CHAPTER 2

DRUG AND EXCIPIENTS PROFILE

This chapter depicts complete description of drug and excipients used for the preparation of formulations in the current study.

2.1 CANDESARTAN CILEXETIL

Structural formula :

![Structural formula of Candesartan Cilexetil]

Molecular weight : 610.67

Molecular formula : C_{33}H_{34}N_{6}O_{6}

Description : White to off-white crystalline powder. It is a racemic mixture containing one chiral center at the cyclohexyloxycarbonyloxy ethyl ester group. Following oral administration, CC undergoes hydrolysis at the ester link to form the active drug candesartan, which is achiral.

Standards : CC contains not less than 98% and not more than 102% of C_{33}H_{34}N_{6}O_{6} calculated on dried basis.
**Solubility**: Freely soluble in chloroform, sparingly soluble in methanol and insoluble in water.

**Storage**: Should be stored in a well closed light-resistant container.

**Melting point**: 157-160 °C

**Loss on drying**: Not more than 0.5%

**Sulphated ash**: Not more than 0.1%

**Heavy metals**: Not more than 10 ppm

**Category**: Selective angiotensin II type I (AT₁) receptor blocker.

**Pharmacology**: CC exerts as selective inhibition of angiotensin II by competitive antagonism of the angiotensin II receptors, which has been speculated to reduce adverse effects and possibly improve clinical efficacy. It displace angiotensin II from the angiotensin I receptor and produce their blood pressure lowering effects by antagonizing angiotensin II-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic response. The biological half-life is approximately 5-9 h and it has only 15% oral bioavailability.

**Uses**: It is used in the treatment of hypertension and prevents cardiovascular mortality and morbidity in patients with heart failure and post myocardial infarction. It can also prevent the development of diabetes mellitus and may therefore be a superior choice in the treatment of hypertension especially in patients at high risk for developing diabetes.
Dose: CC is commercially available in the form of tablets and oral solutions. Solid oral dosage forms are administered once or twice daily with total daily doses ranging from 8 mg to 32 mg for adult hypertension. The oral solution dose range is 0.05 to 0.4 mg/Kg per day. The recommended starting dose is 0.20 mg/Kg. Patients less than 50 Kg body weight, the dose range is 2 to 16 mg per day. The recommended starting dose is 4 to 8 mg and administered once daily or divided into two equal doses. For those greater than 50 Kg, the dose range is 4 to 32 mg per day. The recommended starting dose is 8 to 16 mg.

The recommended initial dose for treating heart failure is 4 mg once or twice daily. The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2-week intervals, as tolerated by the patient (Atacand 1998, Julienne 1999, Stergren 2004).

2.2 HYDROGENATED CASTOR OIL

Description: White to pale yellow powder or flakes. Very faint characteristic odor and almost tasteless in aqueous solution. It consists mainly of the triglyceride of 12-hydroxystearic acid.
Structural formula:

Molecular weight: 939.50

Application: In topical formulations, it is used to provide stiffness to creams and emulsions. In oral formulations, it is used to prepare sustained release tablet and capsule and may be used as a coat or to form a solid matrix.

Compatibilities: Compatible with most natural vegetable and animal waxes.

Safety: Nontoxic and non-irritant material (Raymond et al 2009).

2.3 CETOSTEARYL ALCOHOL

Description: White or cream-colored unctuous masses, or almost white flakes or granules. It has a faint, characteristic sweet odor. On heating, cetostearyl alcohol melts to
a clear, colorless or pale yellow colored liquid free of suspended matter.

**Molecular weight**: 512.941

**Structural formula**:

![Structural formula](image)

**Solubility**: Soluble in ethanol (95%), ether and oil. Practically insoluble in water.

**Melting point**: 48-55 °C

**Density**: 0.97 g/cm³

**Acid value**: ≤ 2.0

**Iodine value**: ≤ 4.0

**Hydroxyl value**: 208-228

**Application**: Emollient, emulsifying agent, viscosity increasing agent, and used to slow the dissolution of water soluble drugs.

**Stability**: Stable under normal storage conditions.

**Storage**: Should be stored in a well-closed container in a cool and dry place.

**Incompatibilities**: Incompatible with strong oxidizing agents and metal salts.
Safety: It is generally regarded as a nontoxic material. (Amley and Weller 1994).

2.4 STEARIC ACID

Description: It is a hard, white or faintly yellow colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor and taste suggesting tallow.

Molecular weight: 284.47

Structural formula:

\[
\text{H}_3\text{C}-\hspace{1cm}\text{C}_17\text{H}_{33}-\hspace{1cm}\text{CH}_2-\hspace{1cm}\text{CH}_2-\hspace{1cm}\text{OH}
\]

Solubility: Freely soluble in benzene, carbon tetrachloride, chloroform and ether. Soluble in ethanol (95%), hexane and propylene glycol. Practically insoluble in water.

Melting point: \(\geq 54 ^\circ\text{C}\)

Density: 0.537 g/cm\(^3\)

Application: It is mainly used in oral formulations as a lubricant and sustained release drug carrier.

Stability: It is a stable material.

Storage: Should be stored in a well-closed container in a cool and dry place.
**Incompatibilities**: Incompatible with most metal hydroxides and may be incompatible with oxidizing agents.

**Safety**: It is generally regarded as a nontoxic and nonirritant material. However, consumption of excessive amounts may be harmful (Amley and Weller 1994).

### 2.5 CARNAUBA WAX

**Description**: Light brown to pale yellow colored flakes, or irregular lumps of a hard, brittle wax. It has a characteristic bland odor and practically no taste. It is free from rancidity.

**Empirical formula**: It is a complex mixture of esters of acids and hydroxy acids, mainly aliphatic esters, \(\omega\)-hydroxy esters, \(p\)-methoxycinnamic aliphatic esters, and \(p\)-hydroxycinnamic aliphatic diesters composed of several chain lengths, in which \(C_{26}\) and \(C_{32}\) alcohols are the most prevalent. Also presents acids, oxypolyhydric alcohols, hydrocarbons, resinous matter and water.

**Solubility**: Soluble in chloroform, ether and petroleum benzene when hot but sparingly soluble when it is cold. It is sparingly soluble in hot ethanol and practically insoluble in water.

**Melting point**: 80-86 °C

**Specific gravity**: 0.990-0.999 at 25 °C
Iodine value : 5-14

Heavy metals : ≤ 20 μg/g

Application : Commonly used in lip balms and also used as a sustained release polymer. It has been experimentally investigated for use in producing microparticles.

Stability : Stable under room temperature.

Storage : Should be stored in a well-closed container, in a cool and dry place.

Safety : Generally nontoxic and nonirritant material and reported that of allergic contact dermatitis from carnauba wax in mascara (Raymond et al 2009).

2.6 MICROCRYSTALLINE CELLULOSE

Description : White, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Structural formula : 

\[
\begin{align*}
\text{CH}_3 & \quad \text{H}_3\text{C} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{O} & \quad \text{CH}_3 \\
\end{align*}
\]

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

**Melting point** : 260-270°C

**Density** : 0.32 g/cm³

**Angle of repose** : 49 °

**Heavy metals** : ≤10 ppm

**Application** : It is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression processes.

**Incompatibilities** : Incompatible with strong oxidizing agents.

**Stability** : Stable under room temperature.

**Storage** : Should be stored in a well-closed container, in a cool and dry place.

**Safety** : Nontoxic and nonirritant material (Raymond et al 2009).

### 2.7 LACTOSE

**Description** : White to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous \( \beta \)-lactose and anhydrous \( \alpha \)-lactose. Anhydrous
lactose typically contains 70-80% anhydrous \( \beta \)-lactose and 20-30% anhydrous \( \alpha \)-lactose.

**Structural formula**: 

![Structural formula of lactose](image)

**Solubility**: Soluble in water, sparingly soluble in ethanol (95%) and ether.

**Melting point**: 223 °C

**Density**: 1.589 g/cm\(^3\)

**Angle of repose**: 39 °

**Heavy metals**: \( \leq 5\mu g/g \)

**Application**: It is widely used in direct compression tableting applications and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture sensitive drugs due to its low moisture content.

**Incompatibilities**: Incompatible with strong oxidizers.

**Storage**: Should be stored in a well-closed container, in a cool and dry place.

**Safety**: Adverse reactions to lactose are largely due to lactose intolerance, which occurs in individuals
with a deficiency of the intestinal enzyme lactase, and is associated with oral ingestion of amounts well over those in solid dosage forms (Raymond et al 2009).

2.8 ETHYLCELLULOSE

Description : White to light tan colored, tasteless, free flowing, powder.

Structural formula :

\[
\begin{align*}
\text{R} &= \text{H or Et} \\
\text{Solubility} & : \text{Freely soluble in chloroform, methyl acetate, tetrahydrofuran and in mixtures of aromatic hydrocarbons with ethanol (95%). Practically insoluble in water.} \\
\text{Melting point} & : 223^\circ\text{C} \\
\text{Density} & : 0.4 \text{ g/cm}^3 \\
\text{Heavy metals} & : \leq 20 \text{ ppm} \\
\text{Application} & : \text{Used as a matrix former in modified release tablet formulation. Drug release through ethylcellulose}
\end{align*}
\]
coated dosage forms can be controlled by diffusion through the film coating.

**Storage** : Should be stored at a temperature not exceeding 32 °C (90 °F) in a dry area.

**Stability** : Ethylcellulose is a stable, slightly hygroscopic material.

**Safety** : Nontoxic, nonallergenic and nonirritating material (Amley and Weller 1994).

### 2.9 Povidone K-30

**Description** : White to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray drying and occur as spheres.

**Molecular weight** : 50,000

**Structural formula** :

![Structural formula](attachment:image)

**Solubility** : Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water, and practically insoluble in ether and mineral oil.

**Melting point** : 150 °C
Acidity/Alkalinity : pH 3.0-7.0 (5% w/v aqueous solution)

Density : 0.29-0.39 g/cm³

Heavy metals : \( \leq 10 \text{ ppm} \)

Application : Tablet binder and enhance dissolution of poorly soluble drugs from solid dosage forms.

Incompatibilities : Thimerosal and some other preservatives efficacy may be adversely affected by the formation of complexes with Povidone.

Storage : Should be stored in an airtight container in a cool and dry place.

Stability : Stable to a short cycle of heat exposure around 110-130 °C.

Safety : It has no irritant effect on the skin and causes no sensitization (Amley and Weller 1994, Raymond et al 2009).

2.10 SODIUM BICARBONATE

Description : White, odorless, crystalline powder with a saline, slightly alkaline taste.

Molecular weight : 84.01
Structural formula: $\text{NaHCO}_3$  

Solubility: Soluble in water, and practically insoluble in ether and ethanol (95%)  

Melting point: 270 °C  

Acidity/Alkalinity: pH 8.3 for a freshly prepared 0.1 M aqueous solution at 25 °C.  

Density: 0.869 g/cm$^3$  

Heavy metals: ≤ 10 ppm  

Application: Used in pharmaceutical formulations as a source of CO$_2$ in effervescent tablets and granules.  

Incompatibilities: Sodium bicarbonate reacts with acids, acidic salts and many alkaloidal salts with the evolution of CO$_2$. It can also intensify the darkening of salicylates.  

Storage: Should be stored in an airtight container in a cool and dry place.  

Stability: It is stable in dry air but slowly decomposes in moist air.  

Safety: When used as an excipient, sodium bicarbonate is generally regarded as an essentially nontoxic and nonirritant material (Raymond et al 2009).
2.11 CITRIC ACID

**Description** : Colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste.

**Molecular weight** : 210.14

**Structural formula** :

```plaintext
O
O
O
O
HO
HO
HO
HO
```

**Solubility** : Soluble 1 in 1.5 parts of ethanol (95%), 1 in less than 1 part of water and sparingly soluble in ether.

**Melting point** : 100 °C

**Acidity/Alkalinity** : pH 2.2 (1% w/v aqueous solution).

**Heavy metals** : ≤ 10 ppm

**Loss on drying** : ≤ 0.25%

**Application** : Used in the preparation of effervescent granules and anhydrous citric acid is widely used in the preparation of effervescent tablets.

**Incompatibilities** : Incompatible with potassium tartrate and alkali.

**Storage** : Should be stored in an airtight container in a cool and dry place.
Stability : Slightly deliquescent in moist air.

Safety : Orally ingested citric acid is absorbed and is generally regarded as a nontoxic material when used as an excipient. However, excessive or frequent consumption of citric acid has been associated with erosion of the teeth (Raymond et al 2009).

2.12 PURIFIED TALC

Description : Very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and free from grittiness.

Empirical formula : Purified, hydrated, magnesium silicate, approximating to the formula \( \text{Mg}_6(\text{Si}_2\text{O}_5)4(\text{OH})_4 \). It may contain small, variable amounts of aluminum silicate and iron.

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

Moisture content : It absorbs insignificant amounts of water at 25°C and relative humidity up to about 90%.

Acidity/Alkalinity : pH 7-10 for a 20% w/v aqueous dispersion

Heavy metals : \( \leq 0.004\% \).2.7

Specific gravity : 2.7-2.8
Application : Used in oral solid dosage formulations as a lubricant and diluent also used as a dissolution retardant in the development of controlled release products.

Incompatibilities : Incompatible with quaternary ammonium compounds.

Storage : Should be stored in an airtight container in a cool and dry place.

Stability : Stable material and may be sterilized by heating at 160 °C for not less than 1 h. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.

Safety : It is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material (Amley and Weller 1994, Raymond et al 2009).

2.13 MAGNESIUM STEARATE

Description : Very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Molecular weight : 591.34
Structural formula:

![Structural formula image]

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

**Melting point**: 126-130 °C

**Flowability**: Poorly flowing, cohesive powder

**Density**: 0.159 g/cm³

**Heavy metals**: ≤ 20 ppm

**Application**: Primarily used as a lubricant in capsule and tablet manufacturing at concentrations between 0.25% and 5.0% w/w.

**Incompatibilities**: Incompatible with strong acids, alkalis, and iron salts.

**Storage**: Should be stored in an airtight container in a cool and dry place.

**Stability**: It is a stable material.

**Safety**: Oral consumption of large quantities may produce a laxative effect or mucosal irritation (Amley and Weller 1994, Raymond et al 2009).
2.14 PONCEAU 4R

**Description**: Red color, fine powder, odorless, consisting essentially of Trisodium 2-hydroxy-1-(4 sulpho-1-naphthylazo)-2-naphthol-6,8 disulphonate and subsidiary coloring matters together with sodium chloride or sodium sulphonate as the principal uncolored matter.

**Molecular weight**: 604.48

**Chemical formula**: $C_{20}H_{11}N_2Na_3O_{10}S_3$

**Structural formula**:

![Structural formula of Ponceau 4R]

**Melting point**: 179-182 °C

**Dye content**: NLT 85%

**Density**: 0.2-0.7g/cm$^3$

**Purity**: NLT 80% of the total coloring matter.

**Heavy metals**: NMT 10ppm
Application : As colorant in food and cosmetics.

Storage : It should be stored at ambient temperature (Amley and Weller 1994, Raymond et al 2009).

2.15 SUNSET YELLOW

Description : Orange color, odorless, solid, fine amorphous powder consisting of disodium salt of 6-hydroxy-5-[(4-sulfophenyl)azo]-2-napthalenesulfonic acid and subsidiary coloring matters together with sodium chloride or sodium sulfate as principal uncolored component.

Molecular weight : 452.37

Chemical formula : C_{16}H_{10}N_{2}Na_{2}O_{7}S_{2}

Structural formula :

![Structural formula of Sunset Yellow](image)

Melting point : 300 °C

Free dye content : Maximum 0.4%

Density : 0.2-0.7 g/cm³

Loss on drying : NMT 15%
Purity : NLT 85% of the total coloring matter.

Heavy metals : NMT 40 ppm

Application : As colorant in food and cosmetics.


2.16 ERYTHROSINE

Description : Cherry pink/red synthetic coal tar dye, odorless, solid, fine amorphous powder consisting essentially of disodium salt of 9-o-carboxyphenyl-6-hydroxy-2,4,5,7-tetraido-3isoxanthrone monohydrate and subsidiary coloring matters together with water, sodium chloride or sodium sulfate.

Molecular weight : 897.88

Structural formula : 

![Structural formula of Erythrosine]

H₃C  
O
O
O
O
O
O
O
O
Al⁺⁺⁺  
O
O
O
O
O
O
O
O
Al⁺⁺⁺
Chemical formula : \( \text{C}_{20}\text{H}_{6}\text{I}_{4}\text{Na}_{2}\text{O}_{5}\cdot\text{H}_{2}\text{O} \)

Melting point : 332.1 °C

Density : 0.3-0.8 g/cm\(^3\)

Loss on drying : NMT 13%

Purity : NLT 87% of the total coloring matter.

Storage : Should be stored at ambient temperature (Raymond et al 2009).

2.17 BRILLIANT BLUE

Description : Granular blue dark powder, odorless consisting essentially of disodium \( \text{I-}[4-(\text{N-ethyl-3-sulfonato benzylamino})\text{phenyl}]\text{-I-}[4-(\text{N-ethyl-3-sulfonato benzyliminio})\text{cyclohexa-2,5-dienylidene}]\text{toluene-2-sulfonate}. \)

Molecular weight : 792.84

Chemical formula : \( \text{C}_{37}\text{H}_{34}\text{N}_{2}\text{Na}_{2}\text{O}_{9}\text{S}_{3} \)

Structural formula : 

![Structural formula image]
<table>
<thead>
<tr>
<th>Property</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>100 °C</td>
</tr>
<tr>
<td>Volatile matter</td>
<td>NMT 13%</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>NMT 40 ppm</td>
</tr>
<tr>
<td>Purity</td>
<td>NLT 85% of the total coloring matter.</td>
</tr>
<tr>
<td>Storage</td>
<td>Should be stored at ambient temperature (Amley and Weller 1994, Raymond et al 2009).</td>
</tr>
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