CHAPTER-4

EXCIPIENTS PROFILE

4.1 Polymers used in transdermal formulations:

4.1.1 Introduction:

Polymer is a substance composed of molecular groups which have long sequences of one or more species of atoms linked to each other by primary, usually covalent bonds. The emphasis upon substances in this definition is to highlight that although the words polymer and macromolecules of which the former is composed [1]. Macromolecules are formed by linking together monomer molecules through chemical reactions, the process by which this is achieved being known as polymerization.
Eg. Polymerization of ethylene is yields polyethylene.

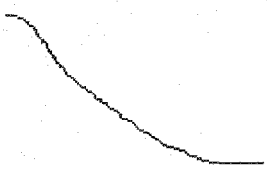
Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek word "polys" means many and "meros" means parts. The key feature that distinguishes polymers from other molecules is the repetition of many identical, similar, or complementary molecular subunits in these chains.

Branched polymers have side chains, or branches, of significant length which are bonded to the main chain at branch points (also known as junction points), and are characterized by their crosslink density or degree of cross linking, which is related directly to the number of junction points per unit volume and are characterized in terms of the number and size of the branches.

Network polymers have three dimensional structures in which each chain is connected to all other by a sequence of junction points and other chains. Such polymers are called as cross linked and characterized by their crosslink density or degree of cross linking, which is related directly to the number of junction points per unit volume.

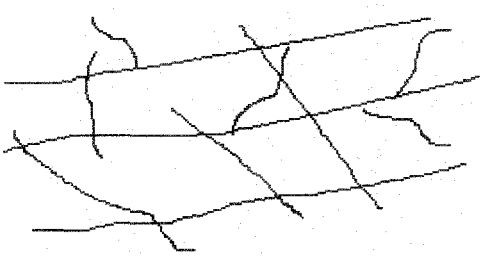
Structures:

The definition of macromolecules implies that they have a linear skeletal structure which may be represented by a chain with two ends. There are also many with non linear skeletal structures of the type shown below



Linear

Branched



Network

Non linear polymer may be formed by polymerization, or can be prepared by linking together (i.e. crosslinking) pre-existing chains.

Homopolymers:

Homopolymer is a polymer derived from one species of monomer [2].

Hypothetically homopolymer can be represented by:

A---A---A---A---A---A---A---A---A---A ⟶ $-[A]_n$

(Homopolymer)

Where, n is the number of repeat unit linked together to form the macromolecule.
Eg. Ethylene, propylene, styrene, methyl methacrylate, vinyl chloride, vinyl acetate, ethylene glycol, tetrafluoroethylene.

Co-polymer:

Co- polymer is a polymer derived from more than one species of monomer.

Statistical Co-polymers [2]*:*

Statistical co-polymers are co-polymers in which the sequential distribution of the repeat units obeys known statistical laws (eg.Markovian).

Random co-polymers:

Random co-polymers are special type of statistical co-polymers in which the distribution of repeat units is truly random. A section of a truly random co-polymer is represented below.

B---B---B---A---B---B---A---B---A

Alternating co-polymers:

Alternating co-polymers have only two different types of repeat units and these are arranged alternatively along the polymer chain.

A---B---A---B---A---B---A---B---A

Block co-polymers:

Block co-polymers are linear co-polymers in which the repeat units exist only in long sequences, or block of the same type. Two common block co-polymers are shown below.

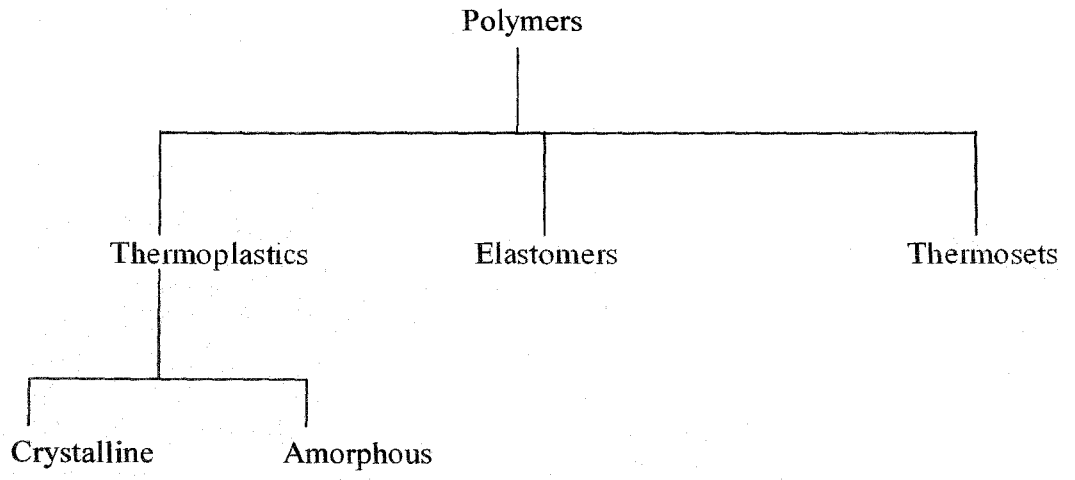
---A---A---A---A---A---A---A---A---A---A---B---B---B---B---B---B---B---B---B---

Graft co-polymers:

Graft co-polymers are branched polymers in which the branches have a different chemical structure to that of the main chain. In their simplest form consist of a main homopolymer chain with branches of a different homoco-polymer.

```
                    B---B---B---B---B---B---B---B---B---
                    |
                    B
                    |
---A---A---A---A---A---A---A---A---A---A---A---A---A---A---A---A---A---A---A---A---A---A---
A---A---A---A---A                                   |
                                                    B
                                                    |
                                                    B---B---B---B---B---B---B---B---B---B---
```

Classification of polymers:

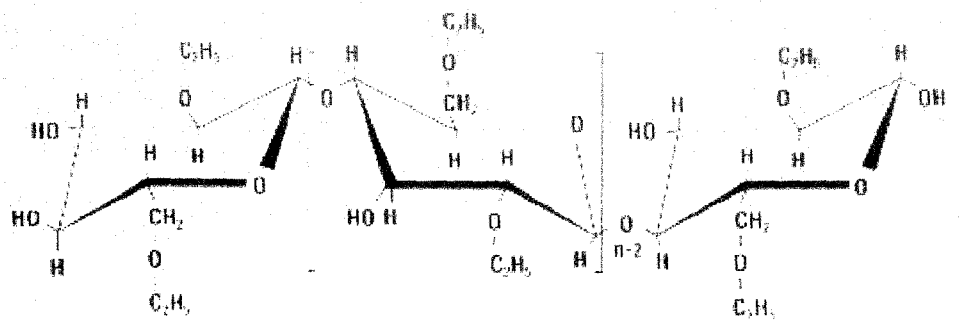


4.1.2 Polymers used under study:

4.1.2.1 Ethyl cellulose (EC) [3,4]:

The grade of ethyl cellulose used in the study has got viscosity range 18-22 cp and ethoxy content 48.49 %.

It is ethyl ether of cellulose and contains 44 and 51 % ethoxy group. It is prepared by reacting ethyl chloride with alkaline cellulose. The –OH group of glucose is ethoxylated to form ethyl cellulose.



Structure of ethyl cellulose

Description:

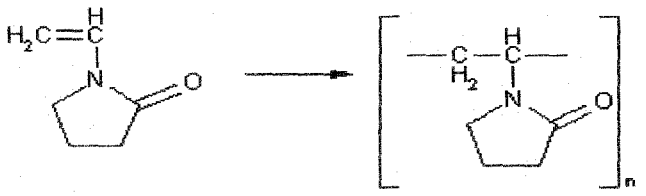
It is a white or pale yellow, odorless, tasteless granular powder. Ethoxyl content of ethyl cellulose for pharmaceutical purpose is 48 to 49 % and degree of substitution is 2.41 to 2.51.

Suitability of ethyl cellulose for controlled release formulation:

- Availability in a wide range of viscosity or molecular weight grades.
- Solubility in a variety of organic solvents.
- Miscibility with various water soluble materials that permit the permeability characteristics of matrix film to be readily changed.
- Cost is comparatively less than other polymer.

4.1.2.2 Polyvinyl pyrrolidone (PVP) [5,6]**:**

Polyvinyl pyrrolidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidone groups, the degree of polymerization of which results in polymers of various molecular weights. The different types of polyvinyl pyrrolidone are characterized by their viscosity in aqueous solution, relatively that of water, expressed as a K – value.



vinyl-pyrrolidone poly(vinyl-pyrrolidone)

Polymerization of polyvinyl pyrrolidone

Description:

A white to slightly creamy-white, hygroscopic powder. Freely soluble in water, alcohol and in methyl alcohol, slightly soluble in acetone, practically insoluble in ether.

pH of a 5 % solution in water is between 3.0 and 7.0. In water it has the useful property of Newtonian viscosity. When dry it is a light flaky powder, which readily absorbs up to 18 % of its weight of atmospheric water. In solution, it has excellent wetting properties and readily forms films.

Uses:

The monomer is carcinogenic and is extremely toxic to aquatic life. However the polymer PVP in its pure form is so safe that not only it is edible by human but also it is used as a blood plasma expander for trauma victims after the first half of 20th century.

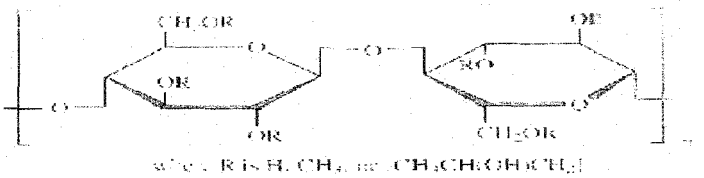
It is used as a binder in many pharmaceutical tablets; being completely inert to humans, it simply passes through. PVP added to Iodine forms a complex; in solution it is known under the trade name Betadine.

PVP binds to polar molecules exceptionally well, owing to its polarity. This has led to its application in coatings for photo-quality ink-jet papers and transparencies, as well as in inks for inkjet printers.

PVP is also used in personal care products, such as shampoos and toothpastes, in paints, and adhesives that have to be moisten, such as old-style postage stamps and envelopes. It has also been used in contact lens solutions and in steel-quenching solutions. PVP is the basis of the early formulas for hair sprays and hair gels, and still continues to be a component of same. As a food additive, PVP is a stabilizer. In molecular biology, PVP can be used as a blocking agent during Western blot analysis.

4.1.2.3 Hydroxy propyl methyl cellulose (HPMC) [7]:

Hydroxy propyl methyl cellulose is mixed hydroxyl alkyl cellulose ether and may be regarded as the propylene glycol ether of methyl cellulose. It is available in many grades. Methocel E_5, E_{15}, E_{4m}, F_{50}, F_{4m}, K_{100}, K_{4m}, K_{15m}.



Structural formula of hydroxy propyl methylcellulose

Description:

It is odorless, tasteless, white or creamy white fibrous or granular powder. Molecular weight is approximately 86,000 and the density = 0.25-0.70 gm/cm^3

Viscosity:

HPMC E15	-	15 cps (2 % aqueous solution)
HPMC E 4M	-	4000 cps (2 % aqueous solution)
HPMC K4M	-	4000 cps (2 % aqueous solution)
pH	-	6.0-8.0 (1 % aqueous solution)

It is soluble in cold water, insoluble in ether and chloroform, but soluble in mixture of methylene chloride and methanol.

Uses:

It is a suspending, viscosity enhancing and film forming agent. K grades are generally suitable as film formers, as thickeners HPMC (with its varieties dependent on viscosity and proportion between its substituents) is most widely used in matrix tablets and other types of controlled release pharmaceutical dosage form, because of its characteristics namely, nontoxic nature of polymer and its capacity to incorporate active principles.

4.1.2.4 Acrycoat S100 (methacrylic acid copolymer type-B) [8]:

Description:

Acrycoat S100 is an anionic co-polymer which confirms to USP/NF, specifications of "methacrylic acid copolymer type-B". It is insoluble in acids and pure water, soluble in neutral to weakly alkaline medium.

Use:

For sustained release and enteric film coating of tablets, pills, pellets, granules, powder etc.

Appearance:

Acrycoat S100 films are colourless and transparent, desired color can be given with pigments.

Solubility:

Insoluble in water, in buffer solution below pH 7.0, and in natural gastric fluids. Soluble in region of intestinal tract, where the fluids are neutral to weakly alkaline and in buffer solutions above pH 7.0.

Applications:

1. Enteric coating for resistance to gastric fluid, (to protect active drug from influence of acids, prevent irritation of gastric mucosa,) or to delay drug release in the intestine, when thick layers are applied.
2. Enteric coating of tablets, pills, for protecting the drug from surrounding environment, particularly air, moisture, light, thus retaining required stability.
3. Masking unpleasant taste and odour, thus overcoming resistance to drug ingestion.
4. Providing product 'identity' for differentiation of products from manufacturing, storage to patient.
5. Imparting cosmetic elegance to product appearance, masking, any noticeable visible differences in tablet core from batch to batch.
6. Reducing risk of interaction between incompatible ingredients.
7. Improves mechanical integrity, eliminating possibility of abrasion chipping etc.
8. Insulating hygroscopic cores.
9. Isolating porous cores.
10. Extending and improving keeping properties.
11. As a binder of film former in the manufacture of porous matrix tablets (wet granulation) with delayed release of the active substance.

Advantages:

- Option of solvent or semi aqueous media.
- Less quantity required, reducing volume of solution, so shortening production time.
- Stability over a broad temperature range.

- Exhibits excellent color value.
- Marginal weight gain in tablets.
- Hydrophobic.

Specifications:

Appearance: White, fine, free flowing powder.

Odour : Weakly aromatic.

Content : Min. 95 % dry polymer.

Acid value : 180 – 200 mg KOH/gm dry substance.

Solubility : Isopropyl alcohol, acetone, methanol, ethanol, methanol/water etc.

Toxicity:

Acrycoat S100 is a high molecular weight polymer. It is not absorbed by the body tissue and is totally safe for human oral consumption. Test for toxicological tolerance show that it does not have pronounced physiological action and is non-toxic.

Grades:

ACRYCOAT S100 - Powder form.

ACRYCOAT S12.5 - Containing 12.5 % dry polymer in isopropanol solutions.

Plasticizer:

Acrycoat S100 films are brittle and to improve film elasticity, use of plasticizer is strongly recommended. The recommended plasticizers are poly-ethylene glycol, dibutyl phthalate, castor oil, diethyl phthalate, triacetin, triethyl citrate etc. usually 10 % of plasticizer will be sufficient, but if necessary, can be increased to 25 %.

Storage:

At low temperature below 40°C in closed container to protect from moisture.

Shelf life:

Minimum 5 years from manufacturing date.

4.1.2.5 Polyvinyl alcohol (PVA) $(C_2H_4O)_n$ [5,9]:

It is obtained by polymerization of vinyl acetate followed by partial or complete hydrolysis of polyvinyl acetate in the presence of catalytic amounts of alkali or mineral acids. Various grades are available and they differ in their degree of polymerization and their degree of hydrolysis, which determine the physical properties of the different grades. They are characterized by the viscosity and the ester value of the substance. The viscosity is 3 to 70 millipascal seconds. The ester value, which characterizes the degree of hydrolysis, is not greater than 280.

Polyvinyl alcohol occurs as a yellowish white powder or transparent granules; soluble in water, slightly soluble in dehydrated alcohol; practically insoluble in acetone.

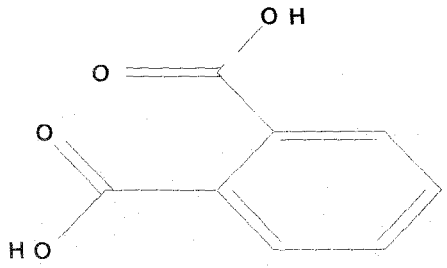
Uses:

Polyvinyl alcohol is a non-ionic surfactant that is used in pharmaceutical manufacturing as a stabilizing agent and as a viscosity increasing agent and lubricant.

Polyvinyl alcohol has also been used in the preparation of gels that dry rapidly when applied to the skin to form a soluble plastic film.

4.2 Other chemicals used during the study:

4.2.1 Dibutyl phthalate [10]:



1,2 benzenedicarboxylic acid

Chemical structure of 1, 2- benzenedicarboxylic acid (Dibutyl phthalate)

Description:

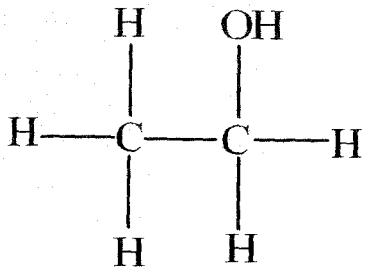
A clear, oily, colorless or very slightly yellow liquid. Practically insoluble in water, miscible with alcohol and ether.

Uses:

It is used as plasticizer.

It is also used as solvent.

4.2.2 Ethanol [11]:



Structure of ethanol

Ethanol is central depressant.

Synonym:

Alcohol

Chemical formula:

CH_3CH_2OH

Description:

Ethanol is a clear colorless, mobile, volatile, readily flammable, hygroscopic liquid. Ethanol (96 %) boils at about 78°C. It is miscible with water, chloroform and ether.

Half life:

Plasma half life is dose dependent.

Volume of distribution:

About 0.6 L/Kg.

Distribution in blood/ plasma:

Whole blood ratio, 1 : 2

Protein binding:

In plasma, not significantly bound.

Dissociation constant:

$pK_a = 15.9$ (25°C)

REFERENCE

1. Malmsten M. Surfactants and Polymers in Drug Delivery. Marcel Dekker, Inc.: New York; 1st Edn. Vol. **122**, 2002, 215-259.
2. Young RJ. and Lovell PA. Introduction to Polymers. Stanley Thornes Publishers Ltd: UK; 2nd Edn. 2002, 3-11.
3. Sweetman SC. Martindale-The complete drug reference. Pharmaceutical Press: London; 34th Edn. 2005, 1579.
4. http://www.dow.com/dowexcipients
5. Sweetman SC. Martindale-The complete drug reference. Pharmaceutical Press: London; 34th Edn. 2005, 1581.
6. Neil MJO, Heckelman PE, Koch CB. and Roman KJ. The Merck Index. Merck & Co., Inc.: USA; 14th Edn. 2006, 7697.
7. Neil MJO, Heckelman PE, Koch CB. and Roman KJ. The Merck Index. Merck & Co., Inc.: USA; 14th Edn. 2006, 4842.
8. http://www.corelpharmachem.com
9. Neil MJO, Heckelman PE, Koch CB. and Roman KJ. The Merck Index. Merck & Co., Inc.: USA; 14th Edn. 2006, 7585.
10. Sweetman SC. Martindale-The complete drug reference. Pharmaceutical Press: London; 34th Edn. 2005, 1503.
11. Moffat AC, Osselton MD. and Widdop B. Clarke's Analysis of Drugs and Poisons. KM Varghese Company: Mumbai; 3rd Edn. Vol. **2**, 2004, 991.