CHAPTER 3
SELECTION OF DRUG AND DRUG PROFILE
3.1 Selection of Drug

Drugs which are effective locally and do not show sensitivity reactions when applied to the eyes can be used for the preparation of the controlled ocular drug delivery systems. Controlled drug delivery systems have an upper edge over eye drops and ointments, as drug is delivered at the site of action and lesser quantity of the drug is required and constant drug concentration is maintained over a predetermined time.

Following parameters should be considered for the selection of the drug for controlled ocular drug delivery systems.

1. It should be non-irritant to the eyes.
2. The treatment with the drug should be for a long period of time.
3. The drug should have less biological half-life.
4. It should be active locally.
5. It should possess good corneal penetration.

In the present research work Acetazolamide and Levobunolol Hydrochloride were selected for the preparation of controlled ocular drug delivery systems i.e. Ocular inserts and Sol to gel systems for the treatment of glaucoma.

Acetazolamide is slightly soluble in water and due to solubility problem; the bioavailability of marketed eye drop is low. The half life of Acetazolamide is short i.e. 4-8 hours. On the basis of above parameters Acetazolamide was selected for the preparation of ophthalmic controlled release preparations. Due to low bioavailability of levobunolol HCl marketed eye drops and short half life i.e. 3-6 hours, this drug was also selected for making ophthalmic controlled release delivery systems.
3.2 Drug Profile

ACETAZOLAMIDE

Classification: Carbonic anhydrase inhibitor
Molecular formula: $\text{C}_8\text{H}_7\text{N}_2\text{O}_5\text{S}_2$
Molecular Weight: 222.24
CAS number: 59-66-5
Chemical Name: 2-acetylamido-1,3,4-thiadiazole-5-sulfonamide

Structure:

\[ \text{Structure Image} \]

Therapeutic category:
Acetazolamide is a potent and reversible carbonic anhydrase inhibitor, effective in the control of fluid secretion, e.g., glaucomas; in the treatment of convulsive disorders, e.g., epilepsies; and in the promotion of diuresis in instances of abnormal fluid retention.

Pharmaceutical status: Official in BP 2005 and USP 2005

Pharmaceutical dosage forms:
Acetazolamide tablets, USP: 125 and 250 mg; Diamox by Lederle
Acetazolamide extended-release capsules: 500 mg; Diamox Sequels by Lederle
Sterile Acetazolamide Sodium, USP: 500 mg; Diamox by Lederle.
Main brand names/main trade names:
Acetamox; Ak-Zol; Apo-Acetazolamide; Atenezol; AZM-Tab; Cidamex; Daranide; Dazamide, Diacarb; Diamox (Merck Index., 2006).

Physical properties:
Acetazolamide is a fine, white to yellowish-white, odorless, crystalline powder. Melting point is 260°C and Dissociation constants (pKa) is 7.2 (25°C).

Solubility: It is soluble 1 in 1400 of water, 1 in 400 of ethanol, and 1 in 100 of acetone. Practically insoluble in carbon tetrachloride, chloroform and ether. It is soluble in solutions of alkali hydroxides. Solubility ranges from 0.8 - 2.8 mg/ml between pH values of 1.7 to 8.0 (B.P. 2006, Parasrampuria et al., 1993).

Storage conditions:
Acetazolamide tablets and extended-release capsules should be stored in a well-closed container at 15°C to 30°C.

Stability:
Acetazolamide is extremely insoluble in aqueous systems and is highly sensitive to hydrolysis. Hydrolysis of acetazolamide in NaOH (0.1 N) follows first-order kinetics; the principle degradation products being acetic acid and 5-amino-1,3,4-thiadiazole-2-sulphonamide. The optimum pH for the stability of Acetazolamide is 4.0 to 5.0 (Alexander et al., 1991; Parasrampuria & Gupta, 1990; Loyd & Martin, 1996).

Methods of analysis:
UV absorption spectroscopy (USP XXII/NF, 1990; Polarography (USP XXII/NF, 1990), High performance liquid chromatography (Gupta & Parasrampuria, 1986; Parasrampuria & Gupta, 1987).

Biopharmaceutics:
Therapeutic concentration range is 15-20 µg/ml (Yakatan et al., 1978). Plasma half-life is about 3 hrs. The 90% of the administered dose is excreted unchanged.
in the urine within the first 24 hrs. Elimination half-life is about 4-8 hrs (Kunka & Matrocks, 1979). Protein binding in plasma is about 90-95%.

Dose: In the treatment of glaucoma 0.25 to 1 g daily.

Toxicity: Fatal cases of agranulocytosis, aplastic anaemia, and thrombocytopenia have been reported (Florey 2006, Connor Davis 1989, Davies 1997).
LEVOBUNOLOL HYDROCHLORIDE USP

Name of the product: Levobunolol Hydrochloride USP

Classification: Beta-adrenergic blocking agent.

Chemical Name: 5-(3-tert-butylanino-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalen-1-one hydrochloride

CAS No: 27912-14-7

Molecular weight: 327.85

Structure:

![Chemical Structure](image)

Description: Colorless to Pink powder

Melting Point: Between 206°C to 211°C

pH: pH of 5% w/v Solution is in between 4.5 and 6.5

Characteristics: A white or pinkish white, crystalline powder. Freely soluble in water; sparingly soluble in ethanol (96%) (USP, 2005).

Pharmacokinetics: It acts as both beta-1- and beta-2-adrenergic receptor agonists. It acts by decreasing the formation of aqueous humor. Onset of action is less than 60 min, Peak effect is achieved in 2-6 hrs. Half Life of levobunolol HCl is 3-6 hrs and Volume of distribution is 1.65 min⁻¹.
Uses: It decreases intraocular pressure in chronic open-angle glaucoma or ocular hypertension.


How Supplied: Ophthalmic Solution: 0.25%, 0.5%

Dosage: Ophthalmic Solution (0.25%, 0.5%)
Adults, usual: 1-2 drops of 0.25% solution in affected eye(s) b.i.d. or 1-2 drops of 0.5% solution in affected eye(s) once a day.

Method of Analysis:
HPLC Method:
Column: Stainless steel column (4mm × 30 cm) packed with stationary phase B (10 μm) (Lichrosorb RP 18).
Mobile Phase: Sodium heptane sulphonate glacial acetic acid, Methanol, Water.
Flow rate: 1.5ml/min.
Maximum Wavelength: 254nm.
Storage: Levobunolol HCl should be protected from light.
Action and use: It is β-adrenoceptor antagonist and hence used in the treatment of glaucoma in eye drops forms.

Contraindications:
Levobunolol HCl is contraindicated in those individuals with bronchial asthma, or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second and third degree atrioventricular block.

Overdose:
No data are available regarding overdosage in humans (PDR, 2006, Davies et al., 1997).