Chapter 3

Drug and Polymer Profile
3.1 DRUG PROFILE\textsuperscript{22-25}

DRUG: CARVEDILOL

Chemical name

(±)-1-(Carbazol-4-yloxy)-3-\{[2-(o-methoxyphenoxy) ethyl] amino\}-2-propanol

Molecular structure

\[
\begin{align*}
\text{Molecular formula:} & \quad C_{24}H_{26}N_2O_4 \\
\text{Molecular weight:} & \quad 406.5 \\
\text{Description} & \quad \text{Carvedilol is long acting beta blocker used in heart diseases and hypertension. It suffers from low bioavailability (30\%) and highly variable serum concentrations among patients because of low solubility. According to Biopharmaceutics classification System (BCS), Carvedilol belongs to Class II drugs with poor solubility and high permeability.}
\end{align*}
\]

Physical properties

Carvedilol is a white powder, crystalline powder, odourless or almost odourless.

Melting point

114-117 °C
**Solubility**

It is freely soluble in dimethyl sulphoxide, soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether; and practically insoluble in water, gastric fluid and intestinal fluid.

**Indication**

Carvedilol is indicated in the management of Hypertension, Congestive heart failure (CHF), as an adjunct to conventional treatments (ACE inhibitors and diuretics).

**Storage**

Carvedilol should be stored in a dry place below 25°C and protected from light.

**Pharmacological properties**

Carvedilol is third-generation, vasodilating non-cardioselective beta blocker which lacks intrinsic sympathomimetic activity (ISA). In addition to the beta blocking effects, it has blocking effects at vascular $\alpha$ receptors, Antioxidant and Calcium antagonist properties. Carvedilol blocks $\alpha_1$, $\beta_1$, $\beta_2$-adrenergic receptors without exhibiting high levels of inverse agonist activity.

**Pharmacokinetics**

**Absorption**

Carvedilol is readily absorbed following oral administration. Peak plasma concentration occur 1-2 hours after oral administration. Plasma concentration achieved is proportional to the oral dose administered. When administered with food, the rate of absorption is slowed as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability. Taking carvedilol with food should minimize the risk of orthostatic hypotension.
**Distribution**

Greater than 98% of Carvedilol is bound to plasma proteins, primarily albumin. Carvedilol is highly lipophilic; the volume of distribution is approximately 2L/Kg and is increased in patients with liver disease.

**Metabolism**

Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation.

**Excretion**

After oral administration, the elimination half-life of Carvedilol is approximately 7-10 hours. Plasma clearance ranges from 500 to 700 mL/min. The metabolites of Carvedilol are excreted primarily via the bile into the faeces. A minor portion is eliminated via kidneys.

**PHARMACODYNAMICS**

**Mechanism of action**

Carvedilol have Non-selective beta adrenoreceptor blocking activity and alpha adrenergic blocking activity. 2–adrenergic receptor blocking property of carvedilol is non-selective for the 21 and 22-adrenoreceptors. Carvedilol has no intrinsic sympathomimetic activity (like propranolol). It has the membrane stabilizing properties. Carvedilol suppresses the rennin angiotensin aldosterone system through 2- blockade, which reduces the release of rennin, thus making fluid retention rare. Carvedilol reduces the peripheral vascular resistance via selective blockade of 11 – adrenoreceptors. Carvedilol attenuates the increase in BP induced by phenyl ephrine, an 11 - adrenoreceptor agonist, but not that induced by angiotensin 2. Carvedilol has no adverse effect on the lipid profile.

**Adverse effect**

The following symptoms may be observed following over dosage; Tiredness, Weakness, Dizziness, Headache, Diarrhoea, Nausea, Vomiting, Vision changes, Joint pain, Cough, Dry eyes, Burning or Tingling on the arms or legs.
Interactions

Interactions of carvedilol with potent inhibitors of CYP2D6 isozyme (such as quinidine, fluoxetine, paroxetine and propafenone) have not been studied, but these drugs would be expected to increase blood levels of R (+) enantiomer of Carvedilol. Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Rifampin reduce plasma concentrations of carvedilol by about 70%. The concomitant administration of amiodarone or fluconazole may reduce the beta blocking properties of carvedilol resulting in further slowing of heart rate or cardiac conduction.

Dosage and Administration

As Antihypertensive: - Oral: Adult: 12.5 mg once daily increased to 25 mg once daily after two days. Elderly: 12.5 mg once daily.

3.2 POLYMER PROFILE

3.2.1 POLYETHYLENE GLYCOL (PEG)

\[
\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH}
\]

PEG

Synonyms

Carbowax, Carbowax sentry, Lipoxol, Lutrol E, PEG, Pluriol E, Polyoxyethylene glycol.

Empirical Formula

\[
\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH}
\]

where n represents the average number of oxyethylene groups.
**Functional Category**

Ointment base, plasticizer, solvent, suppository base, tablet and capsule lubricant.

**Applications in Pharmaceutical Formulation or Technology**

PEGs are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled release system. PEGs are stable, hydrophilic, substances that are essentially non-irritant to the skin.

**Description**

PEG 6000 and above are available as free-flowing milled powders.

**Typical Properties**

**Apparent density:**

- 1.11-1.14 g/cm$^3$ at 25°C for liquid PEGs
- 1.15-1.21 g/cm$^3$ at 25°C for solid PEGs

**pH:** 4.5 to 7.5

**Melting point:**

- 55-63°C for PEG 6000,
- 50-58°C for PEG 4000.

**Solubility**

All grades of polyethylene glycol are soluble in water. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.
Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally they are regarded as non-toxic and non-irritant materials.

3.2.2 HYDROXYPROPYL METHYL CELLULOSE (HPMC) \(^{26,27}\)

Nonproprietary Names

- BP: Hypromellose; JP: Hydroxypropylmethylcellulose;
- PhEur: Hypromellosum; USP: Hypromellose

Synonyms

- Benecel MHPC; E464; hydroxylpropyl methyl cellulose; HPMC; methocel; methylcellulose propylene glycol ether; methyl hydroxypropyl cellulose; Metolose; Tylopur.

Empirical Formula

The PhEur 2005 describes hypromellose as a partly β-methylated and β-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution.

Molecular Weight: Approximately 10,000-1,500,000.

Functional Category

- Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.
Description

Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.

Typical Properties

Acidity/ alkalinity : pH =5.5-8.0 for a 1% w/w aqueous solution.
Ash : 1.5-3.0%, depending upon the grade and viscosity.
Density (bulk) : 0.341g/cm$^3$
Density (tapped) : 0.557g/cm$^3$
Density (true) : 1.326 g/cm$^3$
Melting point : Browns at 190-200$^\circ$C; chars at 225-230$^\circ$C.
Specific gravity : 1.26

Glass transition temperature is 170-180$^\circ$C

Solubility

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether but soluble in mixture of ethanol and dichloromethane, mixture of methanol and dichloromethane and mixture of water and alcohol.

Stability and Storage Conditions

Hypromellose power is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 50-900$^\circ$ C, depending upon the grade and concentration of material. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking. Hypromellose power should be stored in a well closed container, in a cool, dry place.
**Incompatibilities**

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

**Safety**

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products. Hypromellose is generally regarded as a nontoxic and non-irritant material, although excessive oral consumption may have a laxative effect. The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.

LD50 (mouse, IP) : 5g/kg
LD50 (rat, IP) : 5.2g/kg.

**3.2.3 LACTOSE** 28,29

![Lactose structure](image)

**Synonyms:** Anhydrous lactose 60M, milk sugar, Pharmatose DCL 22.

**Chemical name:** O-β-D-galactopyranosil-(1→4) - β-D-glucopyranose.

**Empirical formula** : C_{12}H_{22}O_{11}

**Molecular weight** : 342.30

**Functional category:** Binding agent, directly compressible tableting excipients, lyophilization aid and tablet and capsule filler.
Description:

Lactose occurs as white to off white crystalline particles or powder. Anhydrous lactose typically contains 70-80% anhydrous β-lactose and 20-30% anhydrous α-lactose.

Solubility

Soluble in water; sparingly soluble in ethanol and ether.

Storage conditions

Lactose anhydrous should be stored in a well closed container in cool and dry place.

Incompatibilities

It is incompatible with strong oxidizers.

Application in pharmaceutical formulations:

- Widely used in direct compression tableting applications.
- Tablet and capsule filler.
- Binder.
- Lactose anhydrous can be used with moisture sensitive drugs due to its low moisture content.

Pharmacopoeial specifications

- Loss on drying: ≤0.5%
- Melting point: 232.0°C
- True density: 1.589 g/cm³
- Residue on ignition: ≤0.1%
3.2.4 MICROCRYSTALLINE CELLULOSE (MCC)\(^{28}\)

Synonyms: Cellulose gel, crystalline cellulose, Avicel PH 101, 102.

Non-proprietary name: NF-Microcrystalline cellulose, USP- Microcrystalline cellulose.

Chemical names: Cellulose.

Empirical formula: \((\text{C}_6\text{H}_{10}\text{O}_5)_n\)

Molecular weight: 36,000(approx).

Functional category: Tablet and capsule diluent, tablet disintegrant, suspending and viscosity increasing agent.

Description

Purified, partially de polymerized cellulose occurs as a white, odourless, tasteless, crystalline powder composed of porous particles.

Use concentration (%)

- Adsorbent: 20–90
- Antiadherent: 5–20
- Capsule binder/diluent: 20–90
- Tablet disintegrant: 5–15
- Tablet binder/diluents: 20–90
**Solubility**

Insoluble in water, dilute acids and most organic solvents, slightly soluble in 5% w/v NaOH solution.

**Storage conditions**

Stable, hygroscopic. Store in a well closed container.

**Incompatibilities**

Microcrystalline cellulose is incompatible with strong oxidizing agents.

**Application in Pharmaceutical Formulation:**

- Microcrystalline cellulose is used as a binder/diluent in oral tablet and capsule formulations.
- Microcrystalline cellulose is used as a lubricant and disintegrant agent in tablet formulation.

**Pharmacopoeial Specifications:**

- pH: 5.0–7.0
- Loss on drying: 47.0%
- Residue on ignition: 40.05%
- Sulfated ash: 40.1%
- Heavy metals: 410 ppm
- Density (tapped): 0.478 g/cm$^3$,
- Density (true): 1.512–1.668 g/cm$^3$
- Melting point: chars at 260–270 °C.
3.2.5 POLY VINYL PYRROLIDONE (PVP) \cite{28,30}

Nonproprietary Names

BP : Povidone,
JP : Povidone,
PhEur : Polyvidonum,
USP : Povidone

Synonyms

E1201; Kollidon; Plsdone; Poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; Polyvinyl pyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer

Chemical number and CAS registry number

1-Ethenyl-2-pyrrolidinone homo polymer [9003-39-8]

Empirical Formula and Molecular Weight

\[(C_6H_9NO)_n \text{ 2500-3,000,000}\]

Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

Applications in Pharmaceutical Formulation or Technology

Although Povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms.
In tableting, Povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in dry form and granulated in situ by the addition of the water, alcohol, or the hydro alcoholic solutions.

Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions.

**Uses**

It is used as binder in many pharmaceutical tablets. It simply passes through the body when taken orally. PVP added to iodine forms a complex called povidone-iodine that possesses disinfectant properties. This complex is used in various products like solutions, ointment, pessaries, liquid soaps and surgical scrubs. It is known under the trade name Betadine and Pyodine. It is used in pleurodesis (fusion of the pleura because of incessant pleural effusions). For this purpose, povidone iodine is equally effective and safe as talc and may be preferred because of easy availability and low cost.

Carrier for drugs (10-25% concentration)

Dispersing agent (up to 5% concentration)

Eye drops (2-10% concentration)

Suspending agent (Up to 5% concentration)

Tablet binder, tablet diluent, or coating agent (0.5-5% concentration)

**Typical Properties**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidity/alkalinity</td>
<td>pH = 3.0-7.0 (5% w/v aqueous solution)</td>
</tr>
<tr>
<td>Density (bulk)</td>
<td>0.29-0.39 g/cm³ for Plasdone</td>
</tr>
<tr>
<td>Density (tapped)</td>
<td>0.39-0.54g/cm³ for Plasdone.</td>
</tr>
<tr>
<td>Density (true)</td>
<td>1.180g / cm³</td>
</tr>
</tbody>
</table>
**Moisture content**

Povidone is very hygroscopic, significant amount of moisture being absorbed at low relative humidity.

**Solubility**

Freely soluble in Acids, Chloroform, Ethanol (95%), Ketones, Methanol, and Water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution.

**Storage Conditions**

Povidone darkens to some extent on heating to $150^\circ$C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110-130$^\circ$C; steam sterilization of an aqueous solution does not alter its properties. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

**Incompatibilities**

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

**Safety**

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, Povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. Povidone additionally has no irritant effect on the skin and causes no sensitization.

A temporary acceptable daily intake for Povidone has been set by the WHO at up to $25\text{mg/kg body-weight}$

$LD_{50}$ (mouse, IP): $12\text{g/kg}$
3.2.6 CYCLODEXTRINS

A non-reducing cyclic saccharide consisting of seven α - 1, 4-linked D-glucopyranosyl units.

Nonproprietary Names:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>DOLONEX</td>
</tr>
<tr>
<td>PhEur</td>
<td>DOLONEXum</td>
</tr>
<tr>
<td>USPNF</td>
<td>DOLONEX</td>
</tr>
</tbody>
</table>

Empirical Formula and Molecular Weight

α-Cyclodextrin : C\textsubscript{36} H\textsubscript{60} O\textsubscript{30} - 972
β-Cyclodextrin : C\textsubscript{42} H\textsubscript{70} O\textsubscript{35} - 1135
γ-Cyclodextrin : C\textsubscript{48} H\textsubscript{80} O\textsubscript{40} – 1297

Chemical Name:

Cycloheptaamylose

Functional Category:

Solubilizing agent, stabilizing agent.
Cyclodextrins are cyclic oligosaccharides derived from starch containing at least six D-(+)-glucopyranose units attached by a (1→4) glucoside bonds. The three natural cyclodextrins, α, β, and γ, differ in their ring size and solubility. They contain 6, 7, or 8 glucose units, respectively. Cyclodextrins are bucket-like or cone-like ‘toroid molecules, with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type. Cyclodextrins occur as white, practically odourless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

**Applications in Pharmaceutical Formulation or Technology**

Cyclodextrin inclusion complexes have been used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material. α-cyclodextrin is used mainly in parenteral formulations. However, as it has the smallest cavity of the cyclodextrins it can form inclusion complexes with only relatively few, small sized molecules. γ-cyclodextrin has the largest cavity and can be used to form inclusion complexes with large molecules; it has low toxicity and enhanced water solubility. In oral tablet formulations, β-cyclodextrin may be used in both wet-granulation and direct compression processes. β-cyclodextrin tends to possess poor flow properties. It may require lubricant, (such as 0.1% w/w magnesium stearate) when it is directly compressed. In parenteral formulations, cyclodextrins have been used to produce stable and soluble preparations of drugs that would otherwise have been formulated using a non-aqueous solvent. In eye drop formulations, cyclodextrins form water-soluble complexes with lipophilic drugs such as corticosteroids. They have been shown to increase the water solubility of the drug to enhance drug absorption into the eye; to improve aqueous stability; and to reduce the local irritation. Cyclodextrins have also been used in the formulation of solutions, suppositories, and cosmetics.

**Solubility**

α-cyclodextrin : soluble 1 in 7 parts of water at 20°C, 1 in 3 at 50°C.
\( \beta \)-cyclodextrin : soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 20°C, 1 in 20 at 50°C, practically insoluble in acetone, ethanol (95%), and methylene chloride.

\( \gamma \)-cyclodextrin : soluble 1 in 4.4 parts of water at 20°C, 1 in 2 at 45°C.

**Stability and Storage Conditions**

\( \beta \)-cyclodextrin and other cyclodextrins are stable in the solid state if protected from high humidity. Cyclodextrins should be stored in a tightly sealed container, in a cool, dry place.

### 3.2.7 HYDROXY PROPYL \( \beta \) – CYCLODEXTRIN\(^{31}\)

- **Molecular Formula** : \((C_6H_9O_5)_7(C_3H_7O)n\)
- **Molecular Weight** : 1400
- **Solubility** : Soluble to 100 ml in water
- **Storage** : Store at RT

**Structural Formula**

![Structural Formula](image)

**Biological Activity**

The most widely used modified cyclodextrin, the lipophilic cavity formed by 7 glucose units. Drug solubility in water is greatly enhanced by complexing with HBC.
Properties of Hydroxy Propyl β Cyclodextrin:

A high aqueous solubility: HPβ -CD is infinitely soluble in water at room temperature. At 25°C, HPβ-CD is 65% soluble in water; at 50°C, it is 80% soluble. At higher temperatures, the viscosity of the solution decreases, which facilitates increased dissolution.

Easy complex formation: With HPβ -CD, an aqueous drug complex preparation is very easily formed.

A safe profile: Of all the CD derivatives available, HPβ -CD is the safest, as it does not permeate the membranes. HPβ -CD has been shown to have a reduced haemolytic potential, making it suitable for parenteral use as well as for oral and/or topical applications.

Effects of HPβCD

HP β-CD increases drug solubility, drug dissolution speed, drug bioavailability, reduces drug side-effects and stabilizes drugs.

Advantages

HP β -CD offers following advantages in pharmaceutical formulations:

- Increased solubility for active ingredients
- Increased bioavailability for high permeation, low solubility drugs
- Quicker onset of action
- Reduced side-effects
- Increased shelf-life
- Better compliance
- Reduced toxicity.