CHAPTER IV

4. Drug and excipient profile

4.1 Drug Profile

4.1.1 Tolperisone\textsuperscript{101-103,107-119}

4.1.1.1 Description

Tolperisone, a centrally acting muscle relaxant agent, and it is used as spasmylytic for more than three decades. In our country Tolperisone is used for the management of acute and chronic back pain. Moreover it is also used as spasticity of neurological origin. It has also been used in treatment of condition, which includes dysmenorrhoea, climacteric complaints, lockjaw, and neurolatyism.

(a) Chemical Structure

(b) IUPAC Name: 2-Methyl-1-(4-methylphenyl)-3-(1-piperidinyl)-1-propanone hydrochloride (1:1)

(c) Empirical Formula: \( \text{C}_{16}\text{H}_{23}\text{NO} \)

(d) CAS Registry: 728-88-1

(e) Appearance: White crystalline powder
(2) Physicochemical Properties:-

(a) **Molecular Weight:** - 245.36

(B) **Melting Range:** - 176-178 ºC

(C) **Solubility:** - Soluble in chloroform, methanol and water

### 4.1.1.2 Pharmacology

The tolperisone can block the voltage dependent sodium channels in the neuron. This can maintain inactivated state of the sodium channels for long time, and also the refractoriness. Tolperisone also blocks the calcium channels in a frequency dependent manner in the presynaptic nerve terminal. This presynaptic inhibition occurs in dorsal root ganglia cells at a higher concentration. The Tolperisone inhibit the spinal reflex and produces muscle relaxants action to body. Decreased transmitter release results in depression of excitatory post synaptic potential. Other mechanisms include antagonism of intracellular calcium release from sarcoplasmic reticulum and interference with prostaglandin biosynthesis (anti-inflammatory action). Tolperisone thus inhibits monosynaptic and polysynaptic reflexes due to its depressant and membrane stabilizing mechanism.

### 4.1.1.3 Pharmacokinetics

Pharmacokinetic of Tolperisone HCl are as follows

- **Peak plasma concentration** - 0.5–1.0 h
- **$C_{max}$** - 64.2–784.9 ng/ml
- **$T_{max}$** - 0.90 ±0.31 h
- **Bio-availability of tolperisone** - 17% (due to hepatic first-pass effect)
- **half-Life of Tolperisone HCl** - 1.5 - 2.5 hrs
Elimination of drug - Urine after 8 hours and 24 hours

It can administer into the body through oral, intravenous, intramuscular, intraspinal, etc. routes. The dose required for adult is approximately 75 to 1500 mg/day. The absorption and distribution of Tolperisone HCl is varying from person to person, so that there is variation in pharmacokinetic profile of drugs.

4.1.1.4 Drug interaction

Generally Tolperisone HCl does not produce any interaction with other drug. But it has been found that Tolperisone hydrochloride displayed interaction with the non-steroidal anti-inflammatory drugs, benzodiazepines, alcohol and analgesics.

4.1.1.5 Dosage recommendations

The therapeutic dose Tolperisone HCl is changes as per patient conditions. The selection of dose of Tolperisone to the patient depends upon age and weight. Generally physician prescribed 50 mg of tablets thrice a day to adult, and it can be increase upto daily dose of 600 mg at chronic conditions. While for children the dose required is 5-10 mg/kg/day. The patient suffering from renal or hepatic can take reduced dose.
Fig 4.1: Tolperisone block the voltage dependent sodium channels in the neuron
Fig 4.2: Tolperisone inhibit the spinal reflex
4.1.2 Celecoxib

4.1.2.1 Description

Celecoxib belong to category of sulfa non-steroidal anti-inflammatory drug (NSAID). It is considered that Celecoxib inhibit the COX-2 and is used in the treatment of acute pain. It is also used for the remedy of osteoarthritis, rheumatoid arthritis, painful menstruation and menstrual symptoms. The patients suffering from colon and rectum polyps can be cured by Celecoxib drug.

(a) Chemical Structure

\[ \text{Chemical Structure Image} \]

(b) IUPAC Name: 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(c) Empirical Formula: \( \text{C}_{17}\text{H}_{14}\text{F}_{3}\text{N}_{3}\text{O}_{2}\text{S} \)

(d) CAS Registry: 169590-42-5

(e) Appearance: Yellow crystalline powder

(2) Physicochemical Properties:

(a) Molecular Weight: 381.07

(b) Melting Range: 157-159 °C
(C) **Solubility:** - Very low soluble in water

### 4.1.2.2 Pharmacology

The celecoxib produces therapeutic effect by inhibiting the prostaglandin synthesis. The NSAIDs drug inhibits COX-1 and COX-2 enzyme, and produces therapeutic effect. However celecoxib produces therapeutic effect inhibiting the COX-2 enzyme.

### 4.1.2.3 Pharmacokinetics

Pharmacokinetic profiles of celecoxib are as follows:

- **Peak plasma concentration** - 3 hours
- **C<sub>max</sub>** - 705 ng/ml
- **T<sub>max</sub>** - 2.8 h
- **Bio-availability of celecoxib** - 40%
- **Half-Life of celecoxib** - 11 hrs
- **Elimination of drug** - Urine and feces
- **Protein binding** - 97%
- **Metabolism** - Hepatic

### 4.1.2.4 Drug interaction

The Celecoxib reported drug interaction with patient suffering from poor CYP 2C9 metabolizers. In this case patient can administered this drug safely. The treatment started with lowest dose of celecoxib.

### 4.1.2.5 Dosage recommendations
The celecoxib started with lowest dose in patient for treatment. The drug can be administered at the dose of 200 mg daily or in two divided doses. If required, then patient can also take 200 mg twice daily.

Fig 4.3: Celecoxib block the COX-2
Fig 4.4: Celecoxib block the Inflammatory Prostaglandin
Fig 4.5: Mechanism of NSAIDS
4.2  Excipients

4.2.1  Crospovidone

4.2.1.1  Nonproprietary names

BP : Crospovidone
PhEur : Crospovidone
USP-NF : Crospovidone

4.2.1.2  Synonyms

Crospovidonum; Crospopharm; crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

4.2.1.3  Chemical name and CAS registry number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4.2.1.4  Empirical formula and molecular weight

\((C_6H_9NO)_n > 1\,000\,000\)

The USP32–NF27 mentioned that crospovidone are synthetic crosslinked homopolymer and are insoluble in water. An exact determination of the molecular weight has not been established because of the insolubility of the material.

4.2.1.5  Structural Formula

\[
\begin{align*}
\text{CH}_2 & \text{CH}_2 \\
\text{N} & \\
\text{N} & \\
\end{align*}
\]
4.2.1.6 **Functional Category:** Tablet disintegrant.

4.2.1.7 **Typical Properties:** **Density:** 1.22 g/cm³

4.2.1.8 **Solubility:** Crospovidone are generally insoluble in water and organic solvents

4.2.1.9 **Applications of Crospovidone in pharmaceutical formulation**

Crospovidone is a superdisintegrant, used in tablet due to its disintegrant and dissolution agent. Mostly 2-5% concentration of crospovidone required for formulation of tablets. The crospovidone hydrated by the principle capillary activity and form gels structure. These investigations proposed that the fragment dimension of crospovidone vigorously effect decomposition of analgesic tablets. It can also be used as a solubility enhancer. The crospovidone can be utilized to intensify the solubility of ailing soluble drugs, by employing co-evaporation technique. The drug is adsorbed on to crospovidone in the existence of appropriate solvent; and the solvent is then evaporated. This method leads to improve dissolution rate.

4.2.1.10 **Description**

Crospovidone is available in the form white to creamy-white, finely divided, hygroscopic powder, free flowing, odorless or nearly odorless and practically tasteless.

4.2.1.11 **Stability and storage conditions**

Since crospovidone is hygroscopic, it should be kept in an airtight vessel in a cool, dry place.

4.2.1.12 **Incompatibilities**

Crospovidone is analogous with mainly organic and inorganic pharmaceutical ingredients. When undefended to a elated water level, crospovidone may form molecular adduct with several substances.
4.2.1.13 Safety

The non-irritant and non-toxic property of Crospovidone promotes to use in oral doses of pharmaceutical formulations. During toxicity studies crospovidone it does not produce any adverse effects. However, owing to the lack of available data, an adequate routine uptake in humans has not been stipulated by the WHO.

4.2.2 Sodium starch glycolate\textsuperscript{146-161}

4.2.2.1 Nonproprietary Names

BP : Sodium Starch Glycolate

PhEur : Sodium Starch Glycolate

USP-NF : Sodium Starch Glycolate

4.2.2.2 Synonyms

Carboxymethyl starch, sodium salt; carboxymethylamylum natricum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

4.2.2.3 Chemical name and CAS registry number

Sodium carboxymethyl starch [9063-38-1]

Empirical Formula and Molecular Weight

The USP32–NF27 describes two types of sodium starch glycolate i.e. Type A and Type B. The sodium starch glycolate is made up of sodium salt of carboxymethyl ether of starch.

The molecular weight Sodium starch glycolate is typically $5 \times 10^5$–$1 \times 10^6$. 
4.2.2.4 Structural Formula

![Structural Formula]

4.2.2.5 Functional Category

Tablet and capsule disintegrant.

4.2.2.6 Applications of Sodium starch glycolate in pharmaceutical formulation

- It is greatly applied in oral pharmaceuticals in the form of disintegrant in formulation of tablets.

- Generally sodium starch glycolate are used in formulation, when tablets are manufacture by direct-compression or wet-granulation processes.

4.2.2.7 Description

- Sodium starch glycolate appear white powder

- It is hygroscopic powder

- The granules appeared in irregularly shaped, ovoid or pear-shaped, and the size of granules are between 30–100 mm

- The granules displayed a distinct black when placed between crossed nicol prisms

- The granules get swell when comes in contact with water
4.2.2.8 Stability and storage conditions of sodium starch glycolate

- Sodium starch glycolate are highly stable
- Sodium starch glycolate are hygroscopic nature, so that it required to place in a well-closed container
- It can store for 3 to 4 years

4.2.2.9 Incompatibilities

Sodium starch glycolate has been observed incompatible with ascorbic acid.

4.2.2.10 Safety

Sodium starch glycolate is free from toxic and non-irritating substances, and it is immensely employed in oral pharmaceutical formulations. But on consuming large quantities can produce harmful effect to body.

4.2.3 Microcrystalline cellulose

4.2.3.1 Description

Microcrystalline cellulose (MCC) is odorless, tasteless and crystalline powder. It is available in different particle size.

4.2.3.2 Nonproprietary Names

BP : Microcrystalline Cellulose
JP : Microcrystalline Cellulose
PhEur : Cellulose, Microcrystalline
USP-NF : Microcrystalline Cellulose
4.2.3.3 Synonyms

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

4.2.3.4 Functional category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant

4.2.3.5 Chemical Name and CAS Registry Number - Cellulose [9004-34-6]

4.2.3.6 Empirical Formula and Molecular Weight - \((\text{C}_6\text{H}_{10}\text{O}_5)n\) \((36000)\), where \(n\) - 220

4.2.3.7 Structural Formula

![Structural formula of cellulose](image)

4.2.3.8 Applications of Microcrystalline cellulose in pharmaceutical formulation

- It is used as a binder or diluent in oral tablet and capsule formulations
- Sometime it is employed as glidant in tablets

4.2.3.9 Stability and storage Conditions

Microcrystalline cellulose is a hygroscopic material, so it should keep in well closed vessels in a dry place.
4.2.3.10 Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

4.2.3.11 Safety

- Microcrystalline cellulose is occasionally considered as a relatively nontoxic and nonirritant material.
- It produces little toxic because it is not absorbed systemically.
- It produces laxative effects when consumed bulk quantity of microcrystalline cellulose.
- Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.