4 PREFORMULATION STUDY:

Prior to the development of the major dosage forms, it is essential that certain physical and chemical properties of the drug molecule and other derived properties of the drug powder must be determined. This information will dictate many of the subsequent events and possible approaches in formulation development. This first learning phase is called as preformulation.¹

For the purpose of pre-formulation studies the following studies were done.

- The drug profile of the selected drug Mosapride Citrate di-hydrate.
- Defining the Experimental domain.
- Study of pharmacokinetics and calculation of Dose for Sustained release (SR) tablet.
- Excipient selection for formulation of dosage form.
- Compatibility of chosen excipients.
- Finalising excipients based on statistical experimentation for excipient compatibility.
- Drug identification.
  - Melting point
  - Infrared spectra
  - Standard calibration curve.
  - UV scan.
- Drug and Polymer flow properties.
  - Bulk density
  - Tapped density
  - Carr’s index
  - Angle of repose
  - Hausner’s ratio.
4.1 Drug Profile:

Mosapride citrate dihydrate

4.1.1 Structure:

![Molecular Structure]

4.1.2 Chemical Name:

(±)-4-Amino-5-chloro-2-ethoxy-N-[(4-(4-flurobenzyl)-2-morpholinyl)methyl]benzamide citrate dihydrate.

4.1.3 Description:

An off white, crystalline powder. It is odourless and has a slightly bitter taste.

4.1.4 Physical properties:

a) Solubility: Soluble in Dimethyl formamide. Practically insoluble in water.

b) Residue on ignition: Not more than 0.1% w/w.

c) Molecular formula: C\textsubscript{21}H\textsubscript{25}ClFN\textsubscript{3}O\textsubscript{7}.C\textsubscript{6}H\textsubscript{8}O\textsubscript{7}.2H\textsubscript{2}O

d) Molecular weight: 650.050

e) Melting point: 110-113\degree C.

f) Taste: Bitter.

4.1.5 Pharmacokinetics:

4.1.5.1 Absorption

Mosapride\textsuperscript{3} is quickly absorbed after oral ingestion. Absorption is unaffected by presence of food. Mean plasma levels in humans are 25.1ng/ml, 51.2ng/ml, 157.8ng/ml and 280.6ng/ml after oral doses of 5, 10, 20 & 40mg respectively, within half to one hour. The peaks are dose related and followed a first order decrease with apparent half lives of 1.4 to 2hrs. The C\textsubscript{max} and AUC increased in proportion to the dose, indicating

"Development And Evaluation Of New Drug Delivery System"
linear pharmacokinetics of mosapride up to 40mg. Cmax values after a single dose of 5,10,20 or 40mg are 30.7, 63.6, 182.2or 312.3ng/ml respectively.

4.1.5.2 Distribution:

Mosapride is 93-99% bound to plasma proteins including albumin & alpha-1-acid glycoprotein. The drug distributed to most body tissues, more to the GI tract than to the brain. Mosapride achieves high levels in milk and crosses the placenta.

4.1.5.3 Metabolism:

Most of the drug is metabolized and about 0.1% is excreted unchanged in urine after 48hrs.

Mosapride citrate is metabolized mainly in the liver, where the 4 fluoro-benzyl group is removed, followed by the oxidation of the morpholine ring at position 5 and hydroxylation of the benzene ring at position 3. The main metabolite is M-1[des-4-flurobenzyl] and M-2 is another metabolite. Both have very little activity. The metabolites thus contribute very little to the gastro pro-kinetic activity of Mosapride. Metabolic enzyme is cytochrome P-450, sub family: Mainly CYP 3A4.

4.1.6 Mechanism of action:

Mosapride citrate is a selective 5-HT4 receptor agonist. 5-HT4 receptors are present in the gut in the myenteric plexus, in the neurons of the longitudinal and circular muscles, and in the gut interneurons. Mosapride stimulates these 5-HT4 receptors in the gastrointestinal nerve plexus, which increases the release of acetylcholine, resulting in enhancement of gastrointestinal motility and gastric emptying. Mosapride has affinity only for receptors located in the foregut, and does not stimulate colonic receptors, and therefore rarely causes diarrhoea. In contrast Cisapride and Tegasorod increases colonic motility and results in diarrhoea.

The specificity extends to a lack of affinity to D2 receptors in the brain, in comparison to other pro-kinetic agents. Mosapride does not influence the QT interval even at higher doses.
Mosapride citrate selectively acts on serotonin (5-HT4) receptors, thus accelerating gastrointestinal motility via acetylcholine. However, few studies⁶ have evaluated the influence of Mosapride citrate on autonomic nervous activity and hemo-dynamics. The mean peak power of Electrogastrogram (EGG) increased significantly after the administration of Mosapride citrate. Gastric emptying significantly increased after the administration of Mosapride citrate. However, neither blood pressure nor heart rate changed significantly after the drug was administered. In addition, Spectral analysis of heart rate and blood pressure variabilities showed no significant changes in autonomic nervous activity parameters, QT intervals, QT dispersions. Thus, Mosapride citrate increased gastric motility and emptying without influencing autonomic nervous activity, suggesting that it may be very useful for elderly patients with autonomic imbalance.

4.1.7 Indications⁵

1. Gastro esophageal Reflux Disease (GERD)

2. Functional Dyspepsia.

3. Disorders associated with decreased gastric motility.

4. Nausea/vomiting, Heartburn, Chronic gastritis.

4.1.8 Adverse effects:

1. Abdominal cramps.

2. Diarrhoea/ loose stools.

3. Dry mouth.


5. Nausea.

4.1.9 Interactions:

Mosaprides major degradation⁵ is the Cytochrome P-450(3A4) system. However, electrophysiological studies show that the co administration of drugs that inhibit the CYP3A4 enzymes (Erythromycin, Ketoconazole,etc.) have no effect on Mosapride
indicating satisfactory safety margins exists in relation to rhythm abnormalities, unlike that which occurs with cisapride. Cisapride has a structure that confers on it the properties of a class III anti-arrhythmic agent. In Mosapride the distance between the amine and the fluorinated aromatic ring is short. This unique structure of Mosapride prevents binding with receptors on the cardiomyocytes.

Concomitant use of Mosapride with anti-cholinergic drugs, may decrease the effect of mosapride.\textsuperscript{5}

4.1.10 Dosage\textsuperscript{5}

Adults: 15mg administered daily in 3 divided oral doses before or after meals.

4.1.11 Storage:

Store at 15-30°C in tightly closed container, protect from heat and light.

4.1.12 Special precautions\textsuperscript{5}:

1. If any improvement of gastrointestinal symptoms are not observed after administration for about 2 weeks, it should not be given aimlessly.

2. When 100-330 times of recommended clinical dose (30-100mg/kg/day) of Mosapride citrate was orally administered in rodents for long periods, increased incidence of hepato-cellular adenoma and thyroid follicular cell adenoma was observed.

3. Use in pregnancy and lactation: Safety in pregnant women is not established. It should be used only if the expected therapeutic benefits outweigh the possible risks associated with the treatment. Should be avoided in nursing mothers or breast feeding should be stopped.

4. Use in children: Safety of this drug in children is not established.

5. Use in elderly: Since the physiological functions of the kidneys and liver are generally reduced in the elderly patients, Mosapride should be administered with care by monitoring patient’s condition.
4.1.13 Marketed preparations

## Marketed Formulation

<table>
<thead>
<tr>
<th>Brand</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinetix 5mg</td>
<td>Lupin</td>
</tr>
<tr>
<td>Mic 5mg</td>
<td>Alembic</td>
</tr>
<tr>
<td>Mic 2.5mg</td>
<td>Alembic</td>
</tr>
<tr>
<td>Mosadac 5mg</td>
<td>Zydus Cadilla</td>
</tr>
<tr>
<td>Moza 5mg</td>
<td>Intas Pharmaceuticals</td>
</tr>
<tr>
<td>Moten-Instab 5mg</td>
<td>Ranbaxy</td>
</tr>
<tr>
<td>Normagut 5mg</td>
<td>Wockhardt</td>
</tr>
</tbody>
</table>
4.2 REFERENCES


2. Health 4 india.com


