CHAPTER - 4

SELECTION OF DRUG AND ITS PROFILE
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Contact lens care systems have two major functions i.e. cleaning and disinfecting. Cleaning may consists of daily cleaning with a separate surfactant cleaner at the end of the wearing period or simple mechanical rubbing of the lens on the palm of your hand with an all in one solution. The drug in the contact lens solution should have surface active characteristics as well as the antibacterial, anti fungal and antiprotozoal properties. The most serious complication of the contact lens wear is the sight threatening ocular infection.

A number of potentially pathogenic microorganisms normally exist in the eye as normal ocular flora without causing disease. However under the right conditions opportunistic microorganisms can give rise to serious ocular infections. There are a number of foreign pathogenic microorganisms like viruses, bacteria, yeast, fungi and protozoa which can inadvertently be introduced into the eye via contact lenses and hence disinfection is a vital part. The two most widely used methods of contact lens disinfection have been heat and cold chemical disinfection. Heat disinfection requires a heating unit, a heat resistant contact lens case and electrical power which may be not available always. Heat is rarely used and hence therefore cold chemical disinfection is widely used method.

4.1 Parameters for the Selection of the Drug

Following parameters should be considered for the selection of the drug for multipurpose all in one solution for hydrophilic contact lens care.

(1) The drug should have surface activity i.e cleaning action.

(2) The drug should have antibacterial antifungal antiprotozoal and antianthamoeba activity and should be potent.

(3) The drug should be non irritant to the eyes.

(4) It should be not toxic to the ocular tissues.
(5) The drug should not affect non ionic and ionic type of hydrophilic contact lenses and gas permeable contact lenses.

(6) The drug should not bind itself with tear film like mucin, lipids, mucoproteins, albumin, immunoglobulins, glycoproteins and lysozyme.

In the present research work Polyhexanide was selected in multipurpose solution due to the following reasons.

(1) Polyhexanide hydrochloride at a concentration of 0.0001% is an effective chemical disinfecting agent against the microorganisms typically found on contact lenses.

(2) There have been no reports of corneal toxicity or allergic reactions to date.

(3) It is currently used in an all in one contact lens solution for soft and rigid gas permeable contact lenses. The brands (foreign) available in the market include 'COMPLETE®' manufactured by Allergan.

(4) Polyhexanide has a faster killing rate than other antimicrobial drugs like Polyquad for Serratia marcescense, Pseudomonas aeruginosa and Candida albicans.

Considering the above facts, it was considered to develop multipurpose all in one solution for hydrophilic contact lenses using Polyhexanide hydrochloride as main constituent.

4.2 DRUG PROFILE : POLYHEXANIDE HYDROCHLORIDE

4.2.1 Introduction of Drug :

PHMB (Vantocil) acts as disinfectant and preservative. It typically exhibits good bactericidal activity but slower fungicidal and acanthamoebicide activity and provides long term storage capability for the lens. The usual disinfection time is 4-6 hours. The multipurpose solution containing Polyhexanide or PHMB (Vantocil) meets FDA and ISO primary standards.
4.2.2 Physical Properties:

It is available as aqueous solution of Polyhexamethylene biguanide (PHMB) hydrochloride with active agent as 20% w/v. It is a slightly opalescent, colourless to pale yellow liquid with viscosity at 25°C equivalent to 5 mpas.

pH: The pH of the solution (in CO₂ free water) is 4.0-4.5

Boiling point: 102°C

Solubility: It is freely soluble in Water, Methanol, Ethanol, Acetonitrile and also soluble in glacial acetic acid. Insoluble in Chloroform.

UV absorption: The light absorption is in the range of 230 to 356 nm and exhibit λmax at 235 nm in water.

Clarity and colour of the solution: 1% aqueous solution should be clear.

Storage: Stable under normal conditions of storage. It frozen allow to thaw at room temperature and stir thoroughly before use. Active agent is heat stable and non volatile.

4.2.3 Chemical Properties

It contains not less than 99.5% and not more than 102.8% of N - N'diethyl butane 1, 3 diamine calculated with reference to the anhydrous substance. The structure of Polyhexamethylene biguanide is given below in fig 9.

\[
\begin{array}{cccccc}
\text{H} & \text{H} & \text{H} \\
(\text{CH}_2)_6 & \text{N} & - & \text{C} & - & \text{N} \parallel \text{C} - & \text{N} - (\text{CH}_2)_6 \\
\parallel & \text{NH} & & \parallel & \text{NH} \\
\end{array}
\]

\[\text{HCl} \quad n \quad n=12\]

Fig 9: Structure of Polyhexanide hydrochloride
Molecular Formula: C₉H₂₀N₅HCl

Commercial Name: Vantocil IB – Avecia Biocides

Synonym: Polyhexanide, Polyaminopropyl biguanide, Vantocil, Cosmocil.

Chemical Formula: Polyhexamethylene biguanide (PHMB), Polyaminopropyl biguanide.

IUPAC name: N, N'-Diethylbutane – 1, 3 diamino biguanide.

The levels of Polyhexanide hydrochloride needed to prevent the growth of microorganisms normally found in eye flora are listed in Table V.

MIC’s do not represent effective use levels but do indicate the intrinsic spectrum of activity of Polyhexanide hydrochloride. Polyhexanide IB has a non specific mode of biotical action which means that bacterial resistance is unlikely to occur.

Amount to use: Polyhexanide hydrochloride is used in combination with Disodium edetate (0.1%) thereby reducing the concentration of Polyhexanide.

Table V: Minimum Inhibitory Concentration

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Vantocil IB (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas</td>
<td>100</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus lactis</td>
<td>25</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>5</td>
</tr>
<tr>
<td>Bacillus subtilis</td>
<td>5</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td>200</td>
</tr>
<tr>
<td>Salmonella typhimurium</td>
<td>8</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>20</td>
</tr>
</tbody>
</table>
4.2.4 Mechanism of Action

PHMB is a polymeric biguanide. This compound is antimicrobial and acanthamoebicide. It acts via interaction between the electropositive biguanide group and the plasma membrane the drug may compromise the integrity of mucopolysaccharide plug that seals the ostiole of the cyst, although other factors are likely is be involved. The lethal action of the compound is due primarily to the irreversible loss of essential cellular components through the damaged plasmalemma of the amoeba. Cytoplasmic precipitation is a secondary event. Mole for mole this polymeric biguanide is more affective but its only disadvantage is its non specific binding due to individual +ve charge on the Polymer that reduces its activity. This is the mechanism of action on *Acanthamoeba*, the 12 strains of it on both cysts and trophozoites.

Polyhexanide has high molecular weight and act by attacking the cell walls of microorganisms, while having no toxic effect on ocular structures. The disinfecting process is enhanced by the use of surfactants like Poloxamine and Poloxamers.

As a biguanide it can be classified according to its mode of action as a membrane active compound. As such Polyhexanide is either bacterostatic and bactericidal depending on the concentration and unlike antibiotics, there is no risk of organism resistance developing. The antibacterial/antimicrobial effect of the drug can be described by the following sequence.

- Rapid attraction towards the bacterial surface
- Binding to the receptive site on the bacterial surface.
- Overcoming bacterial defence/ exclusion mechanisms.
- Attraction towards the cytoplasmic membrane.
- Leakage of low molecular weight cytoplasmic components and inhibition of membrane bound enzymes.
- Extensive disruption of cytoplasmic membrane and leakage of macro molecular components and precipitation of cell contents.
Hence one of the unique attributes of Polyhexamethylene biguanide in multipurpose solution is that it kills *Acanthamoeba castellani* and *Acanthamoeba polyphaga*. Both species cause keratitis. It is less prevalent in India but more in U.S.A., New Zealand, England, Scotland.

Polyhexamethylene biguanide acts by attacking the cell wall of micro-organisms, while having no toxic effect on ocular structure. The disinfecting process is enhanced in the presence of surfactants like Polaxamine and Poloxamers. They have higher antibacterial potency than conventional antibacterial agents so they can be used in as much low as 0.002% concentration. PHMB having high molecular weight is unable to enter into the contact lens matrix and thus sensitivity reactions do not occur.

4.2.5 Analytical Methods

Limited analytical methods are available for the estimation of PHMB. The HPTLC and HPLC methods are used. Non-aqueous titrimetric method is available in the literature for concentration of 0.1% used in sanitizers, toiletries and cosmetics preparations. Strip method was used by Excel Industries in association with Aveceia.

Different analytical methods are given below in brief

**Non Aqueous Titrimetric Method:**

Hattori *et al* determined biguanide groups concentration in Polyhexamethylene biguanide by using non-aqueous titration with Perchloric acid (HClO₄). The relative standard deviation for the non-aqueous titration was 0.5% for 8 runs (124)

**Reversed Phase HPLC**

Yiping *et al* have determined Polyhexamethylene biguanide in compound chemical disinfectants by reversed phase High Performance Liquid Chromatography. PHMB was well separated from matrices on a Shiseido C₁₈ column with a temperature at 30°C and using a mobile phase. Acetonitrile and Ammonium acetate adjusted at pH 4.0 with the help of Acetic acid. The detection was performed at 235 nm. The linearity was observed in the range from 100mg/L to 1000mg/L with a relative standard deviation of 1.2% at seven runs. The recoveries at three different levels i.e. 100, 200 and 400 mg/L were 99.06%, 102.4% and 92.92% respectively. This method was simple, rapid and suitable for the routine analysis of PHMB in compound chemical disinfectants (125).
Gen Tech Scientific, Inc. of New York had developed an HPLC method for the determination of Polyhexamethylene biguanide using a column (250 x 10mm ID) with packing as 1 – Jordi 105 A° and 1-Jordi mixed bed wax. The solvent was Water and Glacial acetic acid in the ratio of 90:10 with a flow rate of 1 ml/min at 40°C. The sample was dissolved in alcohol and 200μl was injected (137).

UV Spectrophotometric Method:

Yiping et al scanned the drug solution in chromatographic mobile phase [Acetonitrile and Ammonium acetate acidified with Acetic acid pH 4.0 (16:84 v/v)] in the wavelength of 200-400nm. They observed a sharp λmax at 235.7 nm and therefore 235 nm was used for the detection of Polyhexamethylene biguanide (125). The drug solution (PHMB.HCl) in water also exhibited a λmax at 234 nm. In methanol, the drug exhibited λmax at 236 nm.

TLC Method

For the identification of the drug (PHMB.HCl) the TLC method can be used in which silica gel 60F 254 chromatographic plates were used. The mobile phase was Methanol and Water in the ratio of 8:2. The plates were viewed at 235nm in a UV chamber without using any spray reagent.
4.2.6 Multipurpose Lens Care Regimen

The current multipurpose lens care regimen used globally are listed in Table VI.

Table VI: Composition of Second Generation Contact Lens Solutions

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multisol</td>
<td>Rinsol products, Delhi, India.</td>
<td>Polyhexanide (0.0002%), Disodium edetate (0.1%), HPMC (0.1%), Poloxamine (1%), Citrate (1%) in a sterile buffered base</td>
</tr>
<tr>
<td>Complete</td>
<td>Allergan, U.S.A.</td>
<td>Polyhexanide (0.0001%), EDTA (0.1%), Poloxamer (0.01%), Phosphate and HPMC</td>
</tr>
<tr>
<td>Renu – Multiplus</td>
<td>Bausch &amp; Lomb, U.S.A.</td>
<td>Polyaminopropyl biguanide (0.0001%), Poloxamine, Borate, Boric acid, Hydroxyalkylphosphate (0.03%) and EDTA.</td>
</tr>
<tr>
<td>Solo Care – Soft</td>
<td>Ciba Vision, U.S.A.</td>
<td>Polyhexanide (0.0001%), Sodium chloride, Tri-Klens®, Poloxamer 407, Disod. hydrogen phosphate, EDTA, Sodium dihydrogen phosphate</td>
</tr>
<tr>
<td>Optifree Express</td>
<td>Alcon, U.S.A.</td>
<td>Polidronium chloride (0.001%), Poloxamine, Citrate, Myristamidopropyl amido propyl dimethyl amine, Borate, Sorbitol, Amino methylpropanol, EDTA.</td>
</tr>
<tr>
<td>Concerto Soft</td>
<td>Lunelle, U.S.A.</td>
<td>Polyhexanide (0.0005%), Hexetidine (0.00025%), Poloxamer 407, EDTA, Phosphate, Magrogol 300.</td>
</tr>
</tbody>
</table>