MATERIALS AND METHODOLOGY

3.1 APPARATUS AND EQUIPMENTS USED

Table 3.1 List of apparatus and equipments used

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Apparatus and Equipment</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UV spectrophotometer (UV-1700)</td>
<td>Shimadzu, Japan.</td>
</tr>
<tr>
<td>2</td>
<td>Cuvette (Quartz)</td>
<td>Shimadzu, Japan.</td>
</tr>
<tr>
<td>3</td>
<td>Magnetic stirrer (Temp.controlled)</td>
<td>Remi, India.</td>
</tr>
<tr>
<td>4</td>
<td>Digital balance- (PB 602.S)</td>
<td>Mettler Toledo, Japan.</td>
</tr>
<tr>
<td>5</td>
<td>Hot air oven</td>
<td>Alcon, India.</td>
</tr>
<tr>
<td>6</td>
<td>Incubator</td>
<td>Scientific Instruments Ltd., India.</td>
</tr>
<tr>
<td>7</td>
<td>Differential scanning calorimeter (DSC 6 and 7)</td>
<td>Perkin Elmer, Japan.</td>
</tr>
<tr>
<td>8</td>
<td>Microscope (photomicroscope)</td>
<td>RXL-5T (carton).</td>
</tr>
<tr>
<td>9</td>
<td>Syringe with needle (5ml)</td>
<td>Hindustan medical devices Ltd., Faridabad, India.</td>
</tr>
<tr>
<td>10</td>
<td>pH meter (digital)</td>
<td>Systronics</td>
</tr>
<tr>
<td>11</td>
<td>Tap density apparatus</td>
<td>Rollex India Ltd</td>
</tr>
<tr>
<td>12</td>
<td>Glass wares</td>
<td>Borosil Ltd., Mumbai, India.</td>
</tr>
<tr>
<td>13</td>
<td>Digital balance</td>
<td>Adventurer Ohaus India Ltd.</td>
</tr>
<tr>
<td>14</td>
<td>Vacuum Desiccators</td>
<td>Poly Lab, India.</td>
</tr>
<tr>
<td>15</td>
<td>Wrist action shaking machine</td>
<td>Remi India Ltd., Mumbai, India.</td>
</tr>
<tr>
<td>16</td>
<td>Thermometer</td>
<td>GDP glass, India.</td>
</tr>
<tr>
<td>17</td>
<td>Computer software</td>
<td>MS Office 2003,</td>
</tr>
<tr>
<td>18</td>
<td>Refrigerator</td>
<td>LG electronics Ltd., India.</td>
</tr>
<tr>
<td>19</td>
<td>Mould (Glass)</td>
<td>Borosil Ltd., Mumbai, India.</td>
</tr>
<tr>
<td>20</td>
<td>Gloves</td>
<td>Surgi care Pvt. Ltd., New Delhi, India.</td>
</tr>
<tr>
<td>21</td>
<td>Medical tape</td>
<td>Johnson and Johnson Ltd. India.</td>
</tr>
</tbody>
</table>
### MATERIALS AND METHODOLOGY

<table>
<thead>
<tr>
<th></th>
<th>Micropipette (100-500 microlitres)</th>
<th>Micro lit. Instruments (P) Ltd., Lucknow, India.</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>Aluminium foils</td>
<td>Home foils, New Delhi, India.</td>
</tr>
<tr>
<td>24</td>
<td>Capillary tubes</td>
<td>Kalpatru Scientifics, New Delhi, India.</td>
</tr>
</tbody>
</table>

### 3.2. CHEMICALS & POLYMERS USED

Table 3.2. List of chemicals used

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Chemicals</th>
<th>Grade</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Famotidine drug</td>
<td>AR</td>
<td>Cadila pharmaceuticals, Ahmedabad, Gujrut</td>
</tr>
<tr>
<td>2</td>
<td>Pectin</td>
<td>AR</td>
<td>SD fine chemicals, Mumbai, India</td>
</tr>
<tr>
<td>3</td>
<td>HPMC K4M</td>
<td>AR</td>
<td>Gift sample from Colorcon India Ltd</td>
</tr>
<tr>
<td>4</td>
<td>Sodium alginate</td>
<td>AR</td>
<td>CDH (P) Ltd., New Delhi</td>
</tr>
<tr>
<td>5</td>
<td>Peppermint oil</td>
<td>AR</td>
<td>SD fine chemicals, Mumbai, India</td>
</tr>
<tr>
<td>6</td>
<td>Mineral oil</td>
<td>AR</td>
<td>CDH India</td>
</tr>
<tr>
<td>7</td>
<td>Castor oil</td>
<td>AR</td>
<td>CDH India</td>
</tr>
<tr>
<td>8</td>
<td>Soya bean oil</td>
<td>AR</td>
<td>CDH India</td>
</tr>
<tr>
<td>9</td>
<td>Olive oil</td>
<td>AR</td>
<td>SD fine chemicals, Mumbai, India</td>
</tr>
<tr>
<td>10</td>
<td>Sunflower oil</td>
<td>AR</td>
<td>SD fine chemicals, Mumbai, India</td>
</tr>
<tr>
<td>11</td>
<td>Sodium chloride</td>
<td>AR</td>
<td>CDH (p) Ltd., New Delhi, India</td>
</tr>
<tr>
<td>12</td>
<td>Calcium chloride</td>
<td>AR</td>
<td>SD fine chemicals, Mumbai, India</td>
</tr>
<tr>
<td>13</td>
<td>Magnesium chloride (MgCl₂.2H₂O)</td>
<td>AR</td>
<td>SD fine chemicals, Mumbai, India</td>
</tr>
<tr>
<td>14</td>
<td>Barium Chloride (BaCl₂.2H₂O)</td>
<td>AR</td>
<td>SD fine chemicals, Mumbai, India</td>
</tr>
<tr>
<td>15</td>
<td>Lead nitrate (Pb(NO₃)₂)</td>
<td>AR</td>
<td>SD fine chemicals, Mumbai, India</td>
</tr>
<tr>
<td>16</td>
<td>SnCl₂</td>
<td>AR</td>
<td>SD fine chemicals, Mumbai, India</td>
</tr>
</tbody>
</table>
3.2.1 FAMOTIDINE\textsuperscript{86,87}

\textbf{3.2.1.1 Introduction}

Famotidine is Histamine-2 antagonist. It is widely used in the management of peptic ulcer, duodenal ulcer, gastric eosophagitis, zollinger-ellinson syndrome, etc. It has greater potency to eradicate H.pylori.

\textbf{3.2.1.2 Chemical name:}


\textbf{3.2.1.3 Physicochemical properties:}

\textbf{a) Structural formula:}

\textbf{b) Empirical formula:} C\textsubscript{8}H\textsubscript{15}N\textsubscript{7}O\textsubscript{2}S\textsubscript{3}

\textbf{c) Molecular weight:} 337.43

\textbf{d) Physical form:} Famotidine is a white to pale yellow crystalline powder.

\textbf{e) Melting point:} It exists in two forms which melt at about 163°C and 169°C.

\textbf{f) Solubility:} It is free soluble in dimethylformamide and in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water and ethanol, practically insoluble in ether and in ethyl acetate. It dissolves in mineral acids.

\textbf{3.2.1.4 Pharmacokinetics}\textsuperscript{87}:
Absorption
Famotidine is incompletely absorbed from the GI tract following oral administration, and the drug reportedly undergoes minimal first-pass metabolism. Food may slightly enhance and antacids may slightly decrease the bioavailability of famotidine, but these alterations do not appear to be clinically important.

Distribution
Distribution of famotidine into human body tissues and fluids has not been fully characterized. The apparent volume of distribution of the drug is reported to be 1.1–1.4 L/kg in adults and does not appear to be altered substantially in patients with renal dysfunction. In children 1–15 years of age, a volume of distribution of 1.5–2.07 L/kg has been reported. Following oral or IV administration in rats, famotidine is widely distributed, appearing in highest concentrations in the kidney, liver, pancreas, and submandibular gland. The drug is 15–20% protein bound.

Metabolism
Famotidine is metabolized in the liver to famotidine S-oxide (S-famotidine). The metabolite does not appear to inhibit gastric acid secretion. Orally administered famotidine undergoes minimal metabolism on first pass through the liver.

Elimination
Famotidine is excreted principally in urine via glomerular filtration and tubular secretion. Approximately 25–30 or 65–80% of a dose is excreted unchanged in urine within 24 hours following oral or IV administration, respectively, and approximately 13–49 or 52–82% of a single 40-mg oral or IV dose, respectively, is excreted within 72 hours.

Pharmacokinetics parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral availability</td>
<td>40-45%</td>
</tr>
<tr>
<td>Bound in plasma</td>
<td>15-20%</td>
</tr>
<tr>
<td>Clearance (ml/min/)</td>
<td>250-450</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1-3 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.5-3.5 hr</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal (65-70%)</td>
</tr>
<tr>
<td></td>
<td>Metabolic (30-35%)</td>
</tr>
<tr>
<td>Active metabolite</td>
<td>+++ (S-oxide)</td>
</tr>
</tbody>
</table>
Metabolic Excretion: 30-35% 

C<sub>max</sub> (ng/ml): 81.1 (±7.5) µg/mL 

Volume of Distribution (liters/kg): 1.1-1.4 

Dose: 40mg at bed time or 20mg BD

3.2.1.5. Pharmacological properties:

**Category:** Antiulcer agent

**Mode of action:** H<sub>2</sub> antagonists are the first class of highly effective drugs for acid-peptic disease. A thiazole ring containing H<sub>2</sub> blocker (antihistamine) which binds tightly to H<sub>2</sub> receptors. Famotidine inhibits H<sub>2</sub> receptors in the competitive-noncompetitive manner.

In the gastric parietal cells the terminal enzyme H<sup>+</sup>K<sup>+</sup>ATPase (proton pump) which secretes H<sup>+</sup> ions in the apical canaliculi of parietal cells can be activated by histamine, ACh and gastrin acting via their own receptors located on the basolateral membrane of these cells. Out of the three physiological secretagogues, histamine, acting through H<sub>2</sub> receptors, plays the dominant role. Histamine participated in the acid response to gastrin and ACh at more than one levels, and H<sub>2</sub> antagonists suppress not only histamine but also ACh, pentagastrin and any gastric acid secretory stimulus.
Antisecretory activity: The significant in vivo action of H$_2$ blockers is marked inhibition of gastric secretion. All phases (basal, psychic, neurogenic, and gastric) of secretion are suppressed dose dependently. Secretory responses to not only histamine but all other stimuli (ACh, gastrin, insulin, alcohol, food) are attenuated. This reflects the permissive role of histamine in amplifying responses to other secretagogues. The most prominent action is on basal acid output, but volume, pepsin content and intrinsic factor secretion are also reduced. The usual ulcer healing doses produce 60-70% inhibition of 24hr acid output. The H$_2$ blockers have antiulcerogenic effect. Gastric ulceration due to stress and drugs (NSAIDs, cholinergic, histaminergic) is prevented. They do not have any direct effect on gastric or esophageal motility or on lower esophageal sphincter (LES) tone.
3.2.1.6. Uses:

- To treat duodenal ulcers.
- To treat gastric ulcers.
- Reduces the chance of gastric ulcers in patients who use a group of medicines called NSAIDS and who may be at greater risk.
- Combined with the antibiotics clarithromycin and amoxicillin in the one-week eradication triple therapy for *Helicobacter pylori* infection, as *H. pylori* is the causative factor in the majority of peptic and duodenal ulcers.
- In the prophylaxis of pneumonia
- Short term treatment of gastroesophageal reflux disease.
- Treatment of pathological hypersecretory conditions (e.g. zollinger-ellison syndrome, multiple endocrine adenomas).

3.2.1.7. Side effects:

The following adverse reactions have been stated to occur in more than 1% of patients on therapy with famotidine in controlled clinical trials, and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%).

**Body as a Whole:** fever, asthenia, fatigue

**Cardiovascular:** arrhythmia, AV block, palpitation

**Gastrointestinal:** cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal distress, anorexia, dry mouth

**Hematologic:** rare cases of agranulocytosis, pancytopenia, leukopenia, thrombocytopenia

**Hypersensitivity:** anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection

**Musculoskeletal:** musculoskeletal pain including muscle cramps, arthralgia

**Nervous System/Psychiatric:** grand mal seizure; psychic disturbances, which were reversible in cases for which follow-up was obtained, including hallucinations, confusion, agitation, depression, anxiety, decreased libido; paresthesia; insomnia; somnolence. Convulsions, in patients with impaired renal function, have been reported very rarely.
**Respiratory:** bronchospasm, interstitial pneumonia

**Skin:** toxic epidermal necrolysis/Stevens Johnson syndrome (very rare), alopecia, acne, pruritus, dry skin, flushing

**Special Senses:** tinnitus, taste disorder

**Other:** rare cases of impotence and rare cases of gynecomastia have been reported; however, in controlled clinical trials, the incidences were not greater than those seen with placebo.

**Pediatric Patients**
In a clinical study in 35 pediatric patients < 1 year of age with GERD symptoms [e.g., vomiting (spitting up), irritability (fussing)], agitation was observed in 5 patients on famotidine that resolved when the medication was discontinued.

**3.2.1.8. Drug interactions:**
No drug interactions have been identified. Studies with famotidine in man, in animal models, and in vitro have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

**3.2.1.9. Contraindications:**
Hypersensitivity to any component of these products. Cross sensitivity in this class of compounds has been observed. Therefore, it should not be administered to patients with a history of hypersensitivity to other H2-receptor antagonists.
3.2.1.10 Marketed preparations

Table 3.3 Marketed preparations

<table>
<thead>
<tr>
<th>Name</th>
<th>Company Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACID</td>
<td>Intas Pharmaceutical</td>
</tr>
<tr>
<td>FAMTAC</td>
<td>Nicholas Piramal</td>
</tr>
<tr>
<td>FAMOCID</td>
<td>Sun Pharmaceutical</td>
</tr>
<tr>
<td>TOPCID</td>
<td>Torrent</td>
</tr>
<tr>
<td>FAMONINE</td>
<td>Cadila Pharma</td>
</tr>
</tbody>
</table>

3.2.2 SODIUM ALGINATE

3.2.2.1 Nonproprietary Names

- BP: Sodium alginate
- PhEur: Natrii alginas
- USPNF: Sodium alginate

3.2.2.2. Synonyms

Algin; alginic acid, sodium salt; E401; Kelcosol; Keltone; Protanal; sodium polymannuronate.

3.2.2.3. Chemical Name and CAS Registry Number

Sodium alginate [9005-38-3]

3.2.2.4. Empirical Formula and Molecular Weight

Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid.

The block structure and molecular weight of sodium alginate samples has been investigated.†
3.2.2.5. Structural Formula

![Structural Formula of Sodium Alginate](image)

3.2.2.6. Functional Category

Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

3.2.2.7. Applications in Pharmaceutical Formulation or Technology

- Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant;
- It has been used as a diluent in capsule formulations.
- Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets,
- capsules,
- Aqueous suspensions.
- In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions.
- Recently, sodium alginate has been used for the aqueous microencapsulation of drugs,
- in contrast with the more conventional microencapsulation techniques which use organic-solvent systems. It has also been used in the formation of nanoparticles.
The adhesiveness of hydrogels prepared from sodium alginate has been investigated.

Drug release from oral mucosal adhesive tablets based on sodium alginate has been reported.

Other novel delivery systems containing sodium alginate include an ophthalmic solution that forms a gel in situ when administered to the eye.

Freeze-dried device intended for the delivery of bone-growth factors.

Hydrogel systems containing alginates have also been investigated for delivery of proteins and peptides.

Therapeutically, sodium alginate has been used in combination with an H₂-receptor antagonist in the management of gastroesophageal reflux.

As a hemostatic agent in surgical dressings.

Alginate dressings, used to treat exuding wounds, often contain significant amounts of sodium alginate as this improves the gelling properties.

Sodium alginate is also used in cosmetics and food products.

**3.2.2.8. Description**

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

**3.2.2.9. Pharmacopeial Specification**

**3.2.2.10. Typical Properties**

- Acidity/alkalinity: pH ≈7.2 for a 1% w/v aqueous solution.
- Solubility: practically insoluble in ethanol, ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming a viscous colloidal solution.
- Viscosity (dynamic): various grades of sodium alginate are commercially available that yield aqueous solutions of varying viscosity. Typically, a 1%
w/v aqueous solution, at 20 °C, will have a viscosity of 20–400 mPa s (20–400 cP). Viscosity may vary depending upon concentration, pH, temperature, or the presence of metal ions. Above pH 10, viscosity decreases.

3.2.2.11. Stability and Storage Conditions

Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humidities and a cool temperature. Aqueous solutions of sodium alginate are most stable at pH 4–10. Below pH 3, alginic acid is precipitated. A 1% w/v aqueous solution of sodium alginate exposed to differing temperatures had a viscosity 60–80% of its original value after storage for 2 years. Solutions should not be stored in metal containers.

Sodium alginate solutions are susceptible on storage to microbial spoilage, which may affect solution viscosity. Solutions are ideally sterilized using ethylene oxide, although filtration using a 0.45-μm filter also has only a slight adverse effect on solution viscosity. Heating sodium alginate solutions to temperatures above 70 °C causes depolymerization with a subsequent loss of viscosity. Autoclaving of solutions can cause a decrease in viscosity, which may vary depending upon the nature of any other substances present. Gamma irradiation should not be used to sterilize sodium alginate solutions since this process severely reduces solution viscosity.

Preparations for external use may be preserved by the addition of 0.1% chlorocresol, 0.1% chloroxylenol, or parabens. If the medium is acidic, benzoic acid may also be used.

The bulk material should be stored in an airtight container in a cool, dry place.

3.2.2.12. Incompatibilities

Sodium alginate is incompatible with acridine derivatives, crystal violet, phenylmercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%. Low concentrations of electrolytes cause an increase
in viscosity but high electrolyte concentrations cause salting-out of sodium alginate; salting-out occurs if more than 4% of sodium chloride is present.

3.2.2.13. Method of Manufacture

Alginic acid is extracted from brown seaweed and is neutralized with sodium bicarbonate to form sodium alginate.

3.2.2.14. Safety

Sodium alginate is widely used in cosmetics, food products, and pharmaceutical formulations, such as tablets and topical products, including wound dressings. It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful. A study in five healthy male volunteers fed a daily intake of 175 mg/kg body-weight of sodium alginate for 7 days, followed by a daily intake of 200 mg/kg body-weight of sodium alginate for a further 16 days, showed no significant adverse effects.

The WHO has not specified an acceptable daily intake for alginic acid and alginate salts as the levels used in food do not represent a hazard to health.

Inhalation of alginate dust may be irritant and has been associated with industrial-related asthma in workers involved in alginate production. However, it appears that the cases of asthma were linked to exposure to seaweed dust rather than pure alginate dust.

LD₅₀ (cat, IP): 0.25 g/kg

LD₅₀ (mouse, IV): 0.2 g/kg

LD₅₀ (rabbit, IV): 0.1 g/kg

LD₅₀ (rat, IV): 1 g/kg

LD₅₀ (rat, oral): >5 g/kg

3.2.2.15. Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium alginate may be irritant to the eyes or respiratory system if inhaled as dust. Eye protection, gloves, and a dust respirator are recommended. Sodium alginate should be handled in a well-ventilated environment.

3.2.2.16. Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Guide (oral suspensions and tablets). Included in nonparenteral medicines licensed in the UK.

3.2.2.17. Related Substances

Alginic acid; calcium alginate; potassium alginate; propylene glycol alginate.

3.2.2.18. Comments

A number of different grades of sodium alginate, which have different solution viscosities, are commercially available. Many different alginate salts and derivatives are also commercially available including ammonium alginate; calcium alginate; magnesium alginate, and potassium alginate.

To assist in the preparation of dispersions of sodium alginate, the material may be mixed with a dispersing agent such as sucrose, ethanol, glycerol, or propylene glycol. A specification for sodium alginate is contained in the Food Chemicals Codex (FCC).

3.2.3 PECTIN

3.2.3.1 Nonproprietary Names

- USP: Pectin

3.2.3.2 Synonyms

- Citrus pectin; E440; methopectin; methyl pectin; methylpectinate; mexpectin; pectina; pectinic acid.

3.2.3.3 Chemical Name and CAS Registry Number

- Pectin [9000-65-5]

3.2.3.4 Empirical Formula and Molecular Weight
Pectin is a high-molecular-weight, carbohydrate-like plant constituent consisting primarily of chains of galacturonic acid units linked as 1,4-a-glucosides, with a molecular weight of 30 000–100 000.

3.2.3.5 Structural Formula

![Structural Formula](image)

Pectin is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in an a-(1–4) chain. The acid groups along the chain are largely esterified with methoxy groups in the natural product. The hydroxyl groups may also be acetylated. Pectin gelation characteristics can be divided into two types: high-methoxy and low-methoxy gelation, and sometimes the low-methoxy pectins may contain amine groups. Gelation of high-methoxy pectin usually occurs at pH <3.5. Low-methoxy pectin is gelled with calcium ions and is not dependent on the presence of acid or high solids content. Amidation may interfere with gelation, causing the process to be delayed. However, gels from amidated pectins have the ability to re-heal after shearing.(1)

The USP 28 describes pectin as a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids.

3.2.3.6 Functional Categories

Adsorbent, emulsifying agent, gelling agent, thickening agent, stabilizing agent.

3.2.3.7 Applications in Pharmaceutical Formulation or Technology

- Pectin has been used as an adsorbent and bulk-forming agent, and is present in multi-ingredient preparations for the management of diarrhea, constipation, and obesity
- It has also been used as an emulsion stabilizer.
Experimentally, pectin has been used in gel formulations for the oral sustained delivery of ambroxol.

Pectin gel beads have been shown to be an effective medium for controlling the release of a drug within the gastrointestinal (GI) tract.

It has also been used in a colon-biodegradable pectin matrix with a pH-sensitive polymeric coating, which retards the onset of drug release, overcoming the problems of pectin solubility in the upper GI tract.\(^{6-9}\)

Amidated pectin matrix patches have been investigated for the transdermal delivery of chloroquine\(^{10}\) and gelling pectin formulations for the oral sustained delivery of paracetamol have been investigated in situ.

Pectin-based matrices with varying degrees of esterification have been evaluated as oral controlled-release tablets. Low-methoxy pectins were shown to have a release rate more sensitive to the calcium content of the formulation.

Pectins have been used as a component in the preparation of mixed polymer microsphere systems with the intention of producing controlled drug release.

### 3.2.3.8 Description

Pectin occurs as a coarse or fine, yellowish-white, odorless powder that has a mucilaginous taste.

### 3.2.3.9 Pharmacopeial Specifications

**Table 3.4: Pharmacopeial specifications for pectin.**

<table>
<thead>
<tr>
<th>Test</th>
<th>USP 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>(\leq 10.0%)</td>
</tr>
<tr>
<td>Arsenic</td>
<td>(\leq 3) ppm</td>
</tr>
<tr>
<td>Lead</td>
<td>(\leq 5) mg/g</td>
</tr>
<tr>
<td>Sugars and organic acids</td>
<td>+</td>
</tr>
<tr>
<td>Microbial limits</td>
<td>+</td>
</tr>
<tr>
<td>Assay</td>
<td></td>
</tr>
<tr>
<td>Methoxy groups</td>
<td>(\leq 6.7%)</td>
</tr>
<tr>
<td>Galacturonic acid</td>
<td>(\leq 74.0%)</td>
</tr>
</tbody>
</table>
3.2.3.10 Typical Properties

- Acidity/alkalinity: pH = 6.0–7.2
- Solubility: soluble in water; insoluble in ethanol (95%) and other organic solvents.

3.2.3.11 Stability and Storage Conditions

Pectin is a nonreactive and stable material; it should be stored in a cool, dry place.

3.2.3.12 Method of Manufacture

Pectin is obtained from the diluted acid extract from the inner portion of the rind of citrus fruits or from apple pomace.

3.2.3.13 Safety

Pectin is used in oral pharmaceutical formulations and food products and is generally regarded as an essentially nontoxic and nonirritant material. Low toxicity by the subcutaneous route has been reported.

LD$_{50}$ (mouse, SC): 6.4 g/kg

3.2.3.14 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When pectin is heated to decomposition, acrid smoke and irritating fumes are emitted.

3.2.3.15 Regulatory Statuses

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental paste; oral powders; topical pastes). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

3.2.4 HYDROXY PROPYL METHYL CELLULOSE (HPMC)

3.2.4.1 Nonproprietary Names

BP: Hypromellose
JP: Hydroxypropylmethylcellulose
PhEur: Hypromellosum
USP: Hypromellose

3.2.4.2 Chemical Name and CAS Registry Number
Cellulose Hydroxypropyl methyl ether [9004-65-3]

3.2.4.3 Empirical Formula and Molecular Weight
The PhEur 2005 describes Hypromellose as a partly O-methylated and O-(2 hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be illustrious by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., Hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH (OH) CH3), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups conforming to the limits for the types of Hypromellose. Molecular weight is approximately 10 000–1 500 000.

3.2.4.4 Synonyms: METHOCEL, Hypromellose.
According to the European pharmacopoeia hydroxypropyl methyl cellulose (hypromellose) is partly O-methylated and O-(2-hydroxypropylated) cellulose. The structural formula is as follows:

3.2.4.5 Structure of Hydroxy Propyl Methyl Cellulose:

\[
\begin{align*}
R: & \quad -\text{H}, \ -\text{CH}_3 \text{ or } -\text{CH}_2\text{CH} (\text{CH}_3) \text{ OH.}
\end{align*}
\]
Hypromellose is an inert, odorless, tasteless, nonionic, hydrophilic polymer. It is prepared from purified cellulose, which is obtained from cotton linters or wood pulp. The cellulose is treated with an alkali like sodium hydroxide to produce swollen alkali cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide due to which it gets converted to methylhydroxypropyl ether of cellulose. The final product is then purified and ground to powder or granules.

**Functional Category**

Coating agent, Film-former, Rate-controlling polymer for sustained release, Stabilizing agent, Suspending agent, Tablet binder, Viscosity-increasing agent.

**3.2.4.6 Applications**

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, Hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

Examples of film-coating materials that are commercially available include AcryCoat C, Spectral, and Pharmacoat.

Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and
particles from coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

3.2.4.7 Physicochemical properties of hypromellose:
Physicochemical properties of hypromellose like solubility, glass transition temperature, and viscosity depend upon the ratio of methoxy and hydroxy propoxy groups and the molecular weight. The molecular weight of hypromellose ranges from 10000 to 1500000. Various grades of hypromellose are available which differ in viscosity and extent of substitution. The different grades may be identified by a number indicative of apparent viscosity, in mPa.s, of a 2% aqueous solution at 20OC. The USP identifies hypromellose polymers into four different types according to their relative methoxy-group and hydroxypropoxy-group contents. These are HPMC 1828, HPMC 2208, HPMC 2906, and HPMC 2910. The first two numbers represent the percentage of methoxy groups, the last two numbers the percentage of hydroxypropoxy groups, determined after drying at 105oC for 2hr.

3.2.4.8 Description & Typical Properties:
Hypromellose is a white, yellowish white or grayish white powder or granules, practically odorless, hygroscopic and tasteless, fibrous or granular powder.

- **Acidity/alkalinity**: pH = 5.5–8.0 for a 1% w/w aqueous solution.
- **Ash**: 1.5–3.0%, depending upon the grade and viscosity.
- **Auto ignition temperature**: 360°C
- **Density (bulk)**: 0.341 g/cm³
- **Density (tapped)**: 0.557 g/cm³
- **Density (true)**: 1.326 g/cm³
- **Melting point**: browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.

- **Moisture content**: hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.
**Solubility:** soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

**Specific gravity:** 1.26

**Viscosity (dynamic):** a wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions.

When a water-miscible organic solvent such as ethanol (95%), glycol, or mixtures of ethanol and dichloromethane are used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5–8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the required volume.

### 3.2.4.9 Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material.

### 3.2.4.10 Incompatibility:

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates,
3.2.4.11 Nomenclature:

METHOCEL is a trademark of the Dow Chemical Company for various cellulose ether products. An initial letter indicates the type of cellulose ether, its chemistry, .A. denotes methylcellulose products, .E., .F., and .K. identify different hypromellose products. METHOCEL E and METHOCEL K are most widely used for CR formulations. The number that follows the chemistry designation letter represents the viscosity of that product in millipascal-seconds (mPa.s), measured at 2% concentration in water at 20%. In designation of viscosity, the letter .C. is used to denote a multiplier of 100, and letter .M. is used to denote a multiplier of 1000. Several different suffixes are also used to identify special types of products. .P. is used to denote METHOCEL Premium products, .LV. identifies low-viscosity products, .CR. refers to a controlled release grade, and .LH. denotes products, which have low hydroxypropyl content. EP and JP refer to products that meet European and Japanese Pharmacopoeia requirements respectively.
3.3 METHODOLOGY

3.3.1 Preformulation studies
1. Characterization and analysis of drug
   - *IR Spectroscopy*
   - *UV-Visible Spectroscopy:
2. Calibration curve
3. Solubility profile
4. Melting point determination.
5. Partition coefficient.
6. pH determination
7. Dissociation constant
8. Loss on drying
10. Drug – polymer interaction

3.3.2 Optimization of beads by taking different parameters
- Optimization of beads on the basis of polymer concentration.
- Optimization of beads on the basis of height of syringe dropping the beads.
- Optimization of beads on the basis of different needle size used.
- Optimization of beads on the basis of different rate of dropping.
- Optimization of beads on the basis of speed of magnetic stirrer.
- Optimization of beads on the basis of different concentration of curing agent.
- Optimization of beads on the basis of different curing time.

3.3.3 Preparation and evaluation of beads having different concentration of oil & different ratios of different polymer.

3.3.4 Evaluation of floating Beads.
- Size and morphology of beads,
- Micromeritic study,
- Floating lag time and floating duration,
3.3.5 Preparation and evaluation of beads having different oils of different concentration.

3.3.6 Preparation and evaluation of beads having different curing agents.

3.3.7 Preparation and comparing the dissolution profile of capsule filled with pure drug and floating beads.

3.3.1. PREFORMULATION

DEFINITION:
Prior to the development of the dosage forms, it is vital that certain vital physical and chemical properties of the drug molecule and other consequential properties of the drug powder are determined. The information dictates many of the subsequent events and approaches in formulation development. The first learning phase is known as preformulation.

TIMING AND GOALS OF PREFORMULATION:
The goals of preformulation are, therefore,

- To establish the essential physicochemical parameters of a new drug substance
- To determine its kinetic rate profile
- To establish its physical features.
- To establish its compatibility with common excipients.

Different methods which are included in the preformulation studies of the drug powder are:

- Drug entrapment efficiency,
- Swelling studies
- Drug content.
- Dissolution profile.
- Drug release kinetic studies of the optimized formulation
- Stability studies
3.3.1.1. Characterization and analysis of drug

Fourier Transform-Infrared Spectroscopic analysis (FT-IR)

Drug polymer interactions were studied by FT-IR spectroscopy. One to 2mg of Famotidine and drug laden beads samples were weighed and mixed properly with potassium bromide to a uniform mixture. By applying pressure, a small quantity of the powder was compressed into a thin semitransparent pellet. Taking air as the reference, the IR-spectrum of the pellet from 450-4000 cm⁻¹ was recorded and compared to study any interference.

UV-Visible Spectroscopy:

The first step in preformulation is to establish a simple analytical method. Most drugs absorb light in the ultraviolet wavelengths (190-390 nm) as they are generally aromatic and contain double bonds. The acidic or basic nature of the molecule can be predicted from functional groups. Using the UV spectrum of the drug, it is possible to choose an analytical wavelength (often λ_max) suitable to quantify the amount of drug in a particular solution. Excitation of the molecule in the solution causes a loss in light and energy, and the net change from the intensity of the incident light (I₀) and the transmitted light (I) can be measured. The amount of the light absorbed by a solution of the drug is proportional to the concentration (C) and the path length of the solution (l) through which the light has passed. Beer- Lambert law equation is-

\[
\text{Absorbance (A) = } \log_{10} \left( \frac{I_0}{I} \right) = eCl
\]

Where e is the molar extinction coefficient.

UV Absorption spectrum of Famotidine in Phosphate buffer⁹⁹:

Preparation of Phosphate buffer

Adjust 250 ml of 0.02 M phosphoric acid with sodium hydroxide solution (1 in 10) to a pH of 2.5, dilute with water to 500 ml, and mix.

Preparation of x M Phosphoric acid

98x g of Phosphoric acid was added in q.s. 1000 ml of distilled water.
25 μg/ml solution of Famotidine was prepared in phosphate buffer and was scanned in the wavelength range of 200-400 nm using Shimadzu UV-Visible spectrophotometer (UV-1700) for the determination of the wavelength of the maximum absorption ($\lambda_{\text{max}}$) which is found to be 269.0 nm.

**UV Absorption spectrum of Famotidine in 0.1 N Hydrochloric acid**

**Preparation of x N Hydrochloric acid**

85x ml of Hydrochloric acid was added in q.s. 1000 ml of distilled water.

100 μg/ml solution of Famotidine was prepared in 0.1 N Hydrochloric acid and was scanned in the wavelength range of 200-400 nm using Shimadzu UV-Visible spectrophotometer (UV-1700) for the determination of the wavelength of the maximum absorption ($\lambda_{\text{max}}$) which is found to be 265.0 nm.

**3.3.1.2 Calibration curve of Famotidine in**

0.1N Hydrochloric acid (at $\lambda_{\text{max}}$-265nm)

The stock solutions of Famotidine (100μg/ml) were prepared individually in 0.1 N Hydrochloric acid. The stock solutions were further diluted to make the solutions of the concentration of 1 μg/ml to 25 μg/ml in 0.1 N HCl. The absorbances were determined using Shimadzu UV-Visible spectrophotometer (UV-1700) at $\lambda_{\text{max}}$ 265.0 for 0.1 N Hydrochloric acid.

The solutions were kept for 24 hrs. After which the absorbance were again determined and the calibration curves were plotted (Concentration Vs Absorbance).

**3.3.1.3 Solubility profile:**

The solubility of the agent in the particular solvent indicates the maximum concentration to which a solution may be prepared with that agent and that solvent.

**Preparation of Hydrochloric acid buffer**

50 ml of 0.2 M Potassium Chloride was placed in 200ml volumetric flask, specified volume of 0.2 N Hydrochloric acid was added and final volume was made up with water.

pH (1.2) - 85 ml of 0.2 N HCl
Preparation of phthalate buffer
50 ml of 0.2 M potassium hydrogen phthalate was placed in 200ml volumetric flask, specified volume of 0.2 M sodium hydroxide was added to it and final volume was made up with water.

pH (4.4) - 6.6 ml of 0.2 M NaOH

Preparation of Phosphate buffer
50 ml of 0.2 M potassium dihydrogen phosphate was added in 200 ml volumetric flask, specified volume of 0.2 M sodium hydroxide was added to it and final volume was made up with water.

pH (6.8) - 22.4 ml of 0.2 M NaOH
pH (7.4) - 39.1 ml of 0.2 M NaOH

Preparation of 0.2 M potassium Chloride
14.911 g of Potassium chloride was dissolved in sufficient water and volume was made up to 1000 ml.

Preparation of xM Potassium hydrogen phthalate
204.23x g of Potassium hydrogen phthalate was dissolved in sufficient water and volume was made up to 1000 ml.

Preparation of xM Potassium dihydrogen phosphate
136.09x g of Potassium dihydrogen phosphate was dissolved in sufficient water and volume was made up to 1000 ml.

The solubility of famotidine in different buffer pH were determined by dissolving an excess amount of the drug in 10 ml of various solvents in 10 ml volumetric flask to prepare the saturated solution which was then continuously shaken for 24 hours by using Wrist Action Shaking Machine. The solutions were then filtered, diluted further with the same solvents and the absorbances were determined by Shimadzu UV-Visible spectrophotometer (UV-1700).
3.3.1.4 Melting Point Determination

A characteristic of a pure substance is a defined melting point or melting range. If not pure, the material will display a change in melting point. This phenomenon is commonly used to conclude the purity of a drug substance and in some case the compatibility of various substances before inclusion in the same dosage form.

Melting point of drug was determined by DSC (Mettler Toledo; DSC), Differential scanning colorimetry measures the heat gain or loss resulting from chemical and physical changes within a sample as a function of temperature.

3.3.1.5 Partition Coefficient

A drug molecule must first cross a biological membrane of protein and lipid to produce a pharmacological response, which performs as a lipophilic barrier to most of the drugs. The penetrating ability of the drug molecule is based on its preference for lipids (lipophilic) versus its preference for an aqueous phase (hydrophilic). A drug’s partition coefficient is a degree of its spreading in a lipophilic-hydrophilic phase system and indicates its capacity to penetrate biologic multiphase system.

Stock solution (100mg/50ml) of Famotidine in distilled water was prepared. 50 ml of this solution was transferred to separating funnel and 50ml of octanol was added to it after which it was shaken continuously using Wrist Action Shaking Machine for 70 hrs. It was then kept whole night for separation.

After overnight the two solvents were separated and diluted further with the respective solvents and absorbance was recorded using Shimadzu UV-Visible spectrophotometer (UV-1700).

Partition coefficient was determined using formula

\[ K = \frac{C_1}{C_2} \]

Where \( C_1 \) is the concentration of solute in the octanol and \( C_2 \) is the concentration of solute in the water. \( K \) is the partition coefficient of the drug between water and octanol.

3.3.1.6 pH Determination
pH of the 1% aqueous solution of the drug when determined using Digital pH meter 802 (systronics)

3.3.1.7 pKa/ Dissociation Constant Determination
pKa determination is significant because the degree of ionization has an significant effect on the formulation and pharmacokinetic parameters of the drug. In preparation, often the vehicle is adjusted to a certain pH in order to attain a certain level of ionization of the drug for solubility and stability purpose. In the pharmacokinetic area, the degree of ionization of a drug is a vital affecter of its absorption, distribution and elimination.

3.3.1.8 Loss on drying
Loss on drying was determined by keeping drug powder of known weight at 80°C and at pressure between 1 and 5 mm of mercury for 5 hrs.

Formula used:

\[
\text{Loss on drying} = \frac{\text{Initial weight of drug - final weight of drug}}{\text{Initial weight of drug}} \times 100
\]

3.3.1.9 Micromeritics
Particle size determination:
Particle size distribution was determined by using Photomicroscope RXL-5T (Carton).

Bulk density, tapped density and type of flow:
Bulk density is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantities of granules were carefully poured in to graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume.
The cylinder was then tapped 100 times on hard surface from height of 1 inch at 2 second interval to calculate tapped density.
It was expressed in g/ml and given by

\[
\rho_b = \frac{W}{V_b}
\]
Where, \( \rho_b \) = Bulk Density (untapped density), \( W \) = Weight of Powder, \( V_b \) = Bulk volume of powder.

**Carr’s Consolidation Index:**

Carr’s Index explains flow properties of the granules. It was expressed in percentage and given by

\[
\text{Consolidation Index} = \frac{Tapped\ \text{Density} - Untapped\ \text{Density}}{Tapped\ \text{Density}} \times 100
\]

**Hausner’s ratio:**

Hausner’s ratio = Tapped density / bulk density

**Angle of Repose**

It may be defined as the extreme angle possible amongst the surface of the pile of the powder and horizontal plane. Fixed funnel method was used. A funnel was stationary with its tip at a given height \( h \) above a flat horizontal surface to which a graph paper was located. The granules were sensibly decanted through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using the formula

\[
\tan \theta = \frac{h}{r}
\]

Where,

\( \theta \) = Angle of Repose
\( h \) = Height of Pile
\( r \) = Radius of the base of the pile

**3.3.1.10 Drug Excipients Compatibility Studies**

Drug excipient interaction was determined using following methods:

**Thin Layer Chromatography (TLC)**

Drug and excipients were mixed in ratio of 1:1 and kept under different conditions for 30 days and then analyzed by TLC for any possible interaction at room temperature and at 40°C / 75%RH
Table 3.5 Conditions for thin layer chromatography\textsuperscript{99}

<table>
<thead>
<tr>
<th>Stationary phase:</th>
<th>Precoated silica gel F 254 plate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of spot:</td>
<td>UV Detector (254 nm)</td>
</tr>
<tr>
<td>Preparation of drug sample:</td>
<td>200µg/ml drug solution in methanol and glacial acetic acid.</td>
</tr>
</tbody>
</table>

Rf value was determined using formula:

\[
R_f = \frac{\text{Distance traveled by solute front}}{\text{Distance traveled by solvent front}}
\]

FT-IR spectroscopic studies

For studying drug-excipient interaction, IR spectroscopy was used. The compatibility studies between polymer and drug were also accomplished by FTIR spectral analysis. Drug polymer relations were studied by FT-IR spectroscopy. One to 2mg of Famotidine and drug laden beads samples were weighed and mixed properly with potassium bromide to a uniform mixture. By applying pressure a small quantity of the powder was compressed into a thin semitransparent pellet. Taking air as the reference the IR- spectrum of the pellet from 450- 4000cm\(^{-1}\) was recorded and compared to study any interference.

Visual observation

Drug and excipients were mixed in ratio of 1:1 and kept under the different conditions for 30 days and analyze by visual observation

3.3.2. OPTIMIZATION OF BEADS:

3.3.2.1. Optimization of beads on the basis of polymer concentration (P\(_1\) – P\(_5\))

For optimizing the concentration of polymer, Sodium alginate gel beads were prepared by emulsion gelation method. Different concentrations of sodium alginate
were dissolved in water with gentle agitation to make 25 ml mixture at room temperature. The polymer mixture was extruded, using a syringe into, 100 ml of calcium chloride solution with gentle agitation at room temperature. The gel beads formed were allowed to stand in the solution and washed with distilled water. The beads were dried at room temperature for 6 hrs. Optimization of beads was performed on the basis of formation of beads, its shape and intactness.

3.3.2.2 Optimization of beads on the basis of height of syringe dropping the beads from the surface of curing agent. (P₆-P₁₀)

For optimizing the height of syringe sodium alginate gel beads were prepared in water with gentle agitation to make 25 ml mixture. The emulsion was extruded, using a syringe into, 100 ml of calcium chloride solution with gentle agitation at room temperature. The nozzle of syringe was maintained at different heights from the level of calcium chloride solution. The gel beads formed were allowed to stand in the solution and washed with distilled water. The beads were dried at room temperature for 6 hrs. Prepared beads were optimized on the basis of intactness, shape, size and formation of beads etc.

3.3.2.3 Optimization of beads on the basis of different size of needle used. (P₁₁-P₁₅)

For optimizing the different size of needle the prepared emulsion was extruded using the syringe having different gauge size dropped into 100 ml of calcium chloride solution in a beaker. The gel beads formed were allowed to stand in the solution and washed with distilled water. The beads were dried at room temperature for 6 hrs. Prepared beads were optimized on the basis of intactness, shape, size and formation of beads.

3.3.2.4 Optimization of beads on the basis of different rate of dropping. (P₁₆-P₁₉)
For optimizing the beads on the basis of different rate of dropping the prepared emulsion was extruded using the syringe having different rate of dropping (ml/sec) and prepared beads were optimized.

3.3.2.5 Optimization of beads on the basis of speed of magnetic stirrer. (P20-P24)

For optimizing the beads on the basis of different speed of magnetic stirrer the prepared solution was extruded at constant speed and at constant height from a syringe of fixed gauze size into, 100 ml of calcium chloride solution with different speed of stirring at room temperature. The gel beads formed were allowed to stand in the solution and washed with distilled water. The beads were dried at room temperature for 6 hrs. Prepared beads were optimized on the basis of intactness, shape, size and formation of beads etc.

3.3.2.6 Optimization of beads on the basis of different concentration of curing agent. (P25-P29)

For optimization of beads on the basis of different concentration of curing agent, Sodium alginate was dissolved in water with gentle agitation to make 25 ml mixture at room temperature. The emulsion was extruded, using a syringe of fixed gauze into, 100 ml of different concentrations of calcium chloride solution, keeping all the other parameters constant. The gel beads formed were allowed to stand in the solution and washed with distilled water. The beads were dried at room temperature for 6 hrs. Prepared beads were further optimized on the basis of intactness, shape, size and formation of beads.

3.3.2.7 Optimization of beads on the basis of different curing time. (P30-P34)

For optimization of beads on the basis of different curing time the prepared beads were allowed to stand in the solution for different time intervals and then separated and washed with distilled water. The beads were dried at room temperature for 6 hrs. Prepared beads were optimized on the basis of intactness, shape, size and formation of beads.
3.3.3. FABRICATION OF GEL BEADS WITH OIL AND DIFFERENT BLENDS OF POLYMERS.

Gel beads were prepared by emulsion gelation method 3% of different blends of polymer (sodium alginate, Pectin, HPMC), along with 200mg of drug were dissolved in water with gentle agitation to make 25 ml mixture. The mixture was stirred on magnetic stirrer for 1 hr. and emulsified with different concentrations of mineral oil at room temperature. The drug loaded emulsion was extruded, using a syringe of 22G into, 100ml of calcium chloride solution maintained on gentle agitation at room temperature. The nozzle of syringe was maintained at a height of 5 cm from the level of calcium chloride solution in beaker. The gel beads formed were allowed to stand in the solution for 30 min before being separated and washed with distilled water. The beads were dried at room temperature for 6 hrs. Prepared beads were stored in desiccator until use.

Table 3.6 Formulations with different blends of polymers and oil concentration.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Oil Concentration</th>
<th>Alginate: pectin</th>
<th>Alginate: HPMC</th>
<th>Pectin: HPMC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>P35</td>
<td>P35</td>
<td>P36</td>
<td>P37</td>
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<td>P38</td>
<td>P38</td>
<td>P39</td>
<td>P40</td>
<td>2:1</td>
</tr>
<tr>
<td>P41</td>
<td>P41</td>
<td>P42</td>
<td>P43</td>
<td>1:1</td>
</tr>
<tr>
<td>P44</td>
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<td>P46</td>
<td>1:2</td>
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<td>P50</td>
<td>P51</td>
<td>P52</td>
<td>2:1</td>
</tr>
<tr>
<td>P53</td>
<td>P53</td>
<td>P54</td>
<td>P55</td>
<td>1:1</td>
</tr>
<tr>
<td>P56</td>
<td>P56</td>
<td>P57</td>
<td>P58</td>
<td>1:2</td>
</tr>
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<td>P59</td>
<td>P60</td>
<td>P61</td>
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<td>P62</td>
<td>P63</td>
<td>P64</td>
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<td>P65</td>
<td>P66</td>
<td>P67</td>
<td>1:2</td>
</tr>
<tr>
<td>P68</td>
<td>P68</td>
<td>P69</td>
<td>P70</td>
<td>2:1</td>
</tr>
</tbody>
</table>
3.3.4. PHYSICO-CHEMICAL EVALUATION OF SELECTED MATRICES

3.3.4.1 Study of size and morphology of floating beads:

The diameter of beads was determined by screw gauge. For this purpose, 20 dried beads were randomly selected from each batch and the mean diameter was determined by screw gauge. The least count of screw gauge was 0.005 mm. Color and shape of dried beads of each batch was noted. SEM studies were also performed for analyzing the surface morphology, internal structure and size analysis of dried beads.

6.3.4.2 Micromeritic studies:

**Determination of True Density**

Specific gravity of gel beads was determined by liquid displacement method. Absolute alcohol (95% v/v) was used as displacement media.

**Determination of Bulk Density**

The sample of beads were weighed (M) about 25gms and filled in a 100 ml graduated cylinder, the powder leveled, and the unsettled volume, $V_o$ noted. The bulk density was calculated in g/cm$^3$ by the formula,

$$\text{Bulk Density} = \frac{M}{V_o}$$

Where M is for mass taken and $V_o$ is volume noted.

**Determination of Tapped Density**

The sample of beads weighed about 25 gm and filled in a 100ml graduated cylinder. The mechanical tapping of cylinder carried out using tap density tester at a nominal rate of 250 drops of hour for 500 times initially. The tapped volume $V_o$ noted. Tapping proceed further for an additional tapping 750 times and tapped volume $V_b$ is measured. The difference between two tapping volume was less than 2% so $V_b$ is
considered as a tapped volume $V_f$. The tapped density in g/cm$^3$ is calculated using
following formula.

\[
\text{Tapped Density} = \frac{M}{V_f} \text{ where M is mass taken and $V_f$ is tapped volume.}
\]

**Determination of Carr’s Index and Hausner ratio**
The tapped density and bulk density was measured and carr’s index and Hausner ratio
were calculated using following formula.

\[
\text{Carr’s Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped density}} \times 100
\]

\[
\text{Hausner ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}
\]

**Angle of Repose**
The flow characteristics were measured by angle of repose. A glass funnel was held in
place with a clamp on a ring support over a glass plate and gap between end of funnel
and paper adjusted around 6.4mm. Approximately 100gms of beads were transferred
into the funnel keeping the orifice of the funnel blocked by the thumb. As the thumb
was removed beads were emptied from the funnel, the angle of the heap to the
horizontal plane is measured with the protector.

\[
\text{Angle of repose (θ) = Tan}^{-1}\left(\frac{h}{r}\right)
\]

**3.3.4.3 Floating lag time and floating duration of floating beads:**

**Floating lag time:** is the time taken for all the beads to come over the surface of
solution from the time of dropping.

**Floating time:** is the total time duration the beads remain afloat over the surface.

The floating bead samples (n=10) were placed in a beaker filled with 50 ml of 0.1 N
HCl solution. Temperature was maintained at 37°C. The floating time of beads was
observed for 24 hrs. The preparation was considered to have buoyancy in the test
solution only when all the beads floated in it.

**3.3.4.4 Determination of % drug loading and entrapment efficiency of floating
beads:**

50 mg of beads were weighed and crushed in a pastel mortar and the crushed material
was dissolved in 25 ml of 0.1N HCl solution. Volume of this solution was made up to
50 ml with washings of mortar. This preparation was shaken with the help of wrist
action shaking machine for 5 hrs and then kept for 24 hrs. Then it was clarified. The
filtrate was assayed spectrophotometrically at 265 nm. The drug content and the encapsulation efficiency were determined using following equation.

\[
\% \text{ Drug loading} = \frac{\text{Weight of drug present in bead in gms}}{\text{Weight of quantity of bead in gms}} \times 100
\]

Entrapment Efficiency = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100

3.3.4.5 Swelling studies of floating beads:

Beads were studied for swelling characteristics. Sample from drug-loaded beads of known weight (10mg) were taken, weighed and placed in wire basket of USP dissolution apparatus II. The basket containing beads was put in a beaker containing 100 ml of 0.1 N HCl (pH 1.2) maintained at 37\(^0\)C. The beads were periodically removed at predetermined intervals and weighed. Then the %Swelling index was calculated as per the following formula:

\[
\% \text{Swelling index} = \frac{\text{final weight of beads} - \text{initial weight of beads}}{\text{initial weight of beads}} \times 100
\]

3.3.4.6 Drug release studies of floating beads:

The dissolution of famotidine floating beads was studied using USP Type II dissolution apparatus containing 900 ml of 0.1 N HCl (pH 1.2) maintained at 37\(\pm 0.5\)\(^0\)C and stirred at 50 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. These samples were analyzed for the drug present in them with help of UV spectrophotometer.

3.3.4.7 Drug release kinetic models for dissolution study:

**Zero Order Kinetics:** A zero-order release would be predicted by the following equation.

\[
A_t = A_0 - K_0 t \quad \ldots 1
\]

Where:

- \(A_t\) = Drug release at time \('t'\)
- \(A_0\) = Initial drug concentration
- \(K_0\) = Zero-order rate constant (hr\(^{-1}\)).
When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to $K_0$.

**First Order Kinetics:** A first-order release would be predicted by the following equation

$$\log C = \log C_0 - \frac{Kt}{2.303}$$

Where:
- $C =$ Amount of drug remained at time ‘t’
- $C_0 =$ Initial amount of drug
- $K =$ First-order rate constant (hr$^{-1}$).

When the data is plotted between log cumulative percent drug remaining versus time yields a straight line, indicating that the release follows First-order kinetics. The constant ‘$K$’ can be obtained by multiplying 2.303 with slope values.

**Higuchi’s Model:** Drug released from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation.

$$Q = \frac{1}{\tau \times D} \left(2A - \varepsilon Cs\right)Cst^{1/2}$$

Where,
- $Q =$ Amount of drug released at time ‘t’
- $D =$ Diffusion coefficient of the drug in the matrix
- $A =$ Total amount of drug in unit volume of matrix
- $Cs =$ Solubility of the drug in the matrix
- $\varepsilon =$ Porosity of the matrix
- $\tau =$ Tortuosity
- $t =$ Time (hrs) at which ‘$q$’ amount of drug is released.

Equation-3 may be simplified if one assumes that $D$, $Cs$ and $A$ are constant. Then equation-3 becomes:

$$Q = Kt^{1/2}$$

When the data is plotted according to equation-4 i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to ‘$K$’ (Higuchi, 1963).
Korsmeyer model: The release rates from controlled release polymeric matrices can be described by the equation (5) proposed by Korsmeyer et al.46.

\[ Q = K_1 t^n \] …5

Where,

*Q* is the percentage of drug released at time ‘t’,

*K*₁ is a kinetic constant incorporating structural and geometric characteristic of the tablets and *n* is the diffusional exponent indicative of the release mechanism.

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to ‘*n*’ and the ‘*K*’ can be obtained from Y-intercept.

The value of ‘*n*’ for a cylinder is <0.45 for Fickian release, >0.45 and <0.89 for non-Fickian release, 0.89 for the case II release and > 8.9 for super case II type release.

The succeeding plots were made: cumulative % drug release vs. time (zero order kinetic models); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative percent drug release vs. square root of time (higuchi model); and log cumulative % drug release vs. log time (korsmeyer model).

### 3.3.4.8 Mechanism of Drug Release:

Simple relationship is derived by Korsmeyer et al (1983) which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60 % drug release data was fitted in Korsmeyer- Peppas model:

\[ M_t / M_\infty = K t^n \]

Where, *M*_t/*M*_\infty is fraction of drug released at time *t*, *K* is the rate constant and *n* is the release exponent. The *n* value is used to characterize different release mechanisms as given in table for cylindrical shape formulations:

| Table 3.7 Characterization of different release mechanisms | SURESH GYAN VIHAR UNIVERSITY, MAHAL, JAGATPURA, JAIPUR (RAJASTHAN) | 97 |
3.3.4.9 Accelerated Stability Studies of Optimized Batch.

The stability studies for beads were done by keeping the sample beads from optimized batches at room temperature for 60 days. The beads were filled in capsules and these capsules were packed in aluminum foil. These foils were sealed and stored at room temperature (25°C ± 2°C / 45 % RH ± 5 %) and at accelerated temperature (40°C ± 2°C / 75 % RH ± 5 %). Stability study of optimized batch that is F1 is done the samples were put for 60 days. In the end of 15 days and two months the beads were evaluated for different parameters like morphology, floating time and drug release studies. Methods followed to evaluate these parameters were similar as followed previously.

<table>
<thead>
<tr>
<th>Diffusion exponent (n)</th>
<th>Overall solute diffusion mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.45</td>
<td>Fickian diffusion</td>
</tr>
<tr>
<td>0.45&lt;n&lt;0.89</td>
<td>Anomalous (non-Fickian) diffusion</td>
</tr>
<tr>
<td>0.89</td>
<td>Case-II transport</td>
</tr>
<tr>
<td>n&gt; 0.89</td>
<td>Super case- II transport</td>
</tr>
</tbody>
</table>

3.3.5 FLOATING STUDY WITH DIFFERENT OILS OF DIFFERENT DENSITIES:

Floating study with different oils of different densities such as Castor oil (R.D=0.96), Peppermint oil (R.D=0.90), Mineral oil (R.D=0.84), Sunflower oil (R.D=0.94), Soybean oil (R.D=0.92) and Olive oil (R.D=0.91). The effect of selected factors, such as type of oil, percentage of oil, on morphology and floating properties of optimized beads (F1) was investigated. (Table: 8.22)

3.3.6 STUDY THE EFFECT OF DIFFERENT CURING AGENT ON ALGINATE BEADS
In this study the formation of famotidine beads through inotropic gelation method was investigated using several curing agent such as calcium chloride solution (CaCl$_2$), magnesium chloride (MgCl$_2$·2H$_2$O), barium chloride (BaCl$_2$·2H$_2$O), lead nitrate (Pb(NO$_3$)$_2$), SnCl$_2$, MnCl$_2$ and its various selected characteristics were studied such as size, wall strength, swelling ratio, drug encapsulation and drug release kinetic.

3.3.7 EVALUATION OF CAPSULE FILLED WITH FLOATING BEADS AND COMPARISON WITH PURE DRUG

In the present study we have taken the capsule of size 18.3mm capsule no 2 into which famotidine loaded alginate pectin beads were filled (formulation F$_1$) and various evaluation parameters were evaluated such as floating lag time, floating time, dissolution study and comparing it with that of pure drug filled in capsule.

As the required dose of famotidine is approximately 40 mg per day so we have taken 200 mg of beads which contain the required dose of famotidine. This quantity of drug can be easily encapsulated in capsule of size No. 2 having volume of 18.3mm