LITERATURE REVIEW:

1. **Yajaman Sudhakar et al [2006]**, Studied rapid developments in the field of molecular biology and gene technology resulted in generation of many macromolecular drugs including peptides, proteins, polysaccharides and nucleic acids in great number possessing superior pharmacological efficacy with site specificity and devoid of untoward and toxic effects. However, the main impediment for the oral delivery of these drugs as potential therapeutic agents is their extensive presystemic metabolism, instability in acidic environment resulting into inadequate and erratic oral absorption. Parentral route of administration is the only established route that overcomes all these drawbacks associated with these orally less/inefficient drugs. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms, because it has expanse of smooth muscle which is relatively immobile, abundant vascularization, rapid recovery time after exposure to stress and the near absence of langerhans cells.

2. **Cappello Brunella et al [2006]**, Developed a tablet for the buccal delivery of the poorly soluble drug carvedilol (CAR), based on poly(ethyleneoxide) (PEO) as bioadhesive sustained-release platform and hydroxypropyl-β-cyclodextrin (HPCD) as modulator of drug release. As first, PEO tablets loaded with CAR/HPCD binary systems with different dissolution properties were tested for CAR and HPCD release features and compared to PEO tablets containing only CAR. When the drug was incorporated as CAR/HPCD freeze-dried product, all CAR content was released from the tablet in about 10 h, displaying a constant release regimen after a transient. The effect of HPCD incorporation on the release mechanism, was rationalized on the basis of the interplay of different physical phenomena: erosion and swelling of the tablet, drug dissolution, drug counter-diffusion and complex formation. In the second part of the study, the potential of HPCD-containing PEO tablets as buccal delivery system for CAR was tested. It was found that the incorporation of HPCD in the tablet did not alter significantly its good adhesion properties. The feasibility of buccal administration of CAR was assessed by permeation experiments on pig excised mucosa.

3. **Varshosaz J. et al [2002]**, Prepared buccoadhesive controlled-release tablets for delivery of nifedipine by direct compression of carboxymethyl cellulose (CMC) with carbomer (CP),
which showed superior bioadhesion properties compared to polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), hydroxypropylmethyl cellulose (HPMC), and acacia in a modified tensiometry method in vitro. The tablets containing 30 mg of nifedipine and various amounts of CMC and CP showed a zero-order drug release kinetic. The adhesion force was significantly affected by the mixing ratio of CP:CMC in the tablets.

4. **Leung S.S et al., [1994]**, investigated polymer structure features contributing to mucoadhesion and the expanded nature of mucin and polymer networks; which permits mutual interpenetration/ Interdiffusion of mucin and adhesives results in an increase in contact area and establishment of physical entanglement of two different macromolecules.

5. **Nakanishi T, Kaiho F and Hayashi M, [1998]**, studied the improvement of drug release rate from carbopol 934P formulation and found that, the carboxyl group of Carbopol is dissociate in the alkaline environment, electrostatic repulsion between negatively charged carboxyl groups causes uncoiling and expansion of molecules resulting in swelling of the polymer and gel formation. The gel is composed of closely packed swollen particles, whose swelling increases with increase in the pH. Thus forming thicker and more rigid gel layer.

6. **Santus G et al., [1997]**, studied An In vitro and In vivo investigation of oral bioadhesive controlled release Furosemide formulations and having finding that, the delayed onset of gastric emptying of the bioadhesive formulation resulted in the later onset of Furosemide absorption and also a decreased amount of Furosemide excreted in the urine for the first pooling interval (0-2 Hrs).

7. **Singh M et al., [2002]**, studied Gastro-Retentivity: Its drug delivery potential and showed that, that the extent of drug absorption from GIT is determined by GI Physiology, irrespective of controlled release properties of the device. These include gastro retentive system, delayed release system and colon targeting. Various other approaches have been tried to retain the dosage form in the stomach as a way of increasing the overall rotation time and include floating system, high density pallets, bioadhesive system, swelling systems and shape system. Use of Passage dealing precipitants have recently been highlighted. e.g.: - Salts of Myrestic acid.

8. **Durrani M.J et al., [1994]**, studied on the drug release kinetics from carbomer matrices and shown that, the drug solubility can influence the mechanism of drug release. Atenolol is a higher water-soluble drug demonstrated a square root time dependent drug release. While
Furosemide, poorly water-soluble drug gave zero-order release. So the solubility is having the influence on the drug release in controlled release tablet. It is totally independent on the various grade of the polymer.

9. **Prudat-Christianes C et al., [1996]**, had prepared Aminophylline bioadhesive tablets attempted by wet granulation and having finding that, the wet granulation has limited bioadhesion, because wetting of carbomer and there drying was impossible when their concentration exceed 10%. Wet granulation did not allow obtaining of highly bioadhesive tablets. However wetting and drying steps did not alter the polymer structure or bioadhesive property.

10. **Aggarwal, V. and Mishra B., [1999]**, had prepared the buccoadhesive compacts of Pentazocine using Carbopol 974P and HPMC K4M. Combination of these polymers in the ratio 1:0, 1:1 and 1:2 gave controlled and prolonged invitro release of Pentazocine.


13. **Aggarwal, S.P. et al., [1995]**, Developed Buccal tablets of Diltiazem hydrochloride was by using Carbopol 934P in combination with HPMC 4M as buccoadhesive polymer in the ratio of 1:3 had shown good bioadhesion and drug release.

14. **Denner, V.H.M. et al., [2002]**, also had used porcine mucosa in transport of flecainide and sotalol.

15. **Zhepeng Liu et al, [2005]**, prepared amoxicillin mucoadhesive microspheres by using ethyl cellulose as matrix and carbopol 934P as mucoadhesive polymer for the potential use of treating gastric and duodenal ulcers. The technique used was emulsification/evaporation method. Invitro and invivo mucoadhesive tests showed that amoxicillin mucoadhesive microspheres adhered more strongly to gastric mucus layer than nonadhesive amoxicillin microspheres did and could retain in gastrointestinal tract for an extended period of time.

16. **Yasunori Miyazaki et al.,[2003]**, prepared mucoadhesive microspheres by using oppositely
charged dextran derivatives and cellulose acetate butyrate. The technique used was emulsion-solvent evaporation technique. Invitro mucoadhesion was examined by everted sac method and results indicated that the percentage of adherence to the rat small intestine was affected by the amount of dextran derivatives in the microspheres. After 1.5hr, the adhering percent of the reference microspheres containing 50% of dextran derivatives were 34% and 74% respectively.

17. Lim S.T. et al., [2003], compared a number of novel, potentially mucoadhesive microspheres, prepared by solvent evaporation, composed of hyaluronic acid, chitosan glutamate and a combination of the two with microcapsules of hyaluronic acid and gelatin prepared by complex coacervation. Gentamicin sulphate was used as model drug. The release of gentamycin from hyaluronic acid and combination of hyaluronic acid and chitosan glutamate was 50% longer than chitosan glutamate and was best modeled as a release from a matrix. The degree of mucoadhesion of each formulation was investigated by determining the mucociliary transport rate of the microparticles across an isolated frog palate.

18. Myung Kwan Chun et al., [2005], prepared mucoadhesive microspheres to increase gastric residence time using an inter polymer complexation of poly (acrylic acid) with poly (vinyl pyrrolidone) and solvent diffusion method. A mixture of ethanol/water was used as the internal phase, corn oil was used as the external phase of emulsion, span 80 was used as the surfactant, and acetaminophen was used as the model drug. The release rate of acetaminophen from the complex microspheres was slower than poly (vinyl pyrrolidone) microspheres at pH 2.0 and 6.8.

19. Sandra Kockisch et al., [2005], developed mucoadhesive microspheres that can be utilized for the controlled release of triclosan in oral-care formulations, specifically dental pastes. Using a double-emulsion solvent evaporation technique, triclosan was incorporated into microspheres that were prepared from Gantrez™ MS-955, Carbopol™ 974P, polycarbophil or chitosan and the profiles for its release were established under simulated ‘in use’ conditions. The release of triclosan from microspheres suspended in the non-aqueous paste was found to be sustained over considerable time periods, which were influenced strongly by
the nature of polymeric carrier. The study demonstrated that chitosan is the promising candidate for the sustained release of triclosan in the oral cavity.

20. Sakagami Masahiro et al., [2002], investigated the feasibility of prolonging drug action and/or reducing drug dosage using mucoadhesive beclamethasone dipropionate microspheres for powder inhalation. Beclamethasone dipropionate was spray-dried from ethanol solution or aqueous suspension systems dissolving a mucoadhesive polymer, hydroxyl propyl cellulose which resulted the amorphous and crystalline drug incorporation in the hydroxyl propyl cellulose microspheres, respectively. After evaluation, it appeared that the prolonged lung retention of beclamethasone dipropionate by the use of the hydroxyl propyl cellulose microspheres was attributed to prolonging its pharmacological duration without requiring increased drug dosage.

21. Shojaei A.H.et al., [1998], studied buccal mucosa as a route for systemic delivery. The objective of the article was to review buccal drug delivery by discussing the structure and environment of the oral mucosa and the experimental methods used in assessing buccal drug permeation or absorption. Buccal dosage forms would also be reviewed with an emphasis on bioadhesive polymeric based delivery system.

22. Pramod kumar T.M. et al., [2004], concluded that Carbopole and HPMC are suitable for developing buccoadhesive core-in-cup system of Terbutaline sulphate. These two polymers act in a complymentry fasion in that carbopole increases the bioadhesion while HPMC helps in sustaining the release. Thus, the variation in their ratios could be adjusted to obtain the desired release profiles. Formulations containing a higher proportion of carbopole exhibited high mucoadhesive strength, swelling index and faster release. Thus, the study revealed that the buccoadhesive formulation showed good mucoadhesive properties with sustain release of Terbutaline sulphate.

23. Vaidya V.M. et al., [2009], formulated buccal tablets of Terbutaline sulphate prepared by direct compression method. Carbopole934P, chitosan, HPMC K4M, and HPMC K15M were
used as a polymers. They found that decreasing the content of carbopole 934P result in decrease in adhesion force.

24. **Patel K.R. et al., [2008]**, formulated the mucoadhesive patch containing carvidelol using different mucoadhesive polymers like Chitosan, HPMC, HPC, and Na-CMC alone and in combination with PVP. These patches show satisfactory mucoadhesive characteristic. Incorporation of PVP in the patches enhanced the permeability of carvedilol.

25. **Remun pez Carmen et al., [1998]** describes the preparation of new buccal bilayered devices comprising a drug-containing mucoadhesive layer and a drug-free backing layer, by two different methods. Bilaminated films were produced by a casting / solvent evaporation technique and bilayered tablets were obtained by direct compression. The mucoadhesive layer was composed of a mixture of drug and chitosan, with or without an anionic crosslinking polymer (polycarbophil, sodium alginate, gellan gum), and the backing layer was made of ethylcellulose.

26. **Thimmasetty J.et al., [2008]**, Carvedilol patches were prepared using HPMC, carbopol 934, eudragit RS 100, and ethylcellulose. In vitro release studies were conducted for carvedilol-loaded patches in phosphate buffer (pH, 6.6) solution. Patches exhibited drug release in the range of 86.26 to 98.32% in 90 min. Data of in vitro release from patches were fit to different equations and kinetic models to explain release profiles. Kinetic models used were zero and first-order equations, Hixon-Crowell, Higuchi, and Korsmeyer-Peppas models. In vivo drug release studies in rabbits showed 90.85% of drug release from HPMC carbopol patch while it was 74.63 to 88.02% within 90 min in human volunteers. Good correlation among in vitro release and in vivo release of carvedilol was observed.

27. **Choi Han-Gon et al., [2000]**, For the development of omeprazole buccal adhesive tablets, he studied the release and bioavailability of omeprazole delivered by buccal adhesive tablets composed of sodium alginate, hydroxypropylmethylcellulose (HPMC), magnesium oxide and croscarmellose sodium. Croscarmellose sodium enhanced the release of omeprazole from the tablets. The analysis of the release mechanism showed that croscarmellose sodium changed the release profile of omeprazole from first- to zero-order release kinetics by
forming porous channels in the tablet matrix. However, it decreased the bioadhesive forces and stability of omeprazole tablets in human saliva.

28. **Miller-Nazila Salamat et al., [2005]**, show that advantages associated with buccal drug delivery have rendered this route of administration useful for a variety of drugs. This review highlights the use of mucoadhesive polymers in buccal drug delivery. Starting with a review of the oral mucosa, mechanism of drug permeation, and characteristics of the desired polymers, this article then proceeds to cover the theories behind the adhesion of bioadhesive polymers to the mucosal epithelium. Additionally, we focus on the new generation of mucoadhesive polymers such as thiolated polymers, followed by the recent mucoadhesive formulations for buccal drug delivery.

29. **Choudhary Arpita et al., [2010]**, Carvedilol patches were prepared using HPMC K15 and Carbopol 940. The patches were evaluated for their thickness, folding endurance, weight and content uniformity, swelling behaviour, mucoadhesive strength and surface pH. In vitro release studies were conducted for carvedilol-loaded patches in phosphate buffer (pH, 6.8) solution. The patches exhibited drug release in the range of 77.05 to 97.20% in 8 hours. Data of in vitro release from patches were fitted into kinetic models (Higuchi and Korsmeyer-Peppas models) to explain release profiles. The optimized formulation (patch V) showed first order release followed by zero order.

30. **Martina Lee et al., [2003]**, A physically cross-linked palmitoyl glycol chitosan hydrogel has been evaluated as a controlled release system for the delivery of hydrophobic drugs via the buccal route. All gels were mucoadhesive but less so than the control CP tablets. Denbufylline was detected 0.5 h after dosing with the GCP12 formulation and delivery was sustained for at least 5 h after dosing. In comparison delivery from the CP tablets was not sustained and was first detected 1 h after dosing.

31. **Prajapati RK et al., [2010]**, investigated carvedilol loaded PLGA microspheres were prepared by a spray-drying technique that can be proposed as an alternative to the conventional methods for preparation of microspheres. The investigations of these
microspheres as vehicle for nasal delivery showed that PLGA microspheres may be considered as a promising nasal delivery system.

32. **Pankaj Pant et al., [2010]**, developed gastroretentive mucoadhesive microspheres of clarithromycin to combat *Helicobacter pylori* infection in ulcer patients. Clarithromycin is used for the treatment of *H. pylori*. The microspheres were prepared using Sodium alginate and Hydroxypropyl Methylcellulose as polymer by Ionic Gelation Technique.

33. **Singh Mahendra et al., [2009]**, investigated reducing dosing frequency and improve patient compliance by designing and systematically evaluating sustained release microspheres of verapamil. Verapamil-loaded mucoadhesive microspheres were successfully prepared by emulsification-internal gelation technique with a maximum incorporation efficiency of 93.29±0.26%.

34. **Hardenia Shiv Shankar et al., [2009]**, prepared ethylcellulose microspheres containing ciprofloxacin were prepared and evaluated for in-vitro performance of ciprofloxacin. Ciprofloxacin microspheres containing ethylcellulose were prepared by emulsion solvent diffusion evaporation method and concluded that ethylcellulose microspheres showed reproducible results, with good Mucoadhesive properties and good surface morphology.

35. **Sambathkumar R et al., [2010]**, The mucoadhesive microspheres prepared by using sodium alginate alone and in combination with HPMC K4M and carbopol 974 P. Clarithromycin loaded mucoadhesive microspheres were successfully prepared by emulsification-internal gelation technique with a maximum incorporation efficiency of 93%. The preliminary results show great promise for this delivery strategy in the treatment of *H. Pylori* infection.

36. **Zhepeng Liu et al., [2005]**, prepared Amoxicillin mucoadhesive microspheres were prepared using ethylcellulose as matrix and carbopol 934P as mucoadhesive polymer for the potential use of treating gastric and duodenal ulcers, which were associated with *Helicobacter pylori*. The morphological characteristics of the mucoadhesive microspheres were studied under scanning electron microscope. In vitro release test showed that amoxicillin released faster in pH 1.0 hydrochloric acid than in pH 7.8 phosphate buffer. In
conclusion, the prolonged gastrointestinal residence time and enhanced amoxicillin stability resulting from the mucoadhesive microspheres of amoxicillin might make contribution to H. pylori clearance.

37. **Sruthy N V et al., [2010]**, developed a pH sensitive multiparticulate system intended to approximate the chronobiology of angina pectoris is proposed for site specific release to the colon. The multiparticulate system consisting of drug loaded chitosan microspheres encapsulated within Eudragit S-100 microcapsules was designed for chronotherapeutic delivery of Carvedilol. Drug loaded chitosan microspheres were prepared by emulsion cross linking method in different drug to polymer by emulsion cross linking method in different drug to polymer ratios.

38. **Arya Rajeshwar Kamal Kant et al., [2010]**, prepared and characterized mucoadhesive microspheres with Famotidine as model drug for prolongation of gastric residence time. The microspheres were prepared by the w/o emulsification solvent evaporation method using mucoadhesive polymers sod. CMC and a release controlling polymer sodium alginate. CMC polymer concentration increases the mucoadhesion increased and the drug release rate decreased at higher concentration of sod. alginate. Significant effect of the stirring rate on the size of microspheres was observed.

39. **Patel Jayvadan K.et al., [2005]**, Glipizide microspheres containing chitosan were prepared by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Results of preliminary trials indicate that volume of cross-linking agent, time for cross-linking, Polymer-to-drug ratio and speed of rotation affected characteristics of microspheres. Microspheres were discrete, spherical, and free flowing. The polymer-to-drug ratio had a more significant effect on the dependent variables.

40. **Dhakar Ram Chand et al., [2010]**, formulated and evaluated mucoadhesive microspheres of Rosiglitazone Maleate for treatment of diabetes type-2 by combine the potential advantages of mucoadhesion with controlled drug delivery using various ratio of polymers. Mucoadhesive microspheres were prepared by emulsification solvent evaporation techniques. Microspheres were found discrete, spherical and free flowing. The work has demonstrated that among all the formulations of microspheres, particularly those of formulation containing sodium carboxy methyl cellulose are promising candidates for the sustained release of Rosiglitazone Maleate in the gastrointestinal tract.
Ahmed Mohammed G et al., [2010], developed a new oral drug delivery system utilizing both the concepts of controlled release and mucoadhesiveness, in order to obtain a unique drug delivery system which could remain in stomach and control the drug release for longer period of time. Gastro-retentive beads of captopril were prepared by orifice ionic gelation method in 1:1 and 9:1 ratio of alginate along with mucoadhesive polymers viz; hydroxy propyl methyl cellulose, carbopol 934P, chitosan and cellulose acetate phthalate. The prepared beads were subjected for various evaluation parameters. The alginate-cellulose acetate phthalate beads showed the better sustained release as compared to all other alginate polymer combinations.