2. LITERATURE SURVEY

The design of novel mucoadhesive buccal drug delivery system is primarily aimed to attain on marking a drug delivery system in a particular area of the body for extend phase of time, not only for local targeting of drugs but also used for the improved control of systemic drug delivery. The most significant goals in mucoadhesion buccal delivery system consist of sustained releasing and controlled, drug targeting, rising of residence time, declining of adverse effects and reducing of the first pass effect and long-term drug delivery. Among the various mucosal drug delivery systems are obtainable, mucosa of the buccal cavity was found to be easily accessible and the most suitable site for the delivery system for therapeutic agents for both systemic and local drug delivery.

In buccal drug delivery system the drug is administered through the mucosal membrane lining of the cheeks. The mucin layer subsists in oral mucosa provides a chance to extend mucoadhesive system, which retains at absorption site for delayed period of the time by mucoadhesive binding. The close contact with absorption membrane causes more absorption of the drugs.

2.1 General mucoadhesive buccal delivery systems

Luana Perioli et.al. were prepared and investigated the mucoadhesive drug delivery system for metronidazole by using different mixtures of polyacrylic and cellulose derivatives. Swelling studies, ex-vivo mucoadhesion force, in-vivo and ex-vivo mucoadhesive time, in-vitro and in-vivo drug release studies were carried out with prepared buccal tablets. The mucoadhesive property shows excellent mucoadhesive strength and the highest in vitro
drug release profile which was attained in 2:2 ratio of carbomer 940 and hydroxyethyl cellulose (HEC). It was concluded based on the results of metronidazole mucoadhesive drug delivery system having sustained release with buccal concentrations forever elevated than its MIC\textsuperscript{95}.

Three layered Metoprolol tartarate buccal tablet were prepared by Narendra C et. al. in order to attain objective of evaluation of the effect of formulation variables polymer ratio (HPMC 4KM : carbopol 934P) and core polymer ratio (sodium alginate : HPMC 4KM) as two autonomous variables on bioadhesive strength and release properties by means of a statistical optimization technique. The results were observed that increased in both the formulation variables and as the HPMC: carbopol ratio raises the bio adhesive force also increases\textsuperscript{96}.

In an attempt made by Munasur A P et. al. to study the effect of multi-polymeric blends such as poly acrylic acid (PAA), poly vinyl pyrrolidone (PVP) and CMC on muco-adhesivity and controlled drug release for propranolol HCl matrices by employing Box-Behnken experimental design. The optimal buccal tablet formulation was estimated for surface pH, hydration dynamics, release kinetics, mucoadhesiveness and swelling/erosion. The result explained that it would be potential for buccal drug delivery system\textsuperscript{97}.

Gowthamarajan K et. al. were formulated mucoadhesive buccal tablets of curcumin using a natural mucodhesive polymer derived from cashew nut tree gum (20% concentration), enhancer, 40mg backing layer and (0.1% penetration). From the evaluation studies, it was found to be constant with various physicochemical, \textit{in-vitro} drug release and short term stability
assessment and drug releases was followed anomalous diffusion. They were from the based their findings that cashew nut tree gum can be used as a mucoadhesive polymer to formulate buccal tablets with latent mucoadhesive property\textsuperscript{98}.

Senel S et. al. were reported that formulation of bioadhesive buccal tablet prepared with various proportion of hydroxypropyl methylcellulose and carbomer using sodium glycodeoxycholate (GDC) as a penetration enhancer and results were exhibits good in vitro bioadhesion property without affecting the histological changes such as loss of upper cell layers and the creation of vacuoles as well swelling in the cells after 4 h contact by sodium glycodeoxycholate\textsuperscript{99}.

Soliman Mohammadi-Samani et. al. were developed the method for the preparation of prednisolone buccoadhesive tablets by using polymers such as hydroxyl propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (NaCMC) and carbopol 934 (Cp 934). It was observed from results that the release rates of drug from formulation prepared with HPMC with viscosity grade 60 mPas and Cp 934 alone was rapid and their mucoadhesion force was low as well. However, HPMC viscosity grade 500 mPas and NaCMC depicts moderate mucoadhesion\textsuperscript{100}.

The omeprazole buccal adhesive matrix tablets were set by using different ratio’s of hydroxypropylmethylcellulose (HPMC), sodium alginate, croscarmellose sodium composition and magnesium oxide. However, the ratio of (20:24:6:50:10mg) improved the constancy of drug in human saliva for at least 4 h and which gives a fast release of omeprazole and other hand the plasma concentration of omeprazole in hamsters also increased to reach
a maximum of 370 ng/ml at 45 min after buccal administration and remained at the elevated level of 146–366 ng/ml for 6 h were observed by Han-Gon Choi et al.\textsuperscript{101}.

Gavaskar B et al. has developed mucoadhesive buccal monolayered tablets by using bioadhesive polymers like methocel K15M, Sodium methyl cellulose (NaMC), and sodium alginate. The results observed from the evaluation of dissimilar parameters such as content equivalence, weight equivalence, breadth, surface pH, Swelling index, ex-vivo mucoadhesive strength, hardness, in-vitro drug permeation and in-vitro drug release. It concluded in the current work that mucoadhesive buccal tablets of baclofen can develop the bio availability\textsuperscript{102}.

Gaudanavar PS et al. were developed mucoadhesive buccal tablets of glibenclamide by utilizing the polymers like HPMC K4M, sodium CMC and carbopol 934. The prepared tablets were estimated for different physiochemical factors and release mechanism. The in-vitro release results were also subjected to graphical treatment according to Higuchi’s and Peppa’s equation and the outcome establishes that the release method is diffusion and the rate of release following first order kinetic model\textsuperscript{103}.

Mucoadhesive tablets containing chlorehexidine were formulated by utilizing a mixture of Chitosan and HPMC by employing direct compression technique. The bioadhesive strength, in vitro drug release were carried out in order to know the type of drug release and also the release data were subjected to different release kinetic models for release mechanisms. The fraction of HPMC in the blend increased, the drug release rate reduced with a lowest release rate and when HPMC was utilized alone as bioadhesive
polymer were observed from the results by Akbari J et al.104.

Ramana MV et al. were formulated of metoprolol tartrate tablets by using carbopol-934: HPMC, HEC and CMC by direct compression. The formulations were differentiated for physiochemical factors, *in-vitro* release studies, *in-vivo* placebo studies and mucoadhesive performance. The most excellent mucoadhesive property and *in-vitro* drug release profile were revealed by the tablets containing Carbopol-934 and hydroxyethylcellulose in ratio 2:1105.

Nakhat P D et al. has observed from their newly developed buccoadhesive bilayered tablets containing terbutaline sulphate by using a Methocel-K4M and Carbopol-934P in the ratio of 1:1 shows the maximum bioadhesive strength than the tablet formulated with Carbopol-934P alone106.

The mucoadhesive bilayer buccal tablets containing Atorvastatin calcium by means of bioadhesive polymers such as sodium CMC, carbopol-934P, sodium alginate, HEC along with ethyl cellulose as a backing layer were prepared and evaluated for bioadhesive strength, surface pH and permeability study by Asha S. John et al.107. The results from the above work specify that the mechanism of drug release was found to be non-Fickians diffusion and followed anomalous release was experienced. In other hand, Balamurugan M et al. Formulated and distinguished the mucoadhesive Buccal Tablets for Domperidone by utilising methocel-K4M and chitosan in ratio of 1:1 which exhibits the most excellent mucoadhesive act, *in-vitro* drug release profile and release kinetics follows Hixson Crowel model108.
Prasad B Kadam et. al. were developed buccoadhesive bilayered tablets for atenolol by using a carbopol-934P and hydroxypropyl methylcellulose and sodium alginate. The results observed from characterized of physiochemical parameters, *in-vitro* bioadhesive strength studies of formulated tablets that the blend of hydroxypropyl methylcellulose and carbopol-934P showed more bioadhesive strength than formulation containing sodium alginate alone. *In-vitro* dissolution studies revealed that all the formulations exhibited non-fickian release kinetics\(^{109}\). In order to overcome poor bioavailability of carvedilol (25-30%) which is endorsed to its high first pass metabolism and poor solubility Hirlekar R S et. al. were formulated buccal tablets of carvedilol by employing kneading method using Methyl-\(\beta\)-cyclodextrin complex with drug. The formulations were distinguished for *ex-vivo* permeability, mucoadhesive strength and drug release. The quantity of drug permeated from these tablets across the porcine buccal mucosa at the end of 5 h was 6.2 mg as compared to 2.51 mg from tablets enclosing plain drug. The results it indicates the buccal tablet containing carvedilol to increased bioavailability\(^{110}\).

Bhupinder Singh et. al. were designed mucoadhesive tablets of Atenolol for controlled release delivery system by direct compression technique and it was characterized for bioadhesive strength, *in-vitro* drug release and release kinetics. The developed system exhibited excellent bioadhesive strength and controlled release of the drug with non-Fickian release kinetics approaching zero-order\(^{111}\).
Naresh Yadav et. al. were prepared buccal tablets of Pravastatin by direct compression using mucoadhesive polymers Carbopol 943-P, HPMC K4M and Sodium CMC. The drug release rate from the tablets was found to be increased upto 6 hrs by increasing the concentration of Carbopol 940p and decreased concentration of Na CMC (ratio of 1:1) in the formulation and with this concentration mucoadhesive strength was also increased. But when the concentration of HPMC K4M increased and Carbopol decreased the drug release rate was found to be decreased. All the formulations followed Fickian release mechanism\textsuperscript{112}. In case of Balagani Pavan Kumar et. al. were also attempted prepared buccal tablets of nitroglycerin using Carbopol 934 in varying concentration with secondary polymers like HPMC K4M, HPMC K15M and sodium alginate. Carbopol 934 and Sodium alginate polymers containing tablets showed good swelling upto 8 hrs maintaining the integrity of polymers and (C3) showed better control of drug release and able to release entire amount of drug in 12 hrs than the other formulations. The tablets were evaluated for hardness, thickness, weight variation; friability and drug content were in acceptable range of pharmacopoeial specification\textsuperscript{113}.

Shital K. Thombre et. al. were formulated Pantoprazole buccal tablets using varying concentrations of polymers like Sodium alginate and HPMC utilizing a full $3^2$ factorial design. The \textit{in-vitro} release study reveals that maximum 98.0 % drug release in 6 h was achieved with the formulation F6 which contains the drug, Sodium alginate and HPMC K4M in the (20/17/8) mg respectively. The surface pH, bioadhesive strength and drug content of formulation F6 was found to be 7.1, 27.9, and 98.0 % respectively. The in
vitro release kinetics studies reveal that all the formulations fit well with zero order kinetics and mechanism of drug release is non-Fickian diffusion\textsuperscript{114}.

Sachin S. Darekar et. al. were prepared mucoadhesive bilayered buccal tablet of sumatriptan succinate by varying ratio of HPMC K15M, and HPMC K100LV. A combination of polymers HPMC K15: HPMC K100LV in the ratio of 1:3 shows good mucoadhesive strength of 13.99 g, ex-vivo drug release, upto 90% in 8hr and good mucoadhesive time as 470 min when compared other formulations prepared with other composition ratio\textsuperscript{115}.

2.2 Muccodhesive buccal delivery systems utilizing xanthan gum

Ganesh G N K et. al. were developed buccal drug delivery system for lipophillic drug such labetalol hydrochloride by employing innate mucoadhesive polymer as xanthan gum. They observed from the characterization studies conducted on buccal tablets that the drug shows greater penetration through the buccal membrane and release was followed Fickian diffusion\textsuperscript{116}.

Shah Viral H et. al. were designed and formulated Fluvastatin containing buccal adhesive tablet by means of innate gums such as tamarind gum, xanthan gum and gellan gum. The formulations were characterized for physiochemical parameters of tablets like bioadhesive strength, swelling rate, surface pH, permeation rate and \textit{in-vitro} drug release rate. Release studies reveal that the sustained release of Fluvastatin over several hours may be obtained by combining the Chitosan with natural gums\textsuperscript{117}. 
Amish V. Panchal H et. al. also effort was made to developed mucoadhesive buccal device for Rosuvastatin Calcium (RC) in the form of bilayered tablet with innate gums like Tamarind gum, Gellan gum, Xanthan gum and Chitosan. The bioadhesive polymers used in the formulation exhibits muco-adhesion and permeation enhancement properties as well.\textsuperscript{11,18}

Shukla J B et. al. were developed bucco-mucoadhesive bilayered tablets of Propranolol hydrochloride (PrHCl) with polymers acrypol 934P (AL-P), xanthan gum (XG) and hydroxyl propyl methylcellulose (HPMC K4M). The results from the evaluations of optimised buccal mucoadhesive tablets were observed that it would be an excellent mode to go around the extensive hepatic first-pass metabolism and to progress the bioavailability of Propranolol hydrochloride all the way through buccal mucosa using this developed system.\textsuperscript{11,19}

The mucoadhesive buccal tablets having ondansetron hydrochloride (ODH) produced by Syed Amezuddin Azhar et. al. by utilising polymers like gelatin, chitosan, xanthan gum. The formulations made for mucoadhesion and drug release evaluations by employing sheep buccal mucosa and they ranked based on the mucoadhesion property in order of xanthan gum > chitosan > gelatin. However, the formulation consists of of xanthan gum illustrated optimum drug release and agreeable mucoadhesive properties.\textsuperscript{120}

2.3 **Mucoadhesive Drug delivery systems reported for Nifedipine**

Sheeba F R et. al. were developed formulation by using sodium starch glycolate, cros carmellose sodium, cros povidone for fast-disintegrating sublingual tablets containing Nifedipine in order to meet emergency treatment of anginal pain and hypertension. The prepared fast suspending
tablets were distinguished for post compression evaluation such as, hardness, weight variation, drug content, friability, dissolution time and disintegration time for every formulation and the result observed from above was found to be satisfactory\textsuperscript{121}.

Donga J J et. al. co worker prepared sustained release hydrophilic polymer matrix tablet for the drug nifedipine by using HPMC K100M. The polymers mix made to get attractive release profile. The tablets were also distinguished by all factors to justify the acceptability criteria for official limits and the \textit{in-vitro} drug release rate report was matched up with the marketed product release profile as well. The result it indicates the optimized sustained release matrix tablet of nifedipine achieve a prolonged therapeutic effect\textsuperscript{122}.

Sustained release matrix tablets for water soluble nifedipine hydrochloride by means of multi-unit Chitosan treated alginate was developed by Soumik Ghosh et. al. in order to attain delayed therapeutic effect by constantly releasing medication over an unlimited phase of time. The result exhibits that Chitosan enhanced the swelling of multiple unit systems (MUS) in acidic conditions and decreased the drug release from Multi unit system\textsuperscript{123}. The drug was also formulated in form of microspheres utilizing Eudragit RL100 polymer by adopting solvent evaporation technique by Solmaz Dehghan et. al. optimization of formulation were made by factorial study outcomes and results observed that retarding drug release over the test period of 12 h \textit{in-vitro} studies and microsphere prepared was also found to be spherical with smooth surface morphology\textsuperscript{124}. 
Bertil Abrahamsson et. al. has compared the bioavailability of nifedipine when administered as a push–pull osmotic pump tablet (XL) and a hydrophilic matrix tablet (ER) administrated after fasting, and found that the tablet erosion was affected by food which directed to enhanced absorption rates and increased plasma peak concentrations were observed\textsuperscript{125}. Other workers Longxiao Liu et. al. also developed nifedipine controlled delivery by sandwiched osmotic tablet system comprises of a two attached drug layers and middle push layer (potassium chloride). The suitable orifice size was observed in the range of 0.50–1.41 mm. It was also found that the drug release rate of SOTS could be enhanced by integrating hydrophilic plasticizer in the membrane, while it reduced with hydrophobic plasticizer. It has been concluded that the SOTS gives moderately equivalent \textit{in-vitro} release characters as that of commercialized push–pull osmotic tablet system\textsuperscript{126}.

2.4 Mucoadhesive Drug delivery systems reported for Hydralazine HCl

Oral bioadhesive hydrophilic matrices of hydralazine hydrochloride was developed by utilising carbomer and hydroxypropyl methyl cellulose and optimized once-a-day formulation of hydralazine with admirable controlled release and bioadhesive characteristics with help of response surface plots by Bhupinder Singh et. al.\textsuperscript{127}

Carbomer, Hydroxypropyl methylcellulose, cetyl alcohol and glyceryl dibehenate were used to developed matrix tablets to in order to prevail over its side effects and to raise its bioavailability of hydralazine hydrochloride by Melike Uner et. al.\textsuperscript{128} The slowest drug release rate was observed with the formulation prepared with carbomer followed by cetyl alcohol, glyceryl
dibehenate and hydroxypropyl methylcellulose. Drug release met Higuchi kinetic model in common. Whereas the mechanism of drug release from polymer based tablets was non-Fickian drug release. Saleh A. Al-Suwayeh et. al. formulated tablet using polyethylene glycol 6000 (PEG 6000) and hydroxylpropylmethyl cellulose (HPMC) mix for hydralazine hydrochloride by employing thermal granulation technique. The data obtained was provided strong evidence that prepared tablets exhibits sustained release when compared to the instant release tablets dosage form. In other hand Basavraj K Nanjwade et. al. were formulated microsphere for this drug by using albumin and glutaraldehyde as cross-linking agent it was found that the release activities was considerably synchronized by volume of glutaraldehyde and polymer concentration. In case of floating tablets of hydralazine hydrochloride prepared with. semi synthetic polymers (Hydroxy propyl methyl cellulose) HPMC K100M, HPMCK15M and HPMCK4M and sodium bicarbonate as gas generating agent by Kondi vanitha et. al. which exhibits in-vitro buoyancy and extended drug release.

2.5 Mucoadhesive buccal delivery systems utilizing pectin

Nartaya Thirawong et. al. have evaluated mucoadhesive potency of different pectin with dissimilar degrees of esterification and molecular weights. By employing porcine gastrointestinal (GI) mucosa, i.e. stomach buccal, large intestine and small intestine, adopting a surface analyzer method. The results indicated that the mucoadhesion strength of pectin increased with the enhanced contact force and contact time, and elevated level of esterification and molecular weight.
Miyazaki et. al. were developed oral mucosal bioadhesive tablets using hydroxypropyl methylcellulose (HPMC) and pectin combination to attain sustained release of Diltiazem. Maximum adhesive force was observed with rat peritoneal membrane. And also show a considerable enhancement of bioavailability of diltiazem administered to rabbits sublingually when compared to that accomplished by oral administration\textsuperscript{133}.  

Bioadhesive patches of carvedilol hydrochloride by means of pectin (PE) and Chitosan (CH) by solvent casting method was developed by Amanpreet Kaur et. al. and from the systematically evaluation of \textit{in-vitro} and \textit{in-vivo} studies, It was observed that it possesses good of bioadhesive strength and good stand of bioavailability\textsuperscript{134}.  

Lars Joergensen et. al. have evaluated mucoadhesion strength of pectin by using surface Plasmon resonance (SPR) and atomic force microscopy (AFM) analysis to know definite mucin relations of pectin with a elevated charge density on a molecular scale without intervention from the viscoelastic properties and polyvinyl pyrrolidone and Polyacrylic acid were used as positive and negative control\textsuperscript{135}.  

Porpsak Sriamornsak et. al. were estimated mechanisms of mucoadhesion of different types of pectin with gastrointestinal (GI) mucoadhesion by dimensions of FTIR, contact angle and surface tension studies. The surface tension of dissimilar GI fluids was moderately the same and found to reduce after addition of mucin. The results obtained from this study established that the wetting actions and a chain inters diffusion takes place at the edge of mucin solution and pectin film which sustained the diffusion theory of mucoadhesion\textsuperscript{136}.  