CHAPTER 4

SELECTION OF POLYMERS
AND OTHER EXCIPIENTS
**Selection of Polymers and other Excipients**

The most common approach in designing controlled drug delivery system is the use of polymers. The polymers used in controlled drug delivery system should possess the following characteristics:

1. Polymers should be able to retard the release of the drug from the dosage form.
2. The polymers should be non-irritant and non-toxic to the eye.
3. The polymers should not bind the drug irreversibly i.e. it should allow the release of the drug when in contact with tear fluid or buffer of similar composition.
4. The polymer itself is stable on storage and during the life of the device/formulation.
5. The polymer should not interact chemically with drugs or active constituents.

Polymers which are used very widely in the controlled-release drug delivery system are listed below (Desai *et al.*, 1994).

1. Gums and Mucilages e.g. Arabic gum, Tragacanth, Alginates and Pectin.
2. Cellulose derivatives e.g. Ethyl cellulose, Methyl cellulose, Hydroxypropylcellulose (HPC), Hydroxypropyl-ethylcellulose (HPMC), Hydroxyethylcellulose (HEC) and Sodium carboxymethylcellulose (Na CMC).
3. Polyvinyl derivatives e.g. Polyvinylalcohol (PVP), Polyvinylacetate, Polyvinylpyrrolidone and Polyvinylmethyleneether.
4. Carboxy poly methylene e.g. Carbomer (carbopol).
5. Acrylates e.g. Polymethylacrylamide, Ethyl acrylate, Poly acrylic acid salts and Methacrylates.
6. Miscellaneous e.g. Hylauronic acid, Carageenan, Agarose, Xanthan gum and starch acetate.

Based on the criteria listed earlier the following polymers were selected for the preparation of ophthalmic controlled delivery systems:

**(1) Gelrite® (Kelco division of Merck and Co.)**

It is deacetylated gellan gum and is available under the trade name of Gelrite. It has many potential applications in the pharmaceutical and food industries due to its lack...
of toxicity. It has the unique property that when dispersed in low concentration (< 1%) in water it forms a slightly viscous solution, which can subsequently increase in apparent viscosity in the presence of cations. Gellan gum is an anionic extra cellular polysaccharide material secreted by *Pseudomonas elodea*.

**Gelling Mechanism:**
The likely gelling mechanism of the deacetylated form is based on the formation of double helical functional zones followed by aggregation of the double-helical segments, which leads to a three dimensional network and which is induced to form by cations and heat treatment. Divalent cations in particular can coordinate to carboxylate group to stabilize the gel formed. (Grasdalen and Smidsroed, 1987; Chandrasekaran *et al.*, 1988) and Chandrasekaran and Thailambal, 1990), Chandrashekharan *et al.*, 1987)

The characteristics features of Gelrite<sup>(R)</sup> are as follows:

- **Chemical name:** Gellan gum.
- **Trade name:** Gelrite, Kelcogel.
- **Chemical family:** Polysaccharide gum.
- **LD<sub>50</sub>:** > 5000 mg / kg.

**Eye Irritation:** Not an irritant defined in consumer product safety commission regulations.

**Bulk density:** Approx 50 lb / cu. ft.

**pH 1% solution:** Approx, neutral.

**Solubility:** It is soluble in water, forming viscous solution. Becoming a paste at concentration > at about 5% and gels if heated and cooled. (www.kelco.com).

**Appearance and odour:** white to tan powder, slight odor.

**Hazardous decomposition products:** Thermal decomposition products may include carbon dioxide and carbon monoxide (Grasdalen *et al.*, 1987).
(2) Poloxamer 407 (Pluronic F 127)

CAS registry No: 9003-11-6

Chemical name: Hydro-hydroxypropy (oxyethylene) polyoxypropylenepoly (oxyethylene) block copolymer.

Physical character: White color, waxy, free flowing prill granules or cast solids. Odourless and tasteless.

Cloud point (10% aqueous): >100°C

pH (2.5% aqueous solution): 6.0 – 7.0

Average molecular weight: 12600

Melting Point: 56°C

Surface tension (0.1% aqueous solution): 41 dynes/cm at 25°C

HLB value: 18 – 23

Stability: Polaxamer is a stable material. Aqueous solution is stable in the presence of acids, alkalis and metal ions.

Safety: Nontoxic and nonirritant. Animal toxicity studies shows that it is non irritating to the eye.
(3) Polyvinyl Alcohol (PVA)

Functional category: Viscosity increasing agent

Chemical name: Vinyl alcohol polymer

CAS Registry Number: 9002-89-5

Empirical formula:

<table>
<thead>
<tr>
<th>Range</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Viscosity</td>
<td>200,000</td>
</tr>
<tr>
<td>Medium Viscosity</td>
<td>130,000</td>
</tr>
<tr>
<td>Low Viscosity</td>
<td>30,000</td>
</tr>
</tbody>
</table>

Description: odourless, white to cream colored granular powder.

Melting point: 228 °C

pH in water: 5.0-8.0

Solubility: Freely soluble in hot or cold water. Partially soluble in some poly hydroxy compounds, certain amines and amides.

Stability: Stable to light, rapid degradation at 200°C

Incompatibilities: Incompatible with most inorganic salts.

Safety: Non toxic when applied to eyes or skin, no irritation upto 10% (Handbook of Pharmaceutical excipients, 2005)
(4) 2-Hydroxy Propyl Beta Cyclodextrin (HPβed)

Mol. Formula: \((\text{C}_6\text{H}_{12}\text{O}_3)_6(\text{C}_3\text{H}_7\text{O})_4.5\)
Avg. Mol. Wt.: 1380

Melting point: >200°C

CAS Registry No: 94035-02-6

Chemical Name: \(\beta\)-Cyclodextrin, 2-hydroxypropylether

Physical Properties: Odourless, White solid powder.

Caution: While no human toxicity data is available for this substance, it should be handled with care. Precautions should be taken to avoid contact by all routes of exposure.

Storage: Store tightly sealed at room temperature.

Solubility: Soluble in water (45 g/100 ml). Solutions may be obtained by stirring 30 minutes at room temperature. Alternatively, sonication with cooling may be employed. Solutions may be stored for several weeks at room temperature.

Preservatives

Preservatives are included as a major component of multiple dose eye solutions for the primary purpose of maintaining sterility of the product after opening and during use. Several ophthalmic preservatives and their concentration used is shown in Table 7.
Table 7: Ophthalmic preservatives

<table>
<thead>
<tr>
<th>Type of preservative</th>
<th>Concentration range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarternary ammonium compounds</td>
<td>0.004-0.02%</td>
</tr>
<tr>
<td>Organic mercurials</td>
<td>0.001-0.01%</td>
</tr>
<tr>
<td>Para-hydroxy benzoates</td>
<td>Maximum 0.1%</td>
</tr>
<tr>
<td>Chlorobutanol</td>
<td>0.5%</td>
</tr>
<tr>
<td>Aromatic alcohols</td>
<td>0.5-0.9%</td>
</tr>
</tbody>
</table>

(5) Propyl Paraben

Propylparaben exhibits antimicrobial activity between the pH 4 to 8. Preservative activity decreases with increasing pH due to the formation of phenolate anion. Parabens are more active against yeast and molds than against bacteria (Allwood, 1982).

Synonym: 4-hydroxy benzoic acid propyl ester.

Empirical Formulae: $C_{10}H_{12}O_3$

Molecular Weight: 180.20

Chemical name: Propyl-4-hydroxy benzoate

Physical characteristics: Freely soluble in acetone and ether. It is soluble in water.

Applications: Propyl paraben is widely used as an antimicrobial preservative in cosmetics, food products and pharmaceuticals formulations. It is used in the ophthalmic formulations at concentration of 0.05-0.01%.

(6) Methyl Paraben

Synonym: Methyl para-hydroxy benzoate

Empirical Formula $C_8H_8O_3$

Applications: Methyl paraben is widely used as an antimicrobial preservative
in cosmetics, food products and pharmaceutical formulations. It is used in the ophthalmic formulations at concentration of 0.015-0.05 (Yousef et al., 1973).

(7) Dibutyl phthalate

Description: Dibutyl phthalate is a colorless, oily liquid with a very weak, aromatic odor (B. P. 1999).

Molecular weight: 278.3

Boiling point (at 760 mm Hg): 340°C (644°F)

Specific gravity (water = 1): 1.05 at 20°C (68°F)

Solubility: Insoluble in water; soluble in alcohol, ether, and benzene.

Reactivity: Conditions contributing to instability: Heat or flame.

Incompatibilities: Contact between dibutyl phthalate and nitrates, strong oxidizers, strong alkalies, strong acids, and chlorine should be avoided.

Hazardous decomposition products: Toxic gases such as carbon monoxide may be released in a fire involving dibutyl phthalate.

(8) Poly Vinyl Pyrrolidone (PVP)

Synonyms - Kollidon, Plasdone, Polyvidone, Povidone

Description - Povidone is a fine, white to creamy white, odorless or almost odorless, hygroscopic powder.

Solubility - Freely soluble in acids, chloroform, ethanol, ketones, methanol and water, practically insoluble in ether, hydrocarbons and mineral oil.

Stability and storage - Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. Steam sterilization of an aqueous
solution does not alter its properties (Handbook of Pharmaceutical excipients, 2005).

Since the powder is hygroscopic, it should be stored in an airtight container in a cool and dry place.

Use: Povidone is used as a suspending, stabilizing or viscosity-increasing agent in a number of topical suspensions and solutions. It is used in eye drops at a concentration of 2-10%. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone (Riley et al., 1991, BASF, 1990).

(9) Polyethylene glycol 400 (PEG 400)

Synonym - Macrogol 400

Description: Clear, colorless or almost colorless, viscous liquid.

Solubility: Miscible with water, very soluble in alcohol, in chloroform and in acetone; practically insoluble in solvent ether, and in fixed oils.

Stability and Storage: Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 200 are hygroscopic. Polyethylene glycols do not support microbial growth, nor do they become rancid. PEG and aqueous PEG solutions can be sterilized by autoclaving, filtration or gamma irradiation.

PEG should be stored in well-closed containers in a cool, dry place.

Use: PEGs are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations.

Safety: Generally, they are regarded as nontoxic and non irritant materials (Smyth et al., 1955). However, adverse reactions of relatively low toxicity have been reported.
**Ethylenediaminetetraacetic acid Disodium (EDTA DISODIUM)**

**Description:** Odorless, white, crystalline powder with a slightly acid taste

**Solubility:** Soluble in water and in alcohol, slightly soluble in chloroform, practically insoluble in solvent ether.

**Use:** It has no bactericidal activity but exerts a bacteriostatic effect by chelating trace metals (e.g. magnesium) necessary for the growth of microorganisms. It has also been found to enhance the activity of several preservatives particularly benzalkonium chloride against *Pseudomonas aeruginosa*.

The calcium chelators such as EDTA have been reported to loosen the tight junctions between the superficial epithelial cells thus facilitating paracellular transport (Saettone *et al.*, 1993; Hochman and Artursson, 1994).

EDTA acts on the tight junctions producing ultra-structural changes in the corneal epithelium resulting in a water influx and decrease of the overall lipophilic characteristics (Saettone *et al.*, 1993). This effect may account for the permeability reduction observed in the case of more lipophilic drugs.