3.1 OBJECTIVE OF THE STUDY

The objective of this project is to

a. **Formulate Mouth Dissolving Tablet (MDTs) by using model drugs**

   By different methods including sublimation, direct compression, spray drying technique etc. which should have quick onset of action, not require water for swallowing of tablet, less disintegration and dissolution time hence faster relief to the patient. In order to eliminate the rough texture in mouth, we attempted to prepare high porosity rapidly mouth-dissolving tablets by using water-soluble material along with fulfilling following challenges of MDTs

   i. **Patient compliance:**- pleasant formulation with completely taste masking the model drug

   ii. **Quick disintegration:**- completely soluble, quick dissolving formulation without use of superdisintegrant

   iii. **Industrial adaptability:** - cost effective with sufficient mechanical strength and industrial applicability.

b. **Evaluate the prepared MDTs**

   To evaluate the hardness and friability for its suitability to industrial use as well as disintegration and dissolution studies and to check to for permeability and bioavailability enhancement of the drug by prepared MDT formulation in comparison to pure drug.
3.2 SCOPE AND RELEVANCE OF THE PRESENT WORK

Since very little studies has been carried out in this field and need of the formulation, which eliminates the general requirement of the conventional dosage form (such as water for swallowing, quick onset of action etc) encourage us to go for the study. The advantages of Mouth Dissolving Dosage Forms are increasingly being recognized in both, industry and academia. Their growing importance was underlined recently when European Pharmacopoeia adopted the term "Orodispersible Tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing.

In the last 4-5 years as evident by the articles published in different journals, mouth dissolving tablets has drawn much attention of the scientist at national and international levels. Due to hectic, fast-paced lifestyles, peoples don’t want to take the time to find a glass of water in order to take their pills. Patients suffering from severe migraine headaches or experiencing severe nausea and vomiting refractory to other treatments find it difficult to swallow a tablet. Such problems can be resolved by means of Mouth Dissolving Tablet. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

All the researchers working on MDTs concentrates their research on the disintegration behavior of the tablets using super disintegrants which does not full fill the basic requirements of the mouth dissolving tablets i.e patient compliance. Industries who want to make a MDTs blindly incorporating insoluble taste masking resins, superdisintegrants for disintegration and trading as mouth dissolving tablet. Due to lots of limitations like hardness, mechanical strength, no ease of manufacturing and most important cost of manufacturing, that’s why, industries concentrate whole emphasis on the use of superdisintegrants and make researchers not to work on mouth dissolving tablets instead moves on to mouth disintegrating tablets. Thus we concentrate on formulating mouth dissolving tablets giving complete dissolution of the formulation with minimum residue.
3. Research Envisaged and Selection of Drug Candidate

3.3 PLAN OF WORK

1. Selection of model drugs: on the basis of bitterness and low aqueous solubility.

2. Preliminary studies:
   a. Characterization of the Drugs: Identification and characterization of selected model drugs will be carried by UV Spectroscopy, DSC, SEM, FTIR etc.
   b. Taste masking of drugs: Bitter taste of model drug has to be masked by different methods to give pleasant, soluble complex free from grittiness.
   c. Solubility Enhancement of the drug: Solubility of model drug (poorly soluble) has to be improved in this study.

3. Formulation and evaluation of Mouth dissolving Tablets (MDTs):
   c. Formulation of Mouth Dissolving Tablets: Mouth dissolving tablets of model drugs have to be prepared by different methods (sublimation, effervescent).
   d. Evaluation of the Prepared Tablets: The prepared MDTs will be evaluated for hardness and friability for its suitability to industrial use as well as disintegration and dissolution studies.

4. Ex Vivo In Vivo studies:
   a. Ex-Vivo Permeability Study: Enhancement of drug permeability in formulation in comparison to pure drug have to be evaluated.
   b. In-Vivo Study: Study of In vivo parameter of drug in Formulation after oral administration in animal will be carried out.
      i) Assessment of Pharmacodynamics of Formulation
      ii) Assessment of Pharmacokinetic Parameters
3. Research Envisaged and Selection of Drug Candidate

3.4 SELECTION OF DRUG CANDIDATE

a. Selection of bitter Drug:

Levocetirizine diHCl, a third-generation non-sedative antihistamine chemically active L- enantiomer of cetirizine diHCl was selected as bitter drug as it is US FDA approved for human study and is easily commercial available.

b. Selection of poorly water Soluble Drug:

Cefixime, a third generation cephalosporin antibiotic, has oral bioavailability of about 40 to 50% due to poor aqueous solubility and dissolution rate and permeability being the rate limiting step in its absorption, hence selected as suitable candidate to improve its solubility along with its permeability for formulating its mouth dissolving tablets.

3.6 DESCRIPTION OF LEVOCETIRIZINE DIHCL

Levocetirizine dihydrochloride, an orally active H1-receptor antagonist, chemically, (R)-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride. Levocetirizine dihydrochloride is the active R enantiomer of cetirizine dihydrochloride, a racemic compound with antihistaminic properties.

![Molecular structure of Levocetirizine dihydrochloride]

**Molecular Formula:** \( C_{21}H_{25}ClN_2O_3 \cdot 2\text{(HCl)} \)

**Molecular Weight:** 461.81

**Melting point:** 215-220 °C
3. Research Envisaged and Selection of Drug Candidate

**Solubility:** freely soluble in water; practically insoluble in acetone and dichloromethane.

**Hygroscopicity:** Not hygroscopic

**Partition Coefficient:** \( \log P \) (octanol/water) = -0.61.

### 3.6.1 Mechanism of Action

Levocetirizine, the active enantiomer of cetirizine, is an anti-histamine; its principal effects are mediated via selective inhibition of H1 receptors. Levocetirizine, the R-enantiomer of cetirizine, is a potent and selective antagonist of peripheral H1-receptors.

### 3.6.2 Pharmacodynamics

Levocetirizine dissociates from H1-receptors with a half-life of 115 ± 38 min. After single administration, levocetirizine shows receptor occupancy of 90% at 4 hours and 57% at 24 hours. ECGs did not show relevant effects of levocetirizine on QT interval.

### 3.6.3 Pharmacokinetics

Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9 g h after dosing. Levocetirizine is 90% bound to plasma proteins. The distribution of levocetirizine is restrictive, as the volume of distribution is 0.4 l/kg (table 3.1). The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O-dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involved multiple and/or unidentified CYP isoforms.
3. Research Envisaged and Selection of Drug Candidate

Table 3.1 Pharmacokinetic parameters of levocetirizine diHCl

<table>
<thead>
<tr>
<th>PK parameters</th>
<th>Oral Solution (0.5 mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t (ng.hr/mL)</td>
<td>1954 ± 556</td>
</tr>
<tr>
<td>AUC0-inf (ng.hr/mL)</td>
<td>2020 ± 593</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>227 ± 49</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>0.5 (0.33 – 2.00)*</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>9 ± 3.1</td>
</tr>
<tr>
<td>Vd/F (L)</td>
<td>34 ± 14</td>
</tr>
<tr>
<td>CL/F (mL/min)</td>
<td>44 ± 12</td>
</tr>
</tbody>
</table>

3.6.4 Drug Interactions

In vitro data indicate that levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes. The extent of absorption of levocetirizine is not reduced with food, although the rate of absorption is decreased. In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol.

3.6.5 Dose

Adults and children >6 years: a usual dose of 10 mg is administered daily. Children (2 to 6 years) and patients with renal impairment: usual dose 5 mg daily.
3.7 DESCRIPTION OF CEFIXIME

CEFIXIME:

\[(6R,7R)-7-[[2Z)-(2-Amino-4-thiazolyl)[(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid\]

\[
\text{C}_{16}\text{H}_{15}\text{N}_{5}\text{O}_{7}\text{S}_{2}=453.5
\]

CEFIXIME TRIHYDRATE:

Chemically, Cefixime is \((6R,7R)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid, \(7^2-(Z)-(O-(\text{carboxymethyl}) \text{ oxime})\) trihydrate.

**Molecular Formula:** \(\text{C}_{16}\text{H}_{15}\text{N}_{5}\text{O}_{7}\text{S}_{2} \cdot 3\text{H}_{2}\text{O}\)

**Molecular Weight:** 507.50

**Melting point:** 218-225 °C

**Solubility:** A white/almost white to light yellow crystalline powder. It is slightly soluble in water and alcohol; sparingly soluble in dehydrated alcohol and acetone; freely soluble in methyl alcohol, glycerol and propylene glycol; very slightly soluble in 70% sorbitol and octanol; practically insoluble in ether, ethyl acetate and hexane.

**Dissociation Constant:** \(pK_a = 3.73\)
3. Research Envisaged and Selection of Drug Candidate

3.7.1 Mechanism of Action

Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs); which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

3.7.2 Pharmacodynamics / Pharmacokinetics

Oral Absorption: 40% to 50%
Distribution: Widely throughout the body and reaches therapeutic concentration in most tissues and body fluids.
Protein binding: 65%
Half-life elimination: Normal renal function: 3-4 hours; Renal failure: Up to 11.5 hours
Time to peak, serum: 2-6 hours; delayed with food
Excretion: Urine (50% of absorbed dose as active drug); feces (10%)

3.7.3 Drug Interactions

BCG: Antibiotics may diminish the therapeutic effect of BCG.
Probenecid: May increase the serum concentration of Cephalosporins.
Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. Management: Vaccination with live attenuated typhoid vaccine (Ty21a) should be avoided in patients being treated with systemic antibacterial agents. Use of this vaccine should be postponed until at least 24 hours after cessation of antibacterial agents.

3.7.4 Dose

Adults: 200 to 400 mg daily. Children with a body weight <50 kg: 8 mg/kg body weight daily. Patients with a creatinine clearance <20 mL/min: maximum 200 mg daily.