CHAPTER - III
DRUG AND POLYMER PROFILE

3.1 CAMPTOTHECIN (CPT) PROFILE

Chemical name: 4(S) - Ethyl-4-hydroxy-1H-pyran-3', 4': 6, 7
indolizino [1, 2-b] quinoline-3, 14(4H, 12H)-dione.

Structure:

\[
\begin{array}{c}
\text{HO} \\
\text{O}
\end{array}
\]

CPT has a planar pentacyclic ring structure, that includes a pyrrolo[3,4-β]-quinoline moiety, conjugated pyridone moiety and one chiral center at position 20 within the alpha-hydroxy lactone ring with (S) configuration (the E-ring). Its planar structure is thought to be one of the most important factors in topoisomerase inhibition.

Molecular formula: \( \text{C}_{20}\text{H}_{16}\text{N}_{2}\text{O}_{4} \).

Molecular weight: 348.36 g/mol.

Storage: Store at or below -20°C.

Solubility: Freely soluble in chloroform, methanol, acetonitrile and in DMSO, up to about 10mg/ml. In aqueous solution (less than 1 µg/ml).
Melting point : 258°C.

**Chemical and Physical Index:** It is light yellow powder or light yellow crystalline powder. It is easily deteriorate when it meets light. It is easy to be moistened. It owns the nature of indirect in the solution of chloroform and methanol (8:2). It slightly dissolves in ethanol and chloroform. It is hardly dissolve in water and easily dissolve in sparse alkaline solution.

Camptothecin and camptothecin based drugs, specifically irinotecan and topotecan have been approved by the FDA and are used most often either in conjunction with 5-fluorouracil as a first therapy or sometimes used alone after 5-fluorouracil has failed. Analogs of these molecules have shown upto 1000 fold higher activity but are a great challenge to delivery because of their extreme hydrophobicity. (J. Williams et al., 2003).

The lead compound camptothecin was isolated from the Chinese tree *camptotheca acuminata*. The camptothecin analogs irinotecan and topotecan have activity in colorectal, ovarian and small cell lung cancer.

Camptothecin undergoes a pH dependent hydrolysis. Under physiological conditions i.e. at pH 7 or above the lactone ring of the drug is easily opened to yield carboxylate form while the open ring carboxylate form is inactive.

To protect the active lactone ring, to decreases the hydrolysis rate of Camptothecin and to improve their anticancer activity, polymeric micelles has been applied to encapsulate the drug camptothecin.
All camptothecins have a fused five ring backbone beginning with a weakly basic quinoline moiety and terminating with a lactone ring which is necessary for the biological activity of the camptothecins, the lactone ring is unstable, undergoing reversible, non enzymatic, pH dependent hydrolysis. Consequently the camptothecins exist as an equilibrium mixture of the intact lactone and opened ring carboxylate forms in biological fluids. Substituents on the A and B quinoline rings can modulate the equilibrium position between the closed and opened lactone ring forms through effects on their relative affinities for binding to plasma proteins. For instance, the carboxylate form of camptothecin binds to serum albumin with 200 times greater affinity than the intact lactone and is predominant form in plasma and whole blood (Laurence B Keith et al., 2008).

**Fig 6: pH Dependent Hydrolysis of Camptothecin**

![Diagram of pH Dependent Hydrolysis of Camptothecin]

**Pharmacokinetics**

After intravenous (i.v.) infusion in humans, plasma concentrations decline in a multi exponential manner with a mean terminal elimination half-life of approximately 4 hours. Although the pharmacokinetics are highly variable over the dose range of 50 mg/m² to 350 mg/m², area under the curve (AUC) increases linearly with dose.
Distribution

Camptothecin exhibits moderate plasma protein binding (30% to 68% bound). It is highly bound (approximately 95%) to human plasma proteins. The major plasma protein to which camptothecin bind primarily is albumin.

Indication

It is indicated for the second-line treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU based therapy.

It mainly been applied for cancer of digestive system, for example cancers of the stomach, gullet, intestines and liver cancer. It is also used in cancers of oral cavity, face and head, bladder cancer and lung cancer.

Dosage and Administration

The recommended starting dose is 125 mg/m². All doses should be administered as an intravenous infusion over 90 minutes. The recommended treatment regimen is 125 mg/m² administered once weekly for 4 weeks, followed by a 2-week rest period. Thereafter, additional courses of treatment may be repeated every 6 weeks (4 weeks on therapy, followed by 2 weeks off therapy). Subsequent doses should be adjusted to as high as 150 mg/m² or to as low as 50 mg/m² in 25 mg/m² to 50 mg/m², increments depending upon individual patient tolerance of treatment. Provided intolerable toxicity does not develop, treatment with additional courses may be continued indefinitely in patients who attain a response or in patients whose disease remains stable. Patients should be carefully monitored for toxicity.
MECHANISM OF ACTION

DNA Topoisomerase I Inhibitor

Topoisomerase are the enzymes that wind and unwind the DNA that makes up the chromosomes. The chromosomes must be wound in order for the cell to use the genetic information to synthesize proteins. Camptothecin keeps the chromosomes wound tight and so the cell can’t make proteins. As a result, the cell stops growing, because cancer cells grow and reproduce at a much faster rate than normal cells, they are more vulnerable to topoisomerase inhibition than the normal cells.

Toxicological Information

Skin contact may cause skin irritation. Skin absorption may be harmful if absorbed through the skin. Eye contact may cause eye irritation.

Material may be irritating to mucous membranes and upper respiratory tract. Toxic if swallowed.
3.2 POLYMER PROFILE (Joseph R Robinson et al., 1987)

Methoxy polyethylene glycol -b- polycaprolactone (Me PEG<sub>5000</sub>-b-PCL<sub>13,000</sub> and Me PEG<sub>5000</sub>-b-PCL<sub>5000</sub>)

Poly ethylene glycol (PEG)

![Poly ethylene glycol (PEG)](image)

Approved by the FDA for internal use.

It is soluble in water, methanol, benzene, dichloromethane and is insoluble in diethyl ether and hexane. It is coupled to hydrophobic molecules to produce non-ionic surfactants.

It is a homogenous polymer with a general structure OH-CH<sub>2</sub>-(CH<sub>2</sub>-O-CH<sub>2</sub>)<sub>n</sub>-CH<sub>2</sub>-OH. It is normally synthesized by ring opening polymerization of ethylene oxide. The polymer is usually linear at molecular weights <10kD.

PEG although non biodegradable is readily excretable after administration into living organisms.

PEG when labeled with a near-infrared fluorophore has been used in preclinical work as a vascular agent, lymphatic agent and general tumour imaging agent by exploiting the Enhanced Permeability and Retention Effect of tumours.

High molecular weight PEG has been shown to be a dietary preventive agent against colorectal cancer.
Besides it has an array of ideal properties like low toxicity, excellent solubility in aqueous solutions, low antigenicity and immunogenicity.

When hydrated, PEG forms a dense brush of polymer chains stretching out from the core of the micelle. PEG imparts steric stability by minimizing the interfacial free energy of the micellar core and by impeding hydrophobic intermicellar attractions.

The hydrophilic corona is vital in preventing opsonin adsorption and subsequent clearance by the mononuclear phagocyte system in the liver and spleen. PEG acts as an efficient steric protector of various biologically active macromolecules.

PEG’s are well established non toxic, water soluble biomaterials that form a hydrated polymer brush on the outside of drug carriers such as liposomes, micelles and nanoparticles inhibiting protein adsorption, secondary aggregation and uptake by the RES resulting in prolonged plasma half lives compared to non PEG coated formulations.

The molecular weight of PEG used in micelles has varied between 2000-12000 g/mol and is usually of a length that is greater than or equal to the length of core forming block. PEG is non toxic in nature and is known to impart a protein and cellular stealth properties to surfaces and interfaces.

PEG has shown to reduce aggregation of the micelles and prevent their interactions with serum proteins.

PEG has low toxicity and is a good drug excipient and approves for internal consumption by FDA.
Poly- caprolactone (PCL)

It is a semi crystalline polymer having the melting point of 59 to 64°C (depending on the crystalline size) and glass transition temperature of -60°C.

It can be prepared by ring opening polymerization of e-caprolactone.

It is a Food and Drug Administration (FDA) approved material that is used in the human body as a drug delivery device, suture or adhesion barrier.

PCL is synthetic, semi crystalline, biodegradable polyester that has a proven history of biocompatibility in use in medical devices such as sutures, stents, prosthetics and as a carrier for hydrophobic drugs.

Its slow degradation rate renders it suitable for use in long term delivery systems. Biodegradability can be increased by co polymerization, high permeability to a large number of drug moieties, non toxicand ability to form compatible blends with many other polymers.

This polymer is considerably more hydrophobic than other aliphatic polyesters allowing the polymer to degrade slowly, making it a good candidate for some applications for controlled release.

PCL have been combined with a hydrophilic PEG segment to produce an A-B type diblock copolymer structure.
Advantages of PCL

- Easy control of particle size.
- Good structural stability.
- Solubilization of hydrophobic drugs.
- Stable storage and an ability to deliver drugs showing low interactions with biocomponents such as proteins and cells.

Since these polymers degrade to soluble non toxic oligomers in the part of the Krebs cycle, micelles prepared using these polymers do not need to be removed after delivering in the body.

Storage: store in a cool place. Keep container tightly closed in a dry and well-ventilated place.