2.MATERIALS

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2.1. LIST OF GENERAL CHEMICALS:

S. No.	Name of Particulars	Source
1	Triethanolamine	Universal lab. Pvt. Ltd, Mumbai
2	Dimethyl sulfoxide	SD Fine – chemical Ltd., Mumbai
3	Glacial acetic acid	SD Fine – chemical Ltd., Mumbai
4	Acetone	SD Fine – chemical Ltd., Mumbai
5	light liquid paraffin	SD Fine – chemical Ltd., Mumbai
6	Petroleum ether	Universal laboratories, Mumbai
7	Span 60	SD Fine – chemical Ltd., Mumbai
8	Sodium acetate	SD Fine – chemical Ltd., Mumbai
9	n-Hexane	BDH, Mumbai
10	Zidovudine	Apl Research centere (A division of Aurobindo pharma Ltd) A.P. India.
11	Ethyl cellulose	SD-Fine chemicals, Mumbai
12	Hydroxy propyl methyl cellulose	LOBA chemicals, Kolkata
13	Acryl Coat S100	Corel Pharma, Ahmadabad
14	Glacial acetic acid	Universal Laboratories,Mumbai
15	PVP	LOBA chemical, Kolkata
16	Sodium acetate	SD-Fine chemicals, Mumbai
17	Ethylene diamine tetra acetic acid (EDTA).	SD-Fine chemicals, Mumbai
18	Trichloro acetic acid	SD-Fine chemicals, Mumbai
19	Silica gel	Universal Laboratories,Mumbai
20	Ethanol	Lab Instruments and chemical works, Siliguri
21	Methanol	Universal laboratory,Mumbai
22	Sodium Hydroxide	SD-Fine chemicals, Mumbai
23	Heparin	Qualiges fine chemicals, Mumbai
24	Zidovir Tablet	Cipla Pvt.Ltd
25	Guargum	LOBA chemicals, Kolkata

2.2. LIST OF INSTRUMENTS:

S.No.	Name	Model No.	Source
1	USP XXI paddle type dissolution apparatus	VDA-8DR, USP Standard	Veego, Mumbai
2	UV- Spectrophotometer	UV-1700	Shimadzu, Japan
3	FTIR	Model 8400S	Shimadzu, Japan
4	HPLC	LC – 20AT	Shimadzu, Japan
5	Optical microscope	Olympus-GB	Olympus, India (P) Ltd
6	Hot air oven	---------	Inco-Instrument Chemicals, Ambala
7	Magnetic stirrer	---------	Spinit magnetic Stirrer, Ambala
8	Mechanical stirrer	---------	Inco Instrument Chemicals, Ambala
9	Vaccum oven	---------	Lab Instruments & works, Siliguri
10	Refrigerator	GL 295 TMG4/2007	Intellocool (LG), Siliguri
11	Glassware	---------	Borosil glass
12	Dhona Balance	Dhona 160 D	Siliguri
13	Electronic Balance	PB 303 – S	Mettler Toledo, Ambala
14	Centrifuge	C – 24BL	Remi Cooling Centrifuge, Mumbai.

2.3. POLYMER PROFILE:

2.3.1. Ethyl Cellulose:

Synonyms: Cellulose ethyl ether.[1]

Structure:

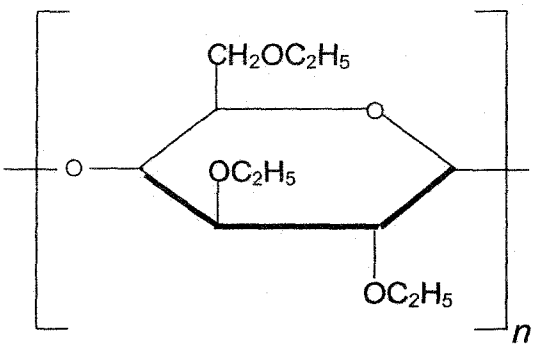

Fig.2.1 –Structure of Ethyl Cellulose

Ethyl cellulose is an ethyl ether of cellulose. When dried at 105° for 2 hours, it contains not less than 44.0 percent and not more than 51.0 percent of ethoxy (-O-C_2H_5) groups.[1]

Packaging and storage: Preserve in well – closed containers.[1]

Description: Free – flowing, white to light tan powder; forms films that have a refractive index of about 1.47; aqueous suspensions are neutral to litmus.[2]

Solubility: The medium type is freely soluble in tetrahydrofuran, methyl acetate, chloroform, or mixture of aromatic hydrocarbons with alcohol, the standard type is freely soluble in alcohol, methanol, toluene, chloroform, or ethyl acetate, both types are insoluble in water, glycerin, or propylene glycol.[2]

Density: 1.45.[3]

Refractive Index: 1.14.[3]

Uses: A tablet binder and film – coating tablets and drug particles.[2]

2.3.2. Carbopol/ Carbomer:

Synonyms[4]: Carboxy polymethylene.

Structure[5]:

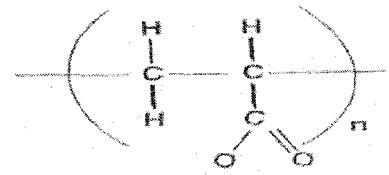

Figure 2.2 Structure of Carbopol/ Carbomer

Properties: Gel looses viscosity on exposure to sunlight. Unaffected by temperature variations, hydrolysis, oxidation and resistant to bacterial growth.[4]

Empirical formula[4]: $(C_3H_4O_2)_X$ $(C_3H_5$ - Sucrose$)_y$.

Pharmaceutical grades: 934 P, 940 P, 971 P and 974 P.[4]

Molecular weight[4]: $1\times 10^6 - 4\times 10^6$.

Viscosity: 29,400 – 39,400 cps at 25 °C with 0.5 % neutralized aqueous solution.[4]

Bulk density[4]: 5g/cm^3.

Tapped density[4]: 1.4 g/cm^3.

pH[4]: 2.5 – 3.0.

Solubility: Soluble in water, alcohol and glycerin.[4]

Uses: Excellent thickening, emulsifying, suspending, and gelling agent. It is used as common compound in bioadhesive dosage forms.[4]

2.3.3. Hydroxyethyl Cellulose:

Properties: Hydroxyethyl cellulose is non – ionic polymer made by swelling cellulose with NaOH and treating with ethylene oxide.[4] Aqueous solutions of ethyl (Hydroxyethyl) cellulose exhibit thermosensitive behavior. However, the viscosity decreases with temperature.[5]

Characteristics[4]: Solutions are pseudo-plastic and slow a reversible decrease in viscosity at evaluated temperatures. Hydroxyethyl cellulose solutions lack yield value. Solution shows only a fair tolerance with water miscible solvents. It is compatible with most water – soluble gums and resins. It acts as synergistic with CMC and sodium alginate. It is used as suspending or viscosity builder, binder, film former and susceptible for bacterial and enzymatic degradation. It shows good viscosity stability over the pH 2 to 12.

Pharmaceutical grades: it is available in grades ranging from 2 to 8,00,000 cps at 2%.[4]

Density: 0.6g/mL.[4]

pH[4]: 6 – 8.5.

Solubility: It is soluble in hot and cold water and gives a clear, colourless solution.[4]

2.3.4. Hydroxy Propyl Methyl Cellulose:

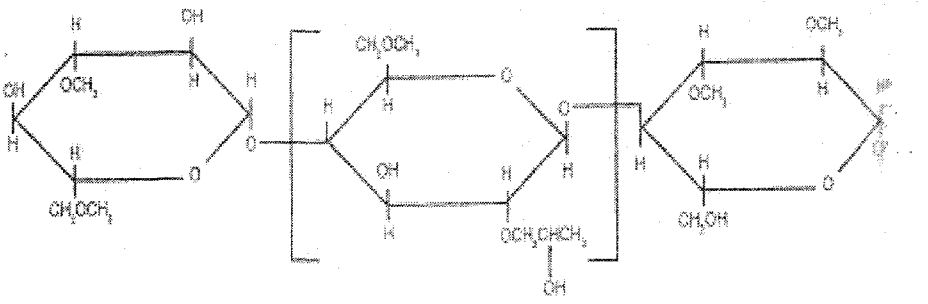

Figure 2.3 –Structure of HPMC

It is mixed alkyl- hydroxyl alkalyl cellulosic ether and may be regarded as the propylene glycol ether of methyl cellulose.

Synonym : Hyperomellose

Chemical Name : Cellulose, 2-hydroxypropyl ether

Molecular Weight : 86,000

Description : An odorless, test less, whit or creamy whit fibrous or granular power.

Specific gravity: 1.3

Density : 0.25 – 0.7 g/cm^3

Degree of polymerization: 460

Ph : 6-8(in 1% aqueous solution)

Solubility: Soluble in cold water, insoluble in alcohol, ether and chloroform but soluble in mixture of methyl alcohol and methylene chloride.

Safety: Human and animal feeding study have been shown HPMC to be safe.

Stability: Very stable in dry conditions, solution stable at pH 3-11 aq. Solution are liable to be a effective by microorganism.

Incompatibility: Extreme pH condition, oxidizing materials.

Application: It is a suspending, film forming and viscosity increasing agent. It is also use as a tablet binder and as an adhesive anhydrous ointment ingredient. It is available in various viscosity ranges and so can modulate drug release from the various devisees.

2.3.5. Poly Vinyl Pyrolidone:

Water soluble polymer made from the monomer N-Vinyl pyrolidone.

Synonym: Polyvidone

Chemical Name: Poly [1-(2-oxo-1-pyrrolidinyl) ethylene]

Molecular Formula: $[C_6H_9NO]_n$

Description: White to slight creamy-white, hygroscopic power, readily absorbs up to 18% of its weight in atmospheric water. In solution, it has excellent wetting properties and readily forms films. In water it has the useful property of Newtonian viscosity.

pH: 3-7 (5% aqueous solution**)**

Solubility: Freely soluble in water, slightly soluble in acetone and practically insoluble in ether.

Application : Used as a binder, used in contact lens, as a food additive and in molecular biology it can be used as blocking agent during western blot analysis.

2.3.6. Acrycoat S-100:

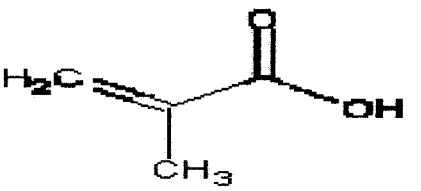

Figure 2.4 Structure of Methacrylic acid

Chemical Name: Methacrylic acid Co-Polymer.

Other Name: Eudragit S-100.

Description: Acrycoat S-100 is an anionic co polymer which confirms to USP/NF specifications of 'METHACRYLIC ACID CO-POLYMER' TYPE – B.

Appearance: White, fine, free flowing powder.

Odour: Weakly aromatic.

Solubility: Soluble in Isopropyl alcohol, Acetone, Methanol, Ethanol, Methanol/Water.

Viscosity: 100 cps

Loss of drying: 2.10%

Identification: Clear brittle formed.

Applications: used in Enteric coating of tablets, pills for protecting the drug from surrounding environment, particularly air, moisture, light, thus retaining required stability, Masking unpleasant taste and odour, thus overcoming resistance to drug ingestion, as a binder of film former in the manufacture of porous matrix tablets with delayed release of the active substance.

2.3.7. GUAR GUM[11]:- :

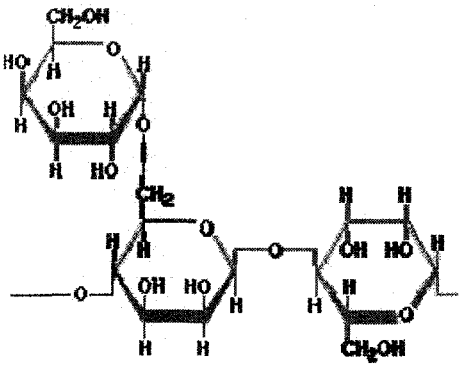

Figure 2.5 structure of GUAR GUM

Guar gum is a nonionic hydrocolloid obtained from the ground endosperm of the legume *Cyamopsis tetragonolobus (family leguminose)*, an annual plant which grows mainly in arid and semi-arid regions. It consists mainly of high molecular weight hydraocollid polysaccharide composed of galactan and mannan units combined through glycosidic linkages.

Empirical Formula:- $C_6H_{12}O_6$

Molecular weight:- 220,000

Solubility:-Soluble in water

Incompatibility:- Incompatible with acetone, tannins strong acid and alkalis. Borate ion , if present in dispersing water, will prevent hydration of guar.

Applications: - Guar gum used as thickener of lotion and cream, tablet binder and as emulsion stabilizer.

2.4 DRUG PROFILE:

2.4.1 Model drug: ZIDOVUDINE.

Synonyms: Azidodeoxythymidine; Azidothymidine; AZT; Zidovudinum.[6]

2.4.2 Chemistry of AZT:

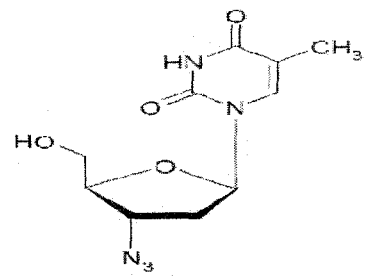

Figure 2.5 –Structure of Zidovudine[6,7,8]

Chemical name: 1-[(2*R*,4*S*,5*S*)-4-azido-5-(hydroxymethyl)tetrahydrofuran-2-yl]-5-methyl- pyrimidine-2, 4(1*H*, 3H)-dione; 1-(3-azido-2, 3-dideoxy-β-D-*erythro*-pentofuranosyl)-5-methyl-pyrimidine-2, 4(1*H*, 3H)-dione, 3'-azido-3'-deoxythimidine (AZT).[7]

Limits: AZT contains not less than 97.0% and not more than 103.0% of $C_{10}H_{13}N_5O_4$, calculated with reference to the dried substance.[7]

Formula[7]: $C_{10}H_{13}N_5O_4$.

Relative molecular mass[7]**:** 267.2.

Melting point[8]**:** 122° to 125°

Storage: AZT should be kept in a tightly closed container, protected from light.[6,8]

Ultraviolet spectrum: Aqueous acid – 207, 266 nm: basic – 266nm.[8]

2.4.3 Physicochemical properties of AZT:

Description: A white or brownish powder.[6]

Dissociation constant: pKa 9.68; 3'- azido-3'- deoxy – 5' β'D – glucopyranuronosyl (GZDV), 3.5.[6]

Partition coefficient: Log P (octanol/water), 0.05.[6]

Solubility: Soluble in ethanol (~ 750 g/l) TS (ethanol (95 %) R), sparingly soluble in water.[7]

2.4.4. Pharmacokinetic properties of AZT:

Disposition in the body: AZT is rapidly adsorbed from the gastro-intestinal tract (66 to 70%), although absorption is delayed if the drug is administered with food. It undergoes extensive first-pass metabolism in the liver where approx. 40% of the oral dose is lost. Metabolism of AZT by the kidney is minimal but rapid metabolism occurs intracellularly in the liver to GZDV. Two other hepatic metabolites have been identified, 3'-amino-3'-deoxythymidine (AMT) and its 5'- *O*- glucuronide derivative GAMT. 5'- glucuronide is the major metabolite in the plasma and urine accounting for 50 to 80% of an administered dose. Metabolism of AZT to AMT occurs in liver and gastro-intestinal microsomes. AZT is highly lipophilic and is widely distributed. It concentrates in the semen where it may exhibit delayed clearance compared to serum. It is excreted in urine as the unchanged drug ad its metabolite (63 to 95 %) via both glomerular filtration and tubular secretion. After an oral dose 72 to 74 % is excreted as the metabolite and 14 to 18% as unchanged drug. After IV administration 45 to 60% is excreted as metabolite and 18 to 19% as the unchanged drug. There is no evidence that AZT accumulates in plasma or tissues. There is significant penetration into CNS with a CNS plasma ratio of about 0.5.[6]

Therapeutic concentration: The trough serum therapeutic concentration range is 0.1 to 0.3 mg/L and peak 1.0 to 1.5mg/L.[6]

Bioavailability: 60 to 70%. This value is erratic in HIV-positive individuals.[6]

Half-life: The half-life of AZT is 0.9 to 1.0 hrs.[6]

Volume of distribution (V_d): Adult (at steady state): 1.4 to 1.6 L/kg, apparent 3.0 L/kg. Children (at steady state): 22 to 64 L/m^2.[6]

Clearance: Adults: total body clearance, 22 to 27 mL/ min/kg, plasma clearance, 1.3L/h/kg. Children: mean total body clearance, 30.9 ml/min/kg. Reduced clearance in hepatic and renal impairment.[6]

Protein binding: 34 to 38% (predominately to albumin); 20% plasma.[6]

Dose: Adult: Oral dose, 500 to 1200 mg daily; intravenous dose, 1 to 2 mg/kg/dose. Children: Oral dose, maximum 200 mg; intravenous dose, $100mg/m^2$/dose.[6]

2.4.5. Pharmacodynamic Properties of AZT:

Category: Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor).[7]

Mechanism of action: It is taken up by the cells of the host where it is converted into in its tri-phosphate form. Subsequently: (1) it, by competitive inhibition, inhibits the reverse transcriptase – viral replication stops. (2) it is also incorporated into the viral DNA chain which is growing (during replication) and terminates the lengthening of the viral DNA chain – stoppage of viral replication.[9]

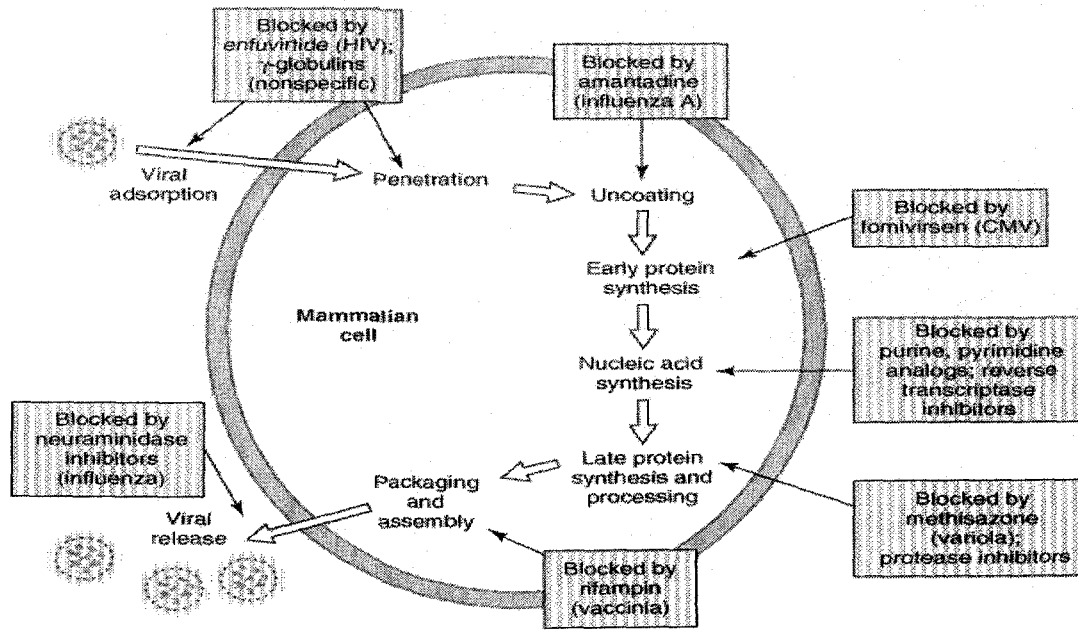

Figure 2.6 Mechanism of action of drugs in the treatment of HIV - infection

Toxicity: The serum toxic concentration range is 0.5 to 3.0 mg/L.[1] Bone marrow depression resulting in anemia, leucopenia and rarely thrombocytopenia can develop. GI upsets can occur. CNS symptoms (headache even seizures) can also occur. ADRs are potentiated by concomitant use of probenecid or cimetidine.[9] Gastrointestinal intolerance, headaches and insomnia may occur but tend to resolve on therapy.[10]

2.4.6. Resistance: [9]

Resistance is associated with point mutations leading to amino acid substitutions at multiple sites in reverse transcriptase, particularly codons 41, 67, 70, 215, and 219.Resistance mutations appear sequentially, and multiple ones are required to confer high-level resistance.

2.4.7.Adverse Effect: [12]

The commonest serious adverse effects reported with AZT are anaemia and leucopenia, mainly neutropenia, occurring within a few weeks of starting treatment. Other reported adverse effects include asthenia, fever, malaise, dizziness, insomnia, myalgia, myopathy, paraesthesia, Dyspepsia, anorexia, taste disturbance, diarrhoea and rashes. Pancreatitis, convulsions and pigmentation of nails, skin, and oral mucosa have occurred. AZT is reported to be carcinogenic in rodents.

2.4.8 Interaction: [10-13]

Paracetamol increases AZT toxicity, probably by competing for glucuronidation. Azole antifungal also inhibit AZT metabolism. Cyclophosphamide and other bone marrow suppressive or cytotoxic agents increased risk of AZT toxicity with atovaquone, chloramphenicol, and valproate.

2.4.9 Dose: [14,15]

HIV infection- (For adult): Oral-500-600 mg daily in divided doses; Intravenous dose-1-2 mg/kg every 4 hr. (For child): Oral-360-480 mg/m^2 daily in 3-4 divided doses; Intravenous dose-80-160mg/m^2 every 6 hr.

Prevention of maternal - foetal HIV transmission- (For adult): Oral-100 mg 5 times daily given after the fourteen week of pregnancy until the start of labour.

2.4.10 Marketed Brands: [14]

Till the date AZT is available in the conventional dosage form such as: RETROVIR, VIRO-Z, ZIDINE-100, ZIDINE-300, ZIDOMAX, ZIDOVIR, ZILION, and ZYDOWIN.

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