2. LITERATURE REVIEW

2.1 Literatures reviewed on buccal films/patches

Thimmasetty J et al.,\textsuperscript{72} enhances the bioavailability of carvedilol by preparing buccal patch. An FTIR and UV method shows no significant interaction between polymer and drug. \textit{In-vitro} and \textit{in-vivo} evaluation got satisfactory results. Good IVIVC has been achieved.

Singh S et al.,\textsuperscript{73} prepared Clotrimazole buccoadhesive films by solvent casting method for orla candidiasis. Their objective is to reduce the frequency of administration by keeping the concentration of Clotrimazole above MIC for a prolonged duration and the drug release follows non-Fickian diffusion.

Satishbabu B K et al.,\textsuperscript{74} prepared bilaminated films of Atenolol by casting/ solvent evaporation technique and characterized for mucoadhesive strength, folding endurance, tensile strength, hydration studies, mucoadhesive time, \textit{in-vitro} drug release and skin permeation.

Sahni J et al.,\textsuperscript{75} prepared insulin as buccal delivery prepared by solvent casting technique and tested for \textit{in-vitro} by using surface pH, release of drug, strength by bioadhesion mechanism and studies related to permeation. The formulation prepared by sodium deoxycholate shows best permeation action.

Tae Hee Kim et al.,\textsuperscript{76} prepared novel mucoadhesive polymer blend film by casting method which consisting of Carbopol, poloxamer, and HPMC.
Vishnu M. Patel et al.,\textsuperscript{77} prepared propranolol hydrochloride buccoadhesive patches employing Eudragit L-100 by solvent casting method. Both buccal and drug patches were stable in human saliva.

Doijad R C et al.,\textsuperscript{78} performed the formulation and evaluation of buccoadhesive buccal delivery systems for isosorbide dinitrate. Drug diffusion follows the kinetics of zero order and mechanism of drug release was found to be diffusion process.

Perumal V A et al.,\textsuperscript{79} Prepared and characterize the monolayered multi polymeric films by emulsification method. The films characterized for drug content, thickness, mucoadhesivity and release of drug data were treated to Higuchi’s model.

Joydip Kundu et al.,\textsuperscript{80} prepared transmucosal films and studied for \textit{in-vitro} stability in simulated saliva of goat buccal mucosa.

Wong C F et al.,\textsuperscript{81} prepared metoprolol tartrate controlled release buccal patches of employing Eudragit NE40D and evaluated various parameters.

Xiangrong Zhang et al.,\textsuperscript{82} Formulated and evaluated the clarithromycin buccoadhesive film. This study was concluded that pore former hydroxypropyl methyl cellulose, lactose, PEG and PVP was released at the beginning of the release process, the rate and extent of water uptake was higher in phosphate buffer pH 6.8 than in pH 5.0.

Alanazi F K et al.,\textsuperscript{83} has formulated buccoadhesive films of Ketorolac tromethamine and subjected to physicochemical characteristics,
swelling studies, buccoadhesive strength, drug permeation studies using buccal mucosa of bovine and drug release.


**Ellen Hagesaether et al.**,\(^8\) studied the factors for drug permeability and mucoadhesion of the films prepared by individual and combination of pectin and chitosan film. The parameters are different based on the proportions of polymer used. The drug permeability and mucoadhesion increased with decreasing concentration of pectin in chitosan film.

**Kharenko E A et al.**,\(^8\) had proposed a method for studying the mucoadhesive strength of different polymers used for buccoadhesive dosage forms.

**Noha Adel Nafee et al.**,\(^8\) prepared mucoadhesive patches for delivery of cetyl pyridinium chloride (CPC) which shows increase swelling by the addition of hydrophilic drug.

**Myung-Kwan Chun et al.**,\(^8\) prepared buccal film and characterized for adhesion time, swelling ratio, and dissolution. The increase in absorption, decrease swelling, increase mucoadhesion and rate of dissolution is due to hydrogen bonding between carbopol and polaxamer.
Deshmane S V et al.,$^{90}$ prepared propranolol three layered buccal film includes a drug layer, adhesive layer, and backing layer. This ensures the suitability for the three layered film of drug.

Rajesh Singh Patel et al.,$^{91}$ reported that mucoadhesive buccal patches of Salbutamol sulphate showing good and satisfactory results on physicochemical and mechanical characteristics. The drug release possible upto 7 h and the films were stable at accelerated conditions.

Attama et al.,$^{92}$ prepared hydrochlorothiazide (HCTZ) patches by solvent casting method. The prepared patches were evaluated for its physicochemical parameters, swelling, mucoadhesion, drug content and drug release.

Cynthia Khoo et al.,$^{93}$ prepared hydrophilic polymers using blends of chitosan, polyvinyl alcohol (PVA), polyethylene oxide (PEO) and PVP, and concluded as good candidates for systems in delivery of oral gingival.

Roy S et al.,$^{94}$ concluded mucoadhesive polymers as a good insight and affect of polomer properties for mucoadhesion to study ability of factors on mucoadhesion.

Bajdik J et al.,$^{95}$ studied the factors influencing the changes in the drug film. The parameters important in this aspect are the the temperature and humidity of air and emulsifier crystallization and film thickness difference is due to increase in storage time.

Vamshi Vishnu Y et al.,$^{96}$ prepared patches of carvedilol which are bioadhesive in nature having permeability. Absorption showed good
characteristics and revealed that buccal absorption was good in case of healthy pigs. This showed the 2.29 folds increase in bioavailability of carvedilol when compare with solution given orally.

**Noha A Nafee et al.,**97 prepared miconazole nitrate mucoadhesive patches shows convenient adhesion. The film elasticity, swelling, surface pH is acceptable. The release of patches was sustained and shows a release of 5 hr and enhanced release rate is obtained by the use of PVP. Elastic property is not been affected when patches kept for a period of 6 months and rate enhanced due to the some change in drugs crystal habit.

**Eouani C et al.,**98 aimed to measure the performance of the muco adhesion and mainly to optimize the delivery of the design of a drug with polymeric mucoadhesion.

**Amir H Shojaei et al.,**99 conducted adhesion studies to know about the copolymer composition effect, substrate and adhesive time of contact, and by the use of computer interfaced material system mainly to know the copolymer film performances.

**Kazuyo Takeuchi et al.,**100 developed a new formulation of analgesic activity for a adhesive film and studied about a film of two layers in which active ingredient is Indomethacin (IM) and polymer is carboxy vinyl to get film texture which acts a bonding and nonadhesive layers which contains PEG (polyethylene glycol).

**Seyed Alireza et al.,**101 aimed to examine mucosal adhesive properties of various polymers for the preparation of buccal adhesive
films and there in-vitro evaluation. Solvent casting method was used to prepare the films, and evaluated by its physical appearance and film forming ability, in-vitro mucoadhesive strength and duration of mucoadhesion.

2.2 Literatures reviewed on buccal tablets

Sonia Pandey et al.,\textsuperscript{102} has developed buccoadhesive bilayered tablets of carvedilol and reported desired permeability for buccal tablets that are suitable for bioadhesion by using 5-6% Carbopol 934P, 65-68%HPMC K4M and 30% Lactose.

Nakhat P D et al.,\textsuperscript{103} has developed buccoadhesive bilayered tablets of terbutaline sulphate. They reported that the carbopol 934P alone has maximum strength of bioadhesion and it get decrease with the decrease in carbopol content. Results demonstrated that effective design and stability of buccoadhesive tablets was been made possible with carbopol 934P and methocel K4M in ratio of 1:1.

Vishnu M. Patel et al.,\textsuperscript{104} has formulated mucoadhesive bilayered buccal tablets of propranolol hydrochloride and which shows drug release of maximum without the disintegration in 12 h. Formulation in which good adhesive strength (28.8±0.99g) and permeation of the drug i.e 68.65±3.68% were made optimized.

Soliman Mohammadi Samani et al.,\textsuperscript{105} has formulated and evaluated buccal mucoadhesive controlled release tablets of Prednisolone and results revealed that there is a remarkable decrease in drug release rate with that of increase in ratios of HPMC or
SCMC/CP 934 when performed on different grades and blends of HPMC 500.

**Luana Perioli et al.,**\(^{106}\) have designed and characterized mucoadhesive bilayered tablets of Flurbiprofen and they reported that a sustain action of release in buccal cavity was achieved at 12 hr which showed anti inflammatory activity of 20 mg tablets.

**Asha S. John et al.,**\(^{107}\) mucoadhesive bilayer buccal tablets of Atorvastatin calcium was formulated and the release rate was found to be a non-Fickians release rate and showed a anomalous release.

**Balamurugan et al.,**\(^{108}\) has developed and characterized the mucoadhesive Buccal Tablets of Domperidone. Tablet containing ratio of 1:1 containing chitosan and methocel K4M exhibited the best mucoadhesive performance. The results shown that profile of good drug release optimized formulation follows Hixson Crowel release kinetics.

**Bhanja Satyabrata et al.,**\(^{109}\) has designed for the preparation of mucoadhesive buccal tablets of Repaglinide and studied for evaluation. FTIR studies revealed that no interaction between drug and polymers. The prepared bilayered tablets showed non-fickian release and follows the first order kinetics.

**Prasad B Kadam et al.,**\(^{110}\) has formulated bilayered buccoadhesive tablets of atenolol. *In-vitro* bioadhesive strength studies showed that formulations containing combination of carbopol 934P and hydroxypropyl methylcellulose showed more bioadhesive strength
than formulation containing sodium alginate alone. *In-vitro* dissolution studies revealed that all the formulations exhibited non-fickian release kinetics.

**Vishnu M. Patel et al.,**\(^{111}\) have prepared Mucoadhesive Buccal devices of Propranolol hydrochloride. The drug release mechanism was non fickian between 0.5 and 1.0 for devices using buccal cavities. This current study concludes a way to bypass first pass effect metabolism by using devices of buccal mucoadhesives PRH and its bioavailability is mainly improved.

**Ravikumar et al.,**\(^{112}\) has prepared and evaluated mucoadhesive tablets of Diltiazem hydrochloride. The optimized formulation showed maximum release of 79% in 8h. The results indicates preparation of buccal tablets with desired properties is possible.

**Hirlekar R S et al.,**\(^{113}\) has developed buccal tablets of carvedilol and it was characterized for drug release, mucoadhesive strength and *ex-vivo* permeability. The amount drug in tablet of buccal mucosa of porcine at the end of 5 h was 6.2 mg as compared to 2.51 mg from tablets containing plain drug. They concluded that buccal tablet containing complexes have improvement in bioavailability.

**Shrikant Charde et al.,**\(^{114}\) has formulated the Lercanidipine hydrochloride control release mucoadhesive tablets the results shown designed tablets with physical characteristics and uniformity in content of drug and weight variation. Types of polymers viscosity and
proportion are parameters in which mucoadhesive strength and release are mainly dependable.

Rajesh Khanna et al.,\textsuperscript{115} they developed Clotrimazole (CLT) erodible tablets for buccoadhesive local delivery. Type of polymer and composition of tablet are functions of characteristics in release and adhesion mainly by the \textit{in-vitro}. A positive and linearity is observed in human volunteers of \textit{in-vivo} evaluation when correlated between the adhesion time of \textit{in-vitro} and \textit{in-vivo} releases.

Han-Gon Choi et al.,\textsuperscript{116} has formulated buccoadhesive tablets of omeprazole using bioadhesive polymers and alkali materials. Magnesium oxide is acts as a stabilizer among different ones because of its strong water proofing effect in omeprazole buccal adhesive tablets. Two tablets composed as tablets containing Omeprazole which are attached to the cheeks of human and using human saliva they are stabilized for 4 h period.

Bhupinder Singh et al.,\textsuperscript{117} Atenolol mucoadhesive tablets are formulated by method using direct compression and characterized for strength of bioadhesion and release parameters. A non-fickian kinetic release is exhibited following zero order with that of compressed matrices. An excellent control release and strength of bio adhesion were made possible with this study.

Dominique Duchene et al.,\textsuperscript{118} This review mainly focused administration of tablets for buccal delivery and intestinal
nanoparticles as two kinds of dosage forms and mainly for administration in the colonic region.

**Chowdary K P R et al.,**¹¹⁹ prepared a formulation with two layers one as immediate using Diltiazem and cross carmellose and other layer as diltiazem, SCMC and ethyl cellulose which were almost equal to sustain release formulations which are done theoretically.

**Varshosaz J et al.,**¹²⁰ has developed the nifedipine control release tablets for buccoadhesive delivery using CMC with carbomer.. Therefore a adhesion by the polymeric ratio of CP: CMC was affected significantly in tablets .Drug release in *in-vitro* and *in-vivo* showed a good correlation (r² =0.989).

**Jafar Akbari et al.,**¹²¹ prepared Chlorhexidine buccal adhesive tablets by direct compression and the results demonstrated increase is observed with HPMC along with blend and slow release rates are observed when HPMC is used alone as a polymer for bioadhesion.

**Emami J et al.,**¹²² has developed and evaluated the controlled-release buccoadhesive tablets of Verapamil hydrochloride and they reported that the formulation obtained from CP-SCMC showed bioadhesive strength of maximum followed by CP-HPMC and SCMC-HPMC.

**Deshmuk V N et al.,**¹²³ has prepared anhydrous Theophylline oral controlled release (CR) tablets by direct compression method. The study is mainly to do the optimization for release of drug and bioadhesive strength *in-vitro.*
Amit Gupta et al.,\textsuperscript{124} they developed the Extended release Buccoadhesive buccal tablet for delivery of Nisoldipine using Progressive hydration technology. Results demonstrated that the drug release mechanism depends on the polymers.

Mario Jug et al.,\textsuperscript{125} they investigated the hydroxypropyl β cyclodextrins and piroxicam interactions of solid stated solutions. The 1:1 PX-HPβCD complex were characterized by DSC, FTIR, and X-ray diffraction. Direct compression method used for the preparation of PX controlled release tablets. The high degree of mucoadhesion was achieved with the use of HPMC and Carbopol 934.

Owens T S et al.,\textsuperscript{126} they worked to prepare sodium fluoride matrix tablets. Results indicated bioadhesive and release profile for extended time are done mainly by design of bioadhesive matrix fluoride tablets mixtures.

2.3 Literature reviewed on mucoadhesive hydrogels

Chein-chi Lin et al.,\textsuperscript{127} have given in a review that polymeric materials like hydrogels absorbs water and mainly not soluble in solutions aqueous in nature due to crosslinking of physical or chemical chains. Classification, network structure, release mechanisms, emerging systems and remaining challenges have discussed.

Alaa Eldeen B. Yassin et al.,\textsuperscript{128} designed a Verapamil as system for extend release by incorporating chitosan beads which are formed by using tripolyphosphate solution at constant rate and glutaraldehyde is
used to cross link. For above formulated beads different evaluation parameters and *in-vitro* release studies were performed.

**Harding D R K et al.,**<sup>129</sup> prepared pH hydrogel beads which are responsible in as new biodegradable substances by ionotropic gelation method and control release study was been made in case of drugs with proteins of small intestine mainly depend on the chitosan which is chemically modified and sodium alginate made characterized as hydrogels beads were being evaluated and by performing the release rate studies.

**Sanjay K. Jain et al.,**<sup>130</sup> have done research work on colonic systems using hydrogel beads and developed multiparticulate system of hydrogel beads of chitosan for enteric coating using crosss linking method along with Eudragit S 100, and in colonic delivery mainly by the study of pH sensitive property biodegradability specifically in case of satranidazole. The evaluation studies and release rate were noted and extended upto 24 h.

**Durga jaiswal et al.,**<sup>131</sup> prepared floating alginate beads by using new emulsion gelation technique. Here emulsion gel beads were prepared using sodium alginate and pectin as the polymer containing oil and water phase containing sodium alginate, pectin and drug Ranitidine HCL which was then extruded in to calcium chloride solution. For the above formulated beads evaluation parameters and drug release studies were performed.
Hongxia Liu et al.,\textsuperscript{132} have fabricated novel core–shell hybrid alginate hydrogel beads, characterised and \textit{in-vitro} release studies were performed.

Nikhil K Sachan et al.,\textsuperscript{133} have fabricated hydrogel beads by using sodium alginate and bora rice starch by ionotropic gelation method. Thus characterised the formed hydrogels and \textit{in-vitro} drug release studies were performed for W/O emulsification and solvent evaporation method used for the preparation of microspheres.

Rajeshwar Kamal Kant Arya et al.,\textsuperscript{134} their work involving mainly on preparation and characterization on mucoadhesive microspheres using Famotidine as drug for gastric residence time. Polymers SCMC for mucoadhesion are used in case of microspheres with release controlling polymer sodium alginate. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy, respectively. \textit{In-vitro} drug release studies were performed and drug release evaluated.

Zhao S et al.,\textsuperscript{135} studied on preparation and design of thermosensitive semi-IPN hydrogels on macromer, sodium alginate and N-isopropyl acrylamide.

Takahiro Goto et al.,\textsuperscript{136} investigated the mucoadhesive characters on hydrogel complex using polymethacrylic acid and ethylene glycol. The drug release was studied with rat as animal model.
3. RESEARCH ENVISAGED

3.1 Background

The development of oral transmucosal systems needs the extra study when in comparison with that of other conventional dosage forms. Bioadhesive tablets are kept in mouth release is been possible where oral mucosa absorbs directly where the drug are usually prepared by direct compression. Buccal patches have been prepared by solvent casting method and evaluated over the past several decades as a viable means of drug delivery to the tissues of the oral mucosa (i.e., buccal, palatal, and gingival tissues). Buccal adhesive patches are generally modified release dosage forms that have the potential to provide for controlled drug delivery from 1 to 24 h depending upon their biopharmaceutical and dissolution characteristics (i.e., slow dissolving Vs non-dissolving). A buccal patch refers broadly to a formulation framing a bioadhesive, that make the formulation that adhere to the oral mucosal tissue (i.e., buccal, palatal, and gingival, etc.) for varying periods of time (i.e., hours to days) to provide prolonged local or systemic drug delivery and these may be either slow dissolving or non dissolving tablets and patches. The FDA refers to these dosage routes and forms as buccal extended release films and tablets, respectively, but are defined more generically here as buccal patches. Buccal patch dosage forms are solid matrices that are generally non dissolvable or slowly dissolvable and can be designed to deliver the drug unidirectionally (i.e. directly into the
buccal tissue), bi-directionally (i.e. directly into the buccal tissue and into the saliva in the oral cavity), and multi-directionally (i.e. drug diffusion from all surfaces of the device).

3.2 Suitability of a drug

- Among H2 receptors Famotidine forms a competitive one, used as an anti-ulcerative agent. In the form of buccal films, buccal tablets and mucoadhesive hydrogels produces controlled delivery of the drug.

- Amount of drug available in Famotidine in oral doses is up to 40 to 45% so we can increases the bioavailability of drug through buccal film and buccal tablets.

- Plasma level is 1-3 h and it is having less first pass effect but in case of buccal film (or) buccal tablet the first-pass metabolism of drug have been avoided and the peak plasma level of drug occur in 12 h so therapy has to be maintained.

- By entrapment of drug in the form of buccal film (or) buccal tablet, the dose could be minimized.

- To improve the patient compliance.

By considering the above points the Famotidine might be a right and suitable candidate for the design of buccal films, buccal tablets and mucoadhesive hydrogels.
3.3 Aim and objective of work

The aim of present investigation is the development and evaluation of novel drug delivery system for H2 receptor antagonist of Famotidine with the following objectives

1. To prepare the buccal film, buccal tablets and mucoadhesive hydrogels of Famotidine with varying proportions of polymer.
2. To study the drug and polymer interaction.
3. To produce better bioavailability.
4. To minimize the dose.
5. To avoid presystemic elimination of the drug within the gastrointestinal tract.
6. A prolong period of time observed in oral cavity
7. Improve the patient compliance.
3.4 Plan of work

Lot of difficulties is involved in delivery of drugs via conventional routes. In the present study, the oral route, especially the buccal route and oral route was utilized as a platform for H2 receptor antagonist deliveries hence achieve of drug administration is minimal and on mucosa, site specificity is mainly achieved on reaching the systemic circulation. It shows a reduction in activity of enzymes in comparison with that of gastrointestinal, nasal region and a part of rectal administration. The work entitled “Development and evaluation of novel drug delivery system of selective H2 receptor antagonist” was planned in an aim to achieve the objectives the experimental work composed of four phases with like Pre-formulation studies, Formulation and evaluation of buccal films, buccal tablets and mucoadhesive hydrogels of Famotidine.

Phase I Pre-formulation studies

- Selection and collection of raw materials
- Drug-polymer compatibility studies by Physical observation
- Drug-polymer interaction studies by FTIR
- Drug-polymer interaction studies by DSC
- UV spectroscopic method development
- Construction of calibration curve
Phase II Formulation and evaluation of buccal films of Famotidine

- Fabrication of drug free buccal films.
- Fabrication of Famotidine buccal films
- Physicochemical evaluation of buccal films of Famotidine.
  - Thickness
  - Weight of films
  - Folding endurance
  - Surface pH
  - Percentage moisture absorption
  - Percentage moisture loss
  - Swelling percentage
  - Water vapor transmission rate
  - Drug content estimation
- Scanning electron microscopy
- Measurement of buccoadhesive strength
- Measurement of mechanical strength
- Drug release and kinetics studies
  - Ex-vivo permeation studies through sheep buccal mucosa
  - Ex-vivo muco irritation by histological examination
- In-vivo drug release studies on rabbits
  - In-vivo drug release kinetics
  - In-vitro In-vivo correlation
- Stability studies
Phase III Formulation and evaluation of buccal tablets of Famotidine

- Formulation of buccoadhesive tablets
- Physico-chemical evaluation of buccoadhesive tablets
  - Weight variation
  - Thickness
  - Friability
  - Hardness
  - Surface pH
  - Drug content
- Measurement of Buccoadhesive strength
- In-vitro swelling studies
- In-vitro drug release and kinetics studies
- Ex-vivo permeation study through sheep buccal mucosa
- Ex-vivo muco irritation by histological examination
- In-vivo drug release studies on rabbits
- In-vivo drug release kinetics
- In-vitro In-vivo correlation
- Stability studies
**Phase IV Formulation and evaluation of mucoadhesive hydrogels of Famotidine**

- Construction of calibration curve at pH 1.2 HCl
- Formulation of mucoadhesive hydrogels
- Evaluation of Famotidine hydrogels
  - Evaluation of micromeritic properties
  - Evaluation of Equilibrium Swelling Ratio
  - Water uptake studies
  - Evaluation of gel fraction
  - Morphological evaluation
  - Physicochemical evaluation
- *In-vitro* test for mucoadhesion
- *In-vitro* drug release and kinetic studies
- Comparison of *in-vitro* drug release with marketed product
- *In-vivo* drug release studies on rabbits
- *In-vitro In-vivo* correlation
- Stability studies