4. DRUG AND EXCIPIENT PROFILE

4.1 Bendamustine:

Bendamustine is an anticancer drug and is derivative of mechlorethamine with a purine-like benzimidazole ring belongs to electrophilic alkyl groups [85].

4.1.1 Brand Name:

It is available in different brand names across different countries examples are Bendeka, Belrapzo,Treanda®,Vivimusta.). In India, it is available commercially with different brand names as lyophilized powder for injection[86]. The brand name and marketed preparation of bendamustine in India are highlighted in table 1.1.

Table.1.1 Bendamustine brands in India:

Sr No.	Brand Name	Strength	volume	Dosage form
1	Bendit	Bendit 100x20 ml	2ml	Bendit Injection
2	Bimode	Bimode 100mg	1ml	Bimode Injection
3	Maxtorin	Maxtorin 100mg	20ml	Maxtorin Injection
4	Mustin	Mustin 100 mg	1 ml	Mustin Injection
5	Purplz	Purplz 100mg	1 ml	Purplz Injection
6	Rolanda	Rolanda 100 mg	1 ml	Rolanda Injection

4.2 Drug category:

Antineoplastic agent, Alkylating agent

4.3 Physicochemical property:

Bendamustine is off-white coloured powder with molecular formula $C_{16}H_{22}Cl_3N_3O_2$. The drug is higher in organic solvents. It's melting point ranges from 150-154ºC. Its molecular Weight is 394.72 g/mol with partition coefficient of 4.23 It is photosensitive in nature.

4.4 Chemical structure:

Chemically, it is 5- [Bis (2-chloroethyl)-amino]-1-methyl-1H-benzimidazole-2-butanoic acid.

The structure of bendamustine is shown in figure.1.5.

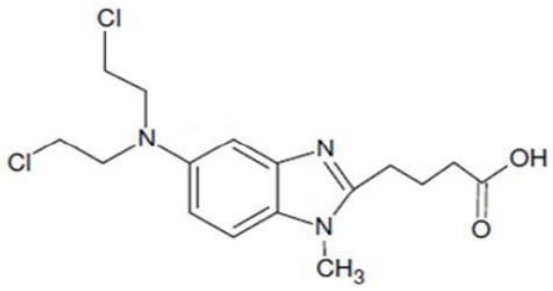

Figure.1.5: Structure of bendamustine

4.5 Pharmacology and mechanism of action:

It is mechlorethamine derivative ableto form electrophilic alkyl groups which can covalently bond to another molecule.

4.5.1 Dosage and route of administration

It is administered parenterally as Injection (i.v. infusion) and for adult dose in Chronic Lymphocytic Leukemia is 100mg.

4.5.2 Pharmacokinetics:

Absorption

Bendamustine is administered through intravenous infusion. After a single IV dose of bendamustine, Cmax occurs at the end of infusion with value of 11.5μg/ml [87].

Distribution

About 95 % bendamustine is bounded to protein (generally to albumin). Data says that it is not probable to dislocate or be dislocated by extremely protein-binding drugs.BM is not extensively distributed in tissues. The volume of distribution (Vs) is around 25 L.It is having short half-lifecauses the rapid metabolism and excretion.

Metabolism

Bendamustine is mostlyhydrolysed to active HP_1 and HP_2 and also metabolised $CYP1A_2$ enzymes to active M_3 and M_4, which effect their extreme concentrations closeto the same time just like the main drug.

Elimination

The findings suggest the half of administered drug excreted through urine and faecal. Bendamustine clearance from plasma is quick and the half life is 40 minutes.

4.5.3 Drug Interactions:

Bendamustine is not approved yet in combination form, butitmayenhanceinclusive response rates when combined with rituximab [88].

4.5.4 Adverse effects/Side effects:

Adverse effects including signs of an allergic reaction, hypersensitive reactions is very common andanaemia, neutropenia, thrombocytopenia, anorexia, diarrhoea, dyspepsia, nausea, pyrexia, constipation, herpes simplex, herpes zoster, pneumonia, fatigue, hypersensitivity, headache, hypokalemia, tumor lysis syndrome, myelosupression, vomiting, cardiac failure, infusion reactions has also seen in patients.

4.6 EXCIPIENT PROFILE:

4.6.1 Chitosan

Chitosan is a sugar used and has linear polysaccharide made up of β--linked D-glucosamine as well as N-acetyl-D-glucosamine [89]. Chitosan is widely used in pharma manufacturing.

Synonyms-Chitosan, Poliglusam,Chicco, Flonac C, Flonac N, Sea Cure Plus, Kytex H.

Structure-

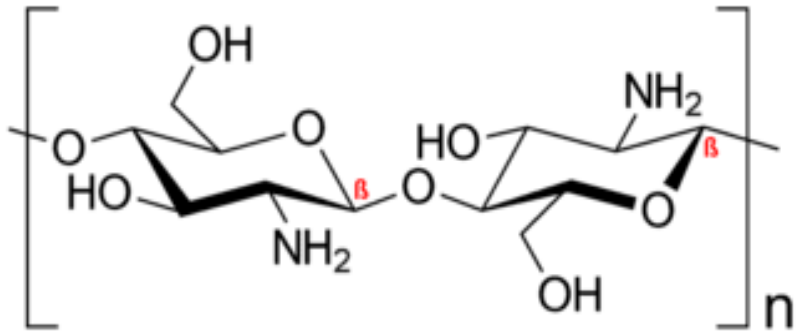

Fig. 1.6 Chemical structure of Chitosan

4.6.2Properties

Physical Properties- Chitosan is off white free flowing powder.However, it has a unique fishy odor, and when added to pharmaceutical preparation, significantly impair the aroma of the preparation.

Molecular Formula- $C_{56}H_{103}N_9O_{39}$

Molecular weight- 1526.5

Solubility- the solubility depends on solvents more ever chitosan is sparingly soluble in water. The solubility is higher in organic solvents.

Acidity/Alkalinity (pH)- Its pH is between 6-6.5.

Density- in the range of 0.20- 0.38 g/mL.

Melting point- The melting point of chitosan is between214.77 - 216.69°C.

4.7Application:

Chitosan having an excellent property and that is why used in various formulation manufacturing [90].

4.8 Sodium Tripolyphosphate (SYP):

Sodium triphosphate is an inorganic compound having formula $Na_5P_3O_{10}$.

Structure-

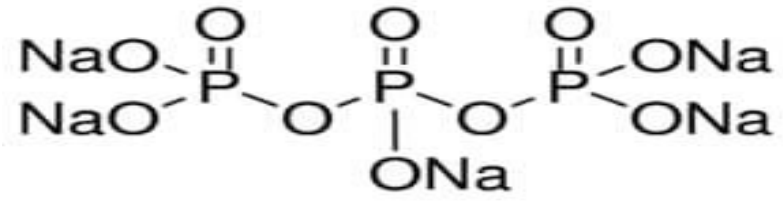

Fig. 1.7: Chemical structure of Tripolyphosphate

4.8.1 Physicochemical properties- It iswhite, freeflowing and odourless powder without any contamination. TPP is Incompatible with strong oxidizing agents and strong acidsand Hygroscopic in nature.

Molar mass- 367.864 g/mol

Density- 2.52 g/cm³

Melting point- 622 °C

Solubility -It is easily soluble in water, and its aqueous solution is alkaline.Sodium Tripolyphosphate is accessible in white crystalline and powder form. It easily dilutes in water and is insoluble in ethanol. The solubility in water is 14.5 g/100 mL (25 °C).

Acidity/Alkalinity (pH)- pH range 5.0–6.5.

4.9 Application:

TPP acts as a stabilizer in the preparation of nanoparticles [91].

4.10. PLGA (Poly lactic-co- glycolic acid):

PLGA or poly is used in the formulations of many nanocarrier systems, due to its biodegradability and biocompatibility. It belongs to the category of polyesters. These polymers are classified on the origin of different substituent (R1, R2) on the support with a primary ester linkage.

4.11 Structure:

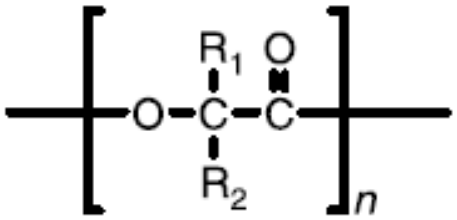

Fig1.8: Chemical structure of PLGA

4.12 Molecular formula-$C_5H_8O_5$

4.13 IUPAC name: 2-(2-hydroxyacetyl)oxypropanoic acid

4.14 Synthesis:

PLGA is prepared by different ratios of monomers, lactic and glycolic acid at 120 °C temperatures.

4.15 Physicochemical properties:

Appearance- Available in white to off- white powder.

Molecular weight-148.11

Density-Pure PLGA powder should have a density of 1.25 g/$cm^{3.}$

Melting Point-240ºC-280ºC

Solubility- It is freely soluble in organic compounds like methylene chloride and others.

Acidity/Alkalinity (pH)-It is basic in nature. pH ranges between 5.5-7.4

4.16 PVA (Polyvinyl alcohol):

PVA is biodegradable and highly flexible, nontoxic polymer used as an emulsifying agent for lowering the solutions interfacial tensions[92].

4.17 Structure:

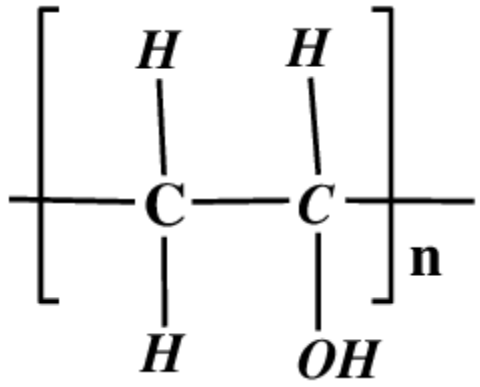

Fig.1.9: Chemical structure of PVA

4.18 Molecular formula- (C_2H_4O)x

4.19 IUPAC name- poly (1-acetyloxiethylene)

4.20 Physicochemical properties:

Appearance- Polyvinyl alcohol appears as odourless white to cream-colored granules or powder.

Molecular weight- 44.5

Melting point- 200ºC

Flash Point- 79.44ºC

Density- 1.19–1.31 g/cm^3

Solubility- solubility of PVA depends on hydrolysis and molecular weight [93]. It is Insoluble in most organic solvents. Its slightly soluble in ethanol and other organic compounds.

4.21 Application:

It's generally used as surfactant in various pharmaceutical industries.