and

tricalcium phosphate, which are employed as diluents and fillers in solid dosage formulation. Dibasic calcium phosphate dihydrate has the empirical formula $CaHPO_4.2H_2O$ and so occurs as a dihydrate. The "di" prefix in the popular name comes from the fact that the HPO_4^{2-} anion is formed by removing two protons from phosphoric acid (H_3PO_4).

Synonyms: Dibasic calcium phosphate, calcium monohydrogen phosphate, monohydrogen calcium phosphate, phosphoric acid calcium salt, calcium phosphate, calcium phosphate dibasic Dibasic Calcium Phosphate Hydrate; Calcium Hydrogen Phosphate; Calcium Hydrogen Phosphate Dihydrate; Calcium Hydrogen Orthophosphate dihydrate; Calcium Monohydrogen Phosphate Dihydrate; Di-Cafos; Dicalcium Orthophosphate; DI-TAB; E341; Emcompress.

Pharmacopoeial Compliance: USP-NF; Ph. Eur; IP; J.P; FCC

Molecular Formula: $CaHPO_4$

Molecular weight: 172.09 g/mol (dihydrate), 136.057 g/mol (anhydrous)

CAS Number: 7757-93-9 (Calcium hydrogen phosphate) and 7789-77-7 (dicalcium phosphate)

EC Number: 231-826-1

UNII Code: O7TSZ97GEP

Structural Formula:

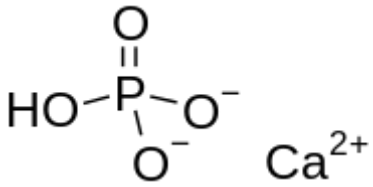


Fig. 5.13: Structure of Dicalcium Phosphate

IUPAC Name: Calcium hydrogen phosphate

Functional Category: Tablet and capsule diluent. Aid in tooth paste as polishing agent.

Description: White triclinic crystalline odourless taste less powder.

Solubility: Insoluble below pH 4.8 (dihydrate and anhydrous forms).

In water 0.02 g/100 mL (anhydrous) and 0.02 g/100 mL (dihydrate)

Practically insoluble in ethanol, ether, and water; soluble in dilute acids.

Structure: Insoluble below pH 4.8 (dihydrate and anhydrous forms)

Angle of repose: 28.3°

pH: pH 12.3-12.5

Melting point: 128°C.

Angle of repose: 33-49°

Bulk density: 0.915 g/ml

Tapped density: 1.17 g/ml

True density: 2.929 g/cm^3 (anhydrous); 2.31 g/cm^3 (dihydrate)

Flash point: Standard state at 25°C, 77°F, and 100 kPa (Non- inflammable)

Specific surface area: 0.44 – 0.46 m^2/g

Moisture content: < 5%

Loss on ignition: 24.5 -26.5%

Assay: 98.0 -105.0% (≥ 98.0%)

Regulatory Status: Dibasic calcium phosphate dihydrate is a permitted pharmaceutical excipient and food ingredient in Europe. It is currently registered with the USP-NF, Ph.Eur, and JP. It is also GRAS-listed and appears in the FDA Inactive Ingredients Database (for oral capsules and tablets). Dibasic calcium phosphate dihydrate is widely used in oral pharmaceuticals, food items, and toothpastes because to its acceptance as a reasonably harmless and non-irritant substance.

Stability & Storage condition: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Applications: Dibasic calcium phosphate dehydrate is used in medicinal formulations because to its superior compactability and flow characteristics. Brittle fracture is the primary deformation mechanism of coarse grades, which considerably lowers strain-rate sensitivity and the potential for tablets to laminate. This is extremely useful during formulation scale-up in new product development, which is less difficult. The sole disadvantage is that dibasic calcium phosphate dihydrate is abrasive, significantly reducing tooling life. As a result, significant quantities of lubricants are necessary in formulations (often greater than 1% w/w for magnesium stearate or sodium stearyl fumarate).

Commercial grades of Dibasic calcium phosphate dihydrate include a milled grade that is commonly used in wet-granulation or roller-compaction, as well as a coarse grade designed for direct-compression applications. Dibasic calcium phosphate dihydrate does not absorb moisture from the environment and remains stable under normal settings. However, if the material is exposed to certain circumstances (high temperature and humidity), it may lose its water of crystallisation. This phenomena has the potential to affect high-temperature operations (such as packing and aqueous film coating) as well as the majority of moisture-sensitive actives.

Incompatibilities: It is incompatible with chelating agents

Handling precaution: Workers should take the necessary measures when working with Dibasic calcium phosphate dihydrate, taking into account the conditions and quantity of material involved. Because the milling grades might produce dust, a respirator or dust mask is required. It may cause irritation to the eyes. Gloves, eye protection, and a dust mask are suggested.

Stability and Storage: Dibasic calcium phosphate dihydrate is a non-hygroscopic, reasonably stable compound. However, if kept or treated wrongly, it might lose its water of crystallisation, affecting the excipient's stability and future dosage form processing. As a result, the bulk material should be properly kept (in a well sealed container in a cold, dry location away from direct heat or moisture).

5.7.2 Colloidal Silicon Dioxide (Aerosil)[13]

Aerosil(R) 200, also known as fumed silica, is used as an anticaking agent in powders and a thickening agent in solutions. Ungraded products supplied in a grade suitable for general industrial use or research purposes and typically are not suitable for human consumption or therapeutic use.

CAS Number: 7631-86-9

EC Number: 231-545-4

Molecular weight: 60.08

Molecular formula: SiO_2

Structural formula:

O = Si = O

Description: White odorless and tasteless crystalline as well as amorphous solid

Solubility: Almost insoluble in water, common acid, can be dissolved in hydrofluoric acid to generate silicon fluoride gas, slowly with the heat of concentrated phosphoric acid.

Melting point: 1,700 °C

Solubility in Water: > 1 mg/l

Density: Approximate 2.2 g/cm^3 (20 °C)

Specific surface area: 450m^2/g

Loss on drying: Less than 1.5% when sample dried at 105 °C

Weight loss on ignition: Not more than 8.5%

SiO2 content based on ignition: >99.8%

Stability: Stable under recommended storage conditions. The physical and chemical properties are stable, easy to form, inert, the melt is layered, and the expansion coefficient is small when heated.

Applications: Pharmaceutical excipients, glidants and suspending agents.

Precaution: Avoid contact with skin and eyes.

Shelf life: 5 years

5.7.3 Polyethylene Glycol 4000[14]

Polyethylene glycol, or PEG, is a hydrophilic polymer. It is easily synthesised from ethylene oxide via anionic ring opening polymerisation into a wide range of molecular weights and end groups. When PEG is crosslinked into networks, it can have a high water content and produce "hydrogels". PEG is an ideal substance for biological applications since it does not elicit an immune response.

Synonyms: Carbowaxes.

IUPAC Name: Polyethylene glycol

CAS Number: 25322-68-3

Chemical Formula: $C_{2n}H_{4n+2}O_{n+1}$, n = 91 units

Chemical Name: Alpha-Hydro-omega-hydroxypoly(oxy-1,2-ethanediyl)

Molecular weight: 4000 (3100-4010)

Structural Formula

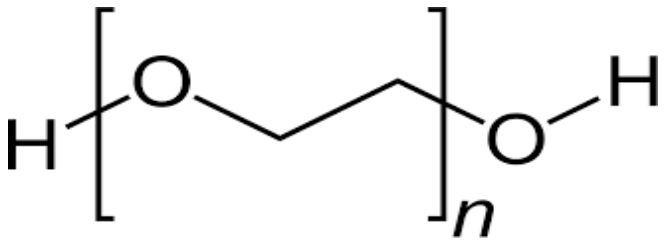


Fig 5.14: Structure of Polyethylene Glycol 4000

Description: White, odourless and slightly sweet flakes or powdered solid

Molar Mass: average molecular weight is about 4,000

Density: 1. 2 g/cm^3

Solubility: Soluble in water, acetone, alcohols, benzene, glycerin, glycols and aromatic hydrocarbons and slightly soluble in aliphatic hydrocarbons.

Melting Point: 53-58°C

pH: 5 – 7

Moisture content: NMT 1%

Flash Point: 138.6°C

Viscosity: 90.0 cSt at 25 °C, 7.3 cSt at 99 °C

Specific gravity: 1.11

Chemical Properties:

1. It is strongly hydrophilic.
2. The partition coefficient of PEG 400 between Hexane and Water is 0.00015.

Uses:

1. Pharmaceuticals: As a solvent, excipient, and coating agent in tablets, capsules, and ointments.
2. Cosmetics: As a humectant, emollient, and thickener in skincare products, hair care products, and makeup.
3. Food: As a food additive, texture modifier, and moisture-retaining agent in beverages, baked goods, and confectionery.
4. Biotechnology: As a precipitant, stabilizer, and protectant in biological samples and biopharmaceuticals.

5. Industrial: As a lubricant, binder, and dispersant in various industrial applications.
6. Polyethylene glycol can be used in medication formulations to increase dissolution rate and oral bioavailability. PEG may be utilised to effectively isolate edible nanoparticles (ENPs), which have powerful anti-cancer and anti-inflammatory properties. PEG acts as a crowding agent, forming a net-like mesh that traps and precipitates nanovesicles. For example, ginger-derived ENPs are separated utilising a cost-effective PEG-based approach rather than ultracentrifugation. PEG can be utilised as a precursor to create degradable hydrogels for the controlled release of hydrophilic and high-molecular-weight medicines.

Benefits: High structural flexibility, low viscosity, solubility in water and many solvents, biocompatible, amphiphilic, high hydration capacity, devoid of steric hinderance, ability to hold moisture avoid drying out, compatibility with many materials and stable.

1. Surfactant
2. The polymer functions as a lubricating coating surface.
3. It is employed as a stationary phase in chromatography.
4. It is employed as a solvent, humectant, lubricant and solubilizer.
5. It is added as a precipitant in Plasmid DNA isolation & Protein crystallization.
6. It is also utilizing microbiology for concentrating viruses by PEG precipitation.
7. It is employed in Gene therapy.
8. In blood bank it is applied as a potentiator for determination of antigen and antibodies.
9. It is employed in toothpaste as a dispersing agent, in food and drinks employed as a foaming agent.
10. It is a part of many lubricants.

Safety:

PEG is regarded as safe and non-hazardous by the FDA. Sometime sensitization and intolerance reactions have been reported in humans exposed to PEG 400 in topically. It was of very low acute oral toxicity in a range of animal species, causing impairment to the digestive tract and diarrhoea in high doses.

Storage: Stored in well closed plastic container in cool well-ventilated place at 25-40 °C

Stability: Stable for more than 2 years when stored at 25 °C in moisture resistant conditions

Precaution: Precaution during handling (protect eyes, avoid inhalation and skin contact).