International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781

A Review: On Buccal Tablets

Rucha Dattatray Kardile.

Submitted: 05-04-2023 Accepted: 15-04-2023

ABSTRACT:
Drug actions can be improved by novel drug delivery system, such as mucoadhesive system. Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and prolongs the residence time of the dosage form at the site of application. Bioadhesion may be defined as the state in which two materials, at least one of which is of a biological nature, are held together for extend periods of time by interfacial forces. Buccal mucosa is the preferred site for both systemic and local drug action. The mucosa has a rich blood supply and it relatively permeable.. This article briefly describes. Introduction to mucoadhesive drug delivery system, structure and function of oral mucosal membrane, buccal drug delivery and mucoadhesive property, theories and mechanism of mucoadhesion, mechanism to increase drug delivery through buccal route, buccal drug delivery system formulation design, characterization of buccal tablet, evaluation of buccal tablet.Buccal route of administration has many advantages such as improving patient compliance, bypassing. The GIT and hepatic first pass effect.

Keywords: Buccal tablet. Mucoadhesive Drug Release.

I. INTRODUCTION[1]:

Bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. When the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion. [1] Mucoadhesion has become an interesting topic for research over the last two decades, for its potential to optimize localized drug delivery, by retaining dosage forms at the site of action or systemic delivery, by retaining a formulation in intimate contact with the absorption site. [2] Mucoadhesive formulations are usually prepared with mucoadhesive polymers. First generation mucoadhesive polymers are hydrophilic in nature, having limited solubility in other solvents, forming high viscous liquid in water and pH sensitive. These characteristics present significant challenges in the formulation development of mucoadhesive formulations. [3-4] Mucoadhesive polymers have been used to formulate tablets, patches, or microparticles, with the adhesive polymer forming the matrix into which the drug is dispersed, or the barrier through which the drug must diffuse. Mucoadhesive ointments and pastes consist of powdered bioadhesive polymers incorporated into a hydrophobic base. Solutions tend to be viscous due to the nature of the mucoadhesive materials. Other proposed mucoadhesive formulations include gels, vaginal rods, pessaries and suppositories. [5]

ADVANTAGES OF MUCOADHESIVE BUCCALDRUG DELIVERY SYSTEMS: (8,9,11,12);Drugs administration via oral mucosa offers several advantages.

1. Ease of administration.
2. Termination of therapy is easy.
3. Permits localization of drug to the oral cavity for aprolonged period of time.
4. Can be administered to unconscious patients.
5. Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
6. A significant reduction in dose can be achieved thereby reducing dose related side effects.
7. Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestine can be administered by this route.
8. Drugs which show poor bioavailability via the oral route can be administered conveniently.
9. It offers a passive system of drug absorption and does not require any activation.
10. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
11. Systemic absorption is rapid.
12. This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781

13. The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.

Disadvantages of mucoadhesive buccal drug delivery:(11)

1. Drugs which are unstable at buccal pH cannot be administered

.2. Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor cannot be administered by this route.

3 Only drug with small dose requirement can be administered.

4 Only those drugs which are absorbed by passive diffusion can be administered by this route.3. Eating and drinking may become restricted.

5 There is an ever present possibility of the patient swallowing the dosage form.

6 Over hydration may leads to slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of the bioadhesive polymers.

Factors Influencing Drug Absorption From The Oral Cavity:(8)

As the oral mucosa is a highly vascular tissue, themain factors that influence drug absorption fromthe mouth are:a) The permeability of the oral mucosa to the drug.b) Physicochemical characteristics of the drug andc) Miscellaneous factors:

a) Permeability of the oral mucosa to drugs ($8_{,9,10}$) :Permeability of the buccal mucosa is 4-4000 timesgreater than that of the skin. As indicated by a widerange in this reported values, there are considerabledifferences in permeability between different regions ofthe oral cavity. In general, permeability of the oralmucosa decreases in the order of sublingual greater thanbuccal and buccal greater than palatal. This is based on the relative thickness and degree of keratinization ofthese tissues.The keratin layer is an effective barrier to penetration ofhuman skin by water soluble substances. Thepermeability barriers of the oral mucosa are supposed toreside within the superficial layers of the epithelium.

It has been shown that for some compounds the barrier topenetration is not the upper one third of the epithelium.Alfano and his coworkers studied the penetration ofendotoxins through non-keratinized oral mucosa. The results indicated that the basement membrane is a ratelimiting barrier to permeation.Some workers have suggested that the permeabilitybarrier in the oral mucosa is a result of intercellularmaterial derived from the so-called "Membrane Coating Granules" (MCGs). The barriers exist in the intermediate cell layers of many stratified epithelia andare of 100-300 nm in diameter1.Other factors which may affect the permeability ofmolecules include exogenous substances placed in themouth for their local effects, such as mouthwashes andtoothpastes, which contain surfactants and nutritional deficiencies

b) Physicochemical characteristics of the drug:[13]

The various physicochemical characters that play animportant role in absorption of drug from the oralcavity are considered below:

i) Molecular weight:Molecules penetrate the oral mucosa more rapidly than ions and smaller molecules more rapidly than larger molecules. In case of hydrophilic substances, the rate of absorption appears to be rapid for small molecules (molecular weight less than 75-100 Da), but permeability falls off rapidly as the molecular size increases.

ii) Degree of ionization: The average pH of saliva is 6.4. Because the unionizedform of a drug is the lipid-soluble-diffusible form, the pKa of the drug plays an important role in its absorption. Adequate absorption through the oralmucosa occurs if the pKais greater than 2 for an acid orless than 10 for a base.

.iii) Lipid solubility: A common way of assessing the lipid solubility of a drug is to measure its oil-water partition coefficient.Partition coefficient between 40-2000 is necessary for optimal drug absorption. If the partition co-efficient exceeds 2000, solubility in the saliva is insufficient to provide the concentration gradient necessary for drug absorption. That is in addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids for absorption.

.iv) pH of the saliva : The saliva pH ranges from 5.5 to 7 depending on theflow rate. At high flow rates, the sodium and bicarbonate concentration increases leading to and increase in the pH. Absorption is maximum at the unionized form of drug in pH of saliva.

c) Miscellaneous:i) Binding to oral mucosa: Systemic availability of drugs that bind to oral mucosa is poor.ii) Storage Compartment: A storage compartment in the buccal mucosa appearsto exist which is responsible for the slow absorption of drugs.iii) Thickness of oral epithelium: Sublingual

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781

absorption is faster than buccal since the epithelium of former region is thinner and immersed in a larger volume of saliva.

STRUCTURE AND FUNCTION OF ORAL MUCOSA.[11]

A stratified, squamous epithelium lines the oral cavity. Three different types of oral mucosa can be identified, i.e. masticatory, lining, and specialized mucosa, The .masticatory mucosa covers the gingiva and hard palate. It comprises a keratinized epithelium strongly attached to underlying tissues by a collagenous connective tissueand as such is able to withstand the abrasion and shearing forces of the masticatory process. The lining mucosa covers all other areas except the dorsal surface of the tongue and is covered by a nonkeratinized and hence more permeable epithelium. This mucosa is capable of elastic deformation and hence stretches to accommodate speech and masticationrequirements. The epithelium in humans varies .in thickness according to the region, e.g., floor of the mouth, 190 μm; hard palate, 310 μm; buccal,580 μm. The regional differences in morphology result in different permeability characteristics that have considerable influence on the design and siting of drug delivery systems. The differentiation process that gives rise to the regional differences occurs as the keratinocytes migrate from the buccal layers to the epithelial surface.Within the basal layer the keratinocytes are cuboidal or columnar with a surrounding plasma membrane and containing the usual intracellular organelles.A constant population of epithelial cells is maintained by the division of the basal keratinocytes at a rate equating to the desquamation of surface cells. Aging and disease can result in a loss of this balance, which can lead to a thickening (hypertrophia) or thinning (atrophia) of the epithelium. The media turnover time is slowerfor keratinized tissue, e.g., hard palate 24 days and buccal mucosa 13 days. Also relevant to the development of drug delivery systems are the surface areas of the human mouth occupied by keratinized (50%) and nonkeratinized (30%) tissues. Percentages are expressed with reference to the total surface area of the mouth. Desmosomes are still present between cells in the surface cell layer where intercellular spaces are both wide and irregular. Membrane-coating granules appear as approximately 200-nm spheres in the prickle cell layers.which subsequently fuse with cell membranes to discharge their contents in the superficial cell layer.

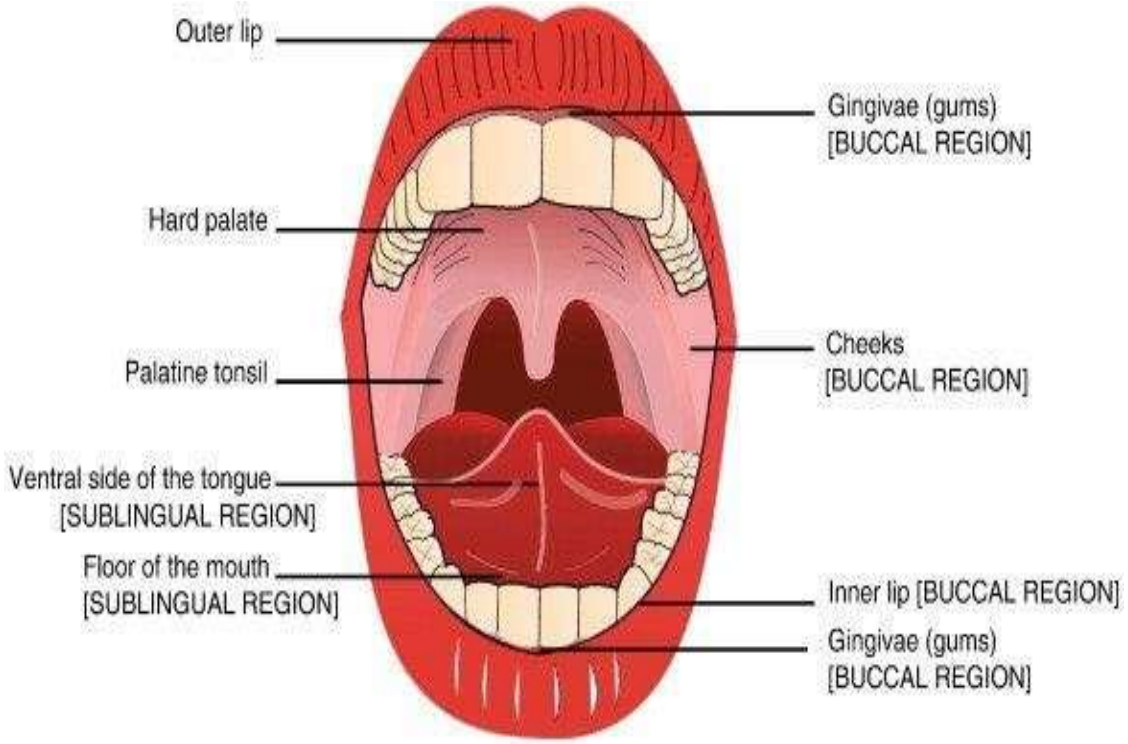
NATURE OF THE LIPID BARRIERS

Phospholipids, cholesterol, and glycosylceramides predominate with the phospholipid fraction composed of sphingomyelin and phosphatidyl-choline, ethanolamine, serine, and inositol. Triglycerides and cholesterol esters are also present with traces of fatty acids and ceramide. This lipid cocktail may well give rise to fluid lamellae.

SALIVA AND MUCUS:

Saliva is essentially a protective fluid for the tissues of the oral cavity. The major component of the mucous secretions are the soluble mucins that can associate to form oligomericmucins. These structures provide both viscoelastic and lubricating properties.Approximately 750 mL of saliva is produced daily in an adult with 60% from the submandibular glands, 30% from the parotids, 5% from the sublingual glands, and around 6% from the minor salivary glands found beneath the epithelium in most regions of the oral mucosa. Saliva is a mixture of serous secretions, which are high in glycosylated protein of low viscosity, and mucus secretions, which have a higher carbohydrate-to-protein ratio and little to no enzymatic activity. The parotids produce almost entirely serous secretions, the submandibular largely mucous secretions, while the sublingual glands produce a mixed serous/mucous secretion. Up to 70% of the total saliva mucin content arises from the minor salivary glands. Saliva contains a variety of esterases (mainly carboxylesterases) that may hydrolyzesusceptible drug ester groups. The mode of administration of tablets for the oral transmucosal delivery of drugs and their disintegration rate were shown to influence saliva secretion and, because of the link between esterase activity and saliva flow rate, saliva esterase activity. The pH of saliva has been reported to vary between 6.5 and 7.5.with the principle buffering function ascribed to the bicarbonate system and to a lesser extent phosphate and protein buffers.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781



Permeability:

It is found that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. As investigative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. The permeability of the oral mucosae is greater in buccal than sublingual. This is depend on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and nonkeratinized, the buccal thicker and (nonkeratinized, and the palatal intermediate in thickness but keratinized. Nowadays, it is believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane coating granules' (MCG). This barrier consists in the outermost 200μm of the superficial layer. Permeation studies are done by using a number of very large molecular weight tracers, like as horseradish peroxidase and lanthanum nitrate. When applied to the outer surface of the epithelium, these tracers penetrate only through outermost layer or two of cells. When applied to the submucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium. As per results, it seems clear that flattened surface cell layers present the main barrier to permeation, while the more isodiametric cell layers are relatively permeable. (6)

Novel buccal dosage forms: (13)

The novel type buccal dosage forms include buccal adhesive tablets, patches, films, semisolids (ointments and gels) and powders.

A. Buccal mucoadhesive tablets:

Buccal mucoadhesive tablets are dry dosage forms that have to be moistened prior to placing in contact with buccal mucosa. Example: a double layer tablet, consisting of adhesive matrix layer of HPC and polyacrylic acid with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate).

B. Patches and Films:

Buccal patches consists of two laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then cut into the required oval shape. A novel mucosal adhesive film called "Zilactin" - consisting of an alcoholic solution of HPC and three organic acids. The film which is applied to the oral mucosal can be retained in place for at least 12 hrs even when it is challenged with fluids.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781

C. Semisolid Preparations (Ointments and Gels):

Bioadhesive gels or ointments have less patient acceptability than solid bioadhesive dosage forms, and most of the dosage forms are used only for localized drug therapy within the oral cavity. One of the original oral mucoadhesive delivery systems -"orabase"- consists of finely ground pectin, gelatin and NaCMC dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 mins.

D. Powders:

HPC and beclomethasone in powder form when sprayed on to the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is seen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hrs

Mucoadhesion Theories:

Although the chemical and physical basis of mucoadhesion are not yet well understood, there are six classical theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon.

Electronic theory :Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength.

Adsorption theory:

According to the adsorption theory, the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in van der Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions. For example, hydrogen bonds are the prevalent interfacial for Absorption theory.According to this theory, after an initial contact between two surfaces, the material adheres because of surface force acting between the atoms in two surfaces. Two types of chemical bonds resulting from these forces can be distinguished as primary chemical bonds of covalent nature and Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

Diffusion theoryAccording to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact. The diffusion coefficient in terms depends on the value of molecular weight between cross linking and decreases significantly as the cross linking density increases.

Wetting theoryThe wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive among the substrate surface.

Cohesive theory

The cohesive theory proposes that the phenomena of bioadhesion are mainly due to intermolecular interaction amongst like molecule. Based upon the above theories, the process of bioadhesion can broadly be classified into two categories namely chemical (electron and absorption theory) and physical (wetting, diffusion and cohesive theory).

MUCOADHESIVE POLYMERS :(9,10,14)

Mucoadhesive polymers are water soluble and water insoluble polymers which are swellable networks jointed by cross linking agents. The polymers should possess optional polarity to make sure it is sufficiently wetted by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. An ideal polymer for a mucoadhesive drug delivery system should have the following characteristics.1. The polymer and its degradation products should be nontoxic and nonabsorbable in the gastrointestinal tract.2. It should be nonirritant to the mucus membrane.3. It should preferably form a strong noncovalent bond with the mucin epithelial cell surfaces.

- It should adhere quickly to moist tissue and should possess some site specificit.
- It should allow easy incorporation of the drug andoffer non hindrance to its release.
- The polymer must not decompose on storage or during shelf-life of the dosage form.
- The cost of polymer should not be high.Some of the mucoadhesive polymers along with their mucoadhesive property are summarized below:

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781

Evaluation of muco-adhesive buccal tablets:

A) Physiological Evaluation :(26)

Hardness and thickness: Hardness is an essential quality control check to be indicated for measuring the capacity of a tablet to withstand mechanical shocks while managing. The test was carried out for three tablets from each formulation using the Monsanto hardness tester; the expected mean and standard deviation values were calculated(26).The thickness of randomly selected three mucoadhesive buccal tablets turned into determined with the assist of vernier calipers. Individual tablets from every formulation have been chosen, and the mean results were noted(27)

Weight variation and friability:

Weight variation was performed for randomly selected 20 tablets from each batch using an electronic balance, and mean values were calculated. The percentage difference in the weight variation should be within the permissible limits and as per the USP(28,29)

Friability is a measure of the mechanical strength of tablets. By using Roche friabilator, a sample of pre-weighed tablets were placed in the plastic chamber then operated for 100 revolutions (4 min and 25 rpm), every rotation tablet wasdropped 6 inches distance, tablets have been reweighed; loss within the weight of the tablet is the measure of friability(30) and is expressed in percent as:

F (%) = [1-WF/Wo]x100

Where, Wo is the weight of the tablets before the test and

WF is the weight of the tablets after test

B) Biological Evaluations:(11)

a) **Mucoadhesion / Bioadhesion:**Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as the adhesion between polymer or copolymer and a biological membrane. In the case of polymer attached to the mucin layer of mucosal tissue, the term "mucoadhesion" is employed.

b) **Theories of Bioadhesion / Mucoadhesion:** (34)

Mucoadhesion is proposed to occur in three stages. Initially, an intimate contact must form between the mucoadhesive and mucus (i.e., they must "wet" each other) then the mucus / mucoadhesive macromolecules interpenetrate and finally the molecules interact with each other by secondary non-covalent bonds. The bonding occurs chiefly through both physical and chemical interactions. Physical or mechanical bonds result from entanglement of the adhesive material and the extended mucus chains. Secondary chemical bonds may be due to electrostatic interactions, hydrophobic interactions, hydrogen bonding and dispersion forces. Covalent bonding such as occurs with cyanoacrylates is also possible for mucoadhesion but is not yetcommon in pharmaceutical systems. Several theories of bioadhesion have been proposed to explain fundamental mechanism(s) of attachment. In a particular system one or more theories can equally well explain or contribute to the formation of bioadhesive bonds various theories propounded to explain mucoadhesion /bioadhesion are: Wetting theory Electronic theory Adsorption theory Diffusion theory Fracture theory

1. **Wetting Theory:**This theory best describes the adhesion of liquid or paste to a biological surface. The work of adhesion can be expressed in terms of surface and interfacial tension (γ) being defined as the energy per cm2 released when an interface is formed.According to Dupre's equation the work of adhesion is given by:

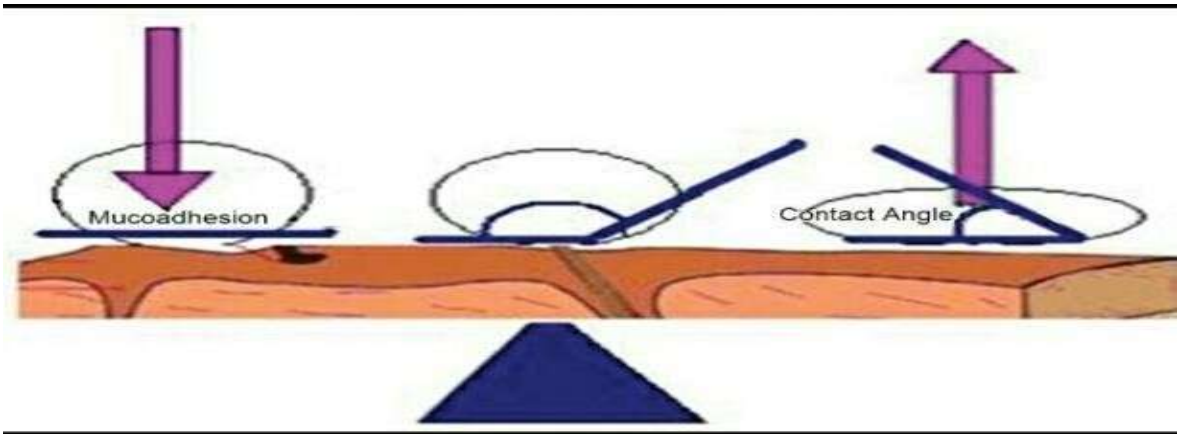
$Wa = \gamma A+\gamma b-\gamma B$ …1

Where the subscript A and B refer to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by: $We = 2\ \gamma A=2\ \gamma\ B$ …2For a bioadhesive material B spreading on a biological substrate. A the spreading coefficient is given by:

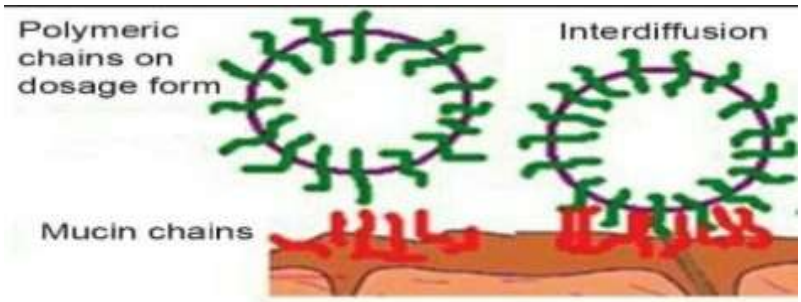
$SB/A = \gamma\ A -(\gamma\ B + \gamma\ AB)$ …3SB/A should be positive for a bioadhesive material to adhere to a biological membrane.

For a bioadhesive liquid B adhering to a biological membrane. A the contact angle is given by: $Cos\ \gamma - (\gamma A - \gamma AB / \gamma B)$.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781



2. **Diffusion Theory:**([33])Voyutski appears to be the first to discuss diffusion as a theory for adhesion. According to this theory the polymer chains and the mucus to a sufficient depth to create a semi-permanent adhesive bond. The polymer chains penetrate the mucus; the exact depth to which it penetrates to achieve sufficient mucoadhesion depends on diffusion coefficient, time of contact and other experimental variables. The diffusion coefficient depends on molecular weight and decreases rapidly as the cross-linking density increases. The molecular weight, chain flexibility, expanded nature of both the mucoadhesive and substrate as well as similarity in chemicals structure are required for good mucoadhesion

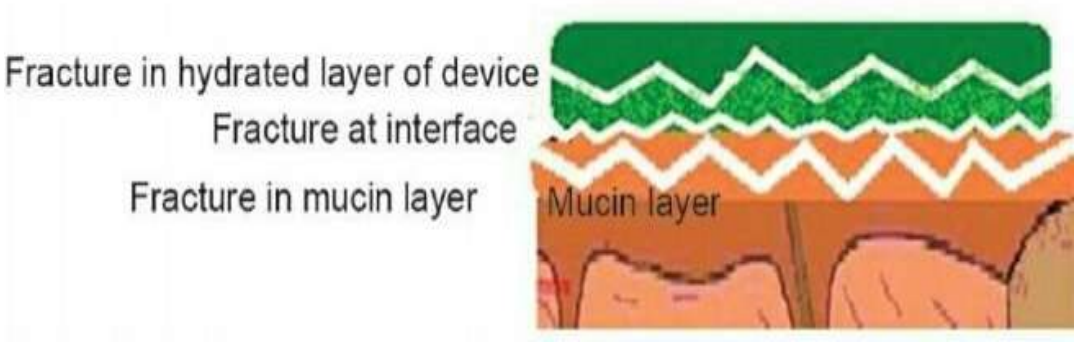


3. **Electronic Theory:**According to this theory electron transfer occurs on contact of adhesive polymer and the mucus glycoprotein network because of difference in their electronic structure. This results in the formation of electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer. The electronic theory of adhesion was suggested by Derjaguin and Smigla.

4. **Fracture Theory:**The fracture theory of adhesion is related to separation of two surfaces after adhesion. The work of fracture of an elastomer network Gc is given by:

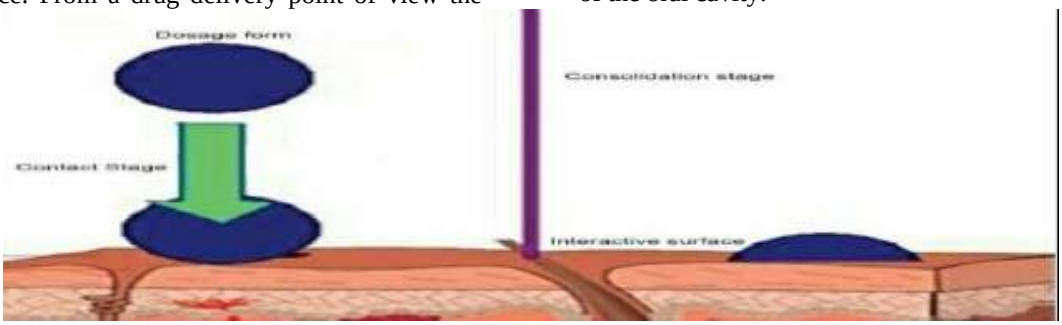
Gc = K McK is a constant dependent on the density of the polymer, effective mass, length and flexibility of a single mucin chain bond and bond dissociation energy. Gc of an elastomeric network increases with molecular weight Me of the network stands.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781



5. Adsorption Theory:

Adsorption theory has been described by Kembell and Hantsherger. According to this theory after an initial contact of two surfaces the material will adhere because of surface forces acting between the atoms in the two surfaces. Weak interaction of Vander Wall type plays an important role. However, if adsorption is due to chemical bonding i.e. chemisorption, then ionic, covalent and metallic bonds play an important role at the interface. From a drug delivery point of view the mechanism of mucoadhesion appears best explained by a combination of diffusion and electronic theory, although other mechanisms may simultaneously be operative at minor level. It may also be more appropriate to restrict the term "mucoadhesion" to describing the adhesion of hydrated dosage forms to those mucus membranes having a substantial mucus layer. The term"bioadhesion" or "mucosal adhesion" may be more suitable to describe adhesion to the mucosal of the oral cavity.



c. CHEMICAL EVALUATIONS: (11) The chemical standards of formulations, in to establish that drug is present in dose required to attain therapeutic level and the same level will be maintained during its storage life or shelf-life.a) Assay for Drug Content: This involves extraction of drug in suitable solvent from buccal tablet and determination of drug content in extract. The drug content should be in close proximity to be labeled or desired dose of drug.b) Drug-Excipient Interaction Studies: By use of various available spectrophotometric and chromatographic methods the incompatibility of drug with excipients or within different excipients can be detected. These interaction studies involves gross physical examination for organoleptic properties (discoloration, mal odour development, precipitation, polymorphism, development of bad taste), infrared spectra of drug versus formation IR spectra in same conditions and thin layer chromatography (TLC). Similarly, incompatibility in accelerated conditions or during storage must be thoroughly scrutinized.c) Accelerated Stability Studies :This involves placing the formulation in accelerated conditions of temperature and humidity in presence of air and determining the drug content at suitable intervals of time. By the data so obtained two conclusions can be drawn. Firstly, the shelf-life of formulation can be established, secondly any incompatibility within formulation, if present can be detected.

In vitro Mucoadhesive Study: (36,37)(40)

Mucoadhesive strength of the tablets was measured on a modified physical balance. Theapparatus consist of a modified double pan physical balance in which a lighter pan has replaced the right pan and left pan had been replaced by a Teflon cylinder (diameter and height) suspended by Teflon ring and copper wire. The left

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781

side of the balance was exactly 5 g heavier than the right side. Another Teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward protrusion of 2 cm height and 1.5 cm diameter on one side. This was kept in petri dish, which was then placed below the left hand set of the balance. Sheep buccal mucosa was used as the model membrane and phosphate buffer 6.8-pH solution was used as a moistening fluid. Sheep buccal mucosa was obtained from slaughterhouse was kept in Krebs˝s buffer at 370C for 2 hours. The underlying mucus membrane was separated and washes thoroughly with phosphate buffer 6.8-pH solution. It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in petri dish.Two side of the balance were made equal, before the study keeping a 5 g weight was placed on the right pan. Petri dish with Teflon block was kept below the left hand set up of the balance. The tablet was stuck on to the lower side of the hanging Teflon cylinder. Fivegram weight from the right pan was then removed. This lowered the Teflon cylinder along the tablet over the membrane with a weight of 5 g. this was kept undisturbed for five minutes. Then the weight on the right hand side was slowly added in an increment of 0.5 g until the tablet just separated from the membrane surface. The excess weight on the right pan i.e. total weight minus 5 g was taken as a measure of the mucoadhesive strength.
Forceofadhesion(N)=Mucoadhesivestrength/1000× 9.81 **Surface pH determination of Mucoadhesive tablets: (38)**

The surface pH of the tablets was determined in order to investigate the possibility of any side effects, on the oral cavity. As acidic or alkaline pH was found to cause irritation to the buccal mucosa, hence attempt was made to maintain surface pH close to the neutral pH. Mucoadhesive buccal tablets were swells for two hours on the surface of agar gel plate. The surface pH was measured by pH paper placed on the core surface of the swollen tablet.

Swelling study : (39)
The swelling rates of the mucoadhesive tablets of carvedilol were evaluated using a 1% w/v agar gel plate. An agar gel plate waschosen as the simple model of the mucosa can keep an amount of water that resembles the secreting fluid in and around the buccal mucosa required for bioadhesion and subsequent swelling of the formulation to provide adequate release of the drug. Method: - Four tablets of every batch were weighed and then kept on the agar gel plate surface in petridishes, which were placed in an incubator at 370C + 0.10C. Then, these all swollen tablets were weighed at different intervals; the excess water on the surface of tablets was removed by using filter paper. The average weight was
calculated and theswelling index was calculated by the formula,

$$\text{Swelling Index (S.I.)} = \{(Wt-Wo)/Wo\} \times 100$$

Where, S.I. = swelling index
Wt = average weight of tablet at time t
Wo = average weight of dry tablet before placing on the agar Plate

Data Analysis:(35)

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model using PSP-DISSO – v2 software. Based on the r-value, the best-fit model was selected.

1. Zero order kinetics:(18)Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and No equilibrium conditions are obtained can be represented by the following equation,

$$Q_t = Q_o + K_o t$$

Where Q t = amount of drug dissolved in time t.
Q o = initial amount of the drug in the solution and K o = zero order release constant.

2. **First order kinetics:**To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$\log Q_t = \log Q_o + K_1 t/2.303$$

Where
Qtis the amount of drug released in time t, Qo is the initial amount of drug in the solution and K1 is the first order release constant.

3. **Higuchi model:**Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

$$Q_t = K_H \cdot t1/2$$

Where Qt= amount of drug released in time t,
KH = Higuchi dissolution constant.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781

4. Krosmeyer and Peppas release model:(18)
To study this model the release rate data are fitted to the following equation,

$$Mt / M = K \cdot t^{n}$$

Where Mt / M is the fraction of drug release, K is the release constant,
t is the release time and n is the diffusional coefficient for the drug release that is dependent on the shape of the matrix.

Drug absorption pathways

The drug transport mechanism through the buccal mucosa involves two major routes: transcellular (intracellular) and paracellular (intercellular) pathways . Studies with microscopically visible tracers such as small proteins and dextrans suggest that the major pathway across stratified epithelium of large molecules is via the intercellular spaces where there is a barrier to penetration as a result of modifications of the intercellular substance in the superficial layers. It is generally recognized that the lipid matrix of the extracellular space plays an important role in the barrier function of the paracellular pathway, especially when the compounds such as peptides are hydrophilic and have a high molecular weight (21). The absorption potential of the buccal mucosa is influenced by the lipid solubility and molecular weight of the diffusant. Absorption of some drugs via the buccal mucosa is found to increase when carrier pH is lowered and decreased by an increase in pH (22). In general, for peptide drugs, permeation across the buccal epithelium is thought to be through paracellular route by passive diffusion. Recently, it was reported that the drugs having a monocarboxylic acid residue could be delivered into systemic circulation from the oral mucosa via its carrier (23).The permeability of oral mucosa and the efficacy of penetration enhancers have been investigated in numerous in vitro and in vivo models. Various kinds of diffusion cells, including continuous flow perfusion chambers, Ussing chambers, Franz diffusion cells and Grass–Sweetana, have been used to determine the permeability of oral mucosa (24). Cultured epithelial cell lines have also been developed as an in vitro model to study drug the transport and metabolism at biological barriers as well as to elucidate the possible mechanisms of action of penetration enhancers (25). Recently, TR146 cell culture model was suggested as a valuable in vitro model of human buccal mucosa for permeability and metabolism studies with enzymatically labile drugs, such as leu-enkefalin, intended for buccal drug delivery.

Mucoadhesion Theories:

Although the chemical and physical basis of mucoadhesion are not yet well understood, there are six classical theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon.

Electronic theory :

Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength.

Adsorption theory

According to the adsorption theory, the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in van der Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions. For example, hydrogen bonds are the prevalent interfacial for Absorption theory.According to this theory, after an initial contact between two surfaces, the material adheres because of surface force acting between the atoms in two surfaces. Two types of chemical bonds resulting from these forces can be distinguished as primary chemical bonds of covalent nature and Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

Diffusion theory

According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact. The diffusion coefficient in terms depends on the value of molecular weight between cross linking and decreases significantly as the cross linking density increases.

Wetting theory

The wetting theory postulates that if the contact angle of liquids on the substrate surface is

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781

lower, then there is a greater affinity for the liquid to the substrate surface. If two substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive among the substrate surface.

Cohesive theory

The cohesive theory proposes that the phenomena of bioadhesion are mainly due to intermolecular interaction amongst like molecule. Based upon the above theories, the process of bioadhesion can broadly be classified into two categories namely chemical (electron and absorption theory) and physical (wetting, diffusion and cohesive theory).

MUCOADHESIVE POLYMERS :(13,14,35)

Mucoadhesive polymers are water soluble and water insoluble polymers which are swellable networks jointed by cross linking agents. The polymers should possess optional polarity to make sure it is sufficiently wetted by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. An ideal polymer for a mucoadhesive drug delivery system should have the following characteristics.1. The polymer and its degradation products should be nontoxic and nonabsorbable in the gastrointestinal tract.2. It should be nonirritant to the mucus membrane.3. It should preferably form a strong noncovalent bond with the mucin epithelial cell surfaces.

- It should adhere quickly to moist tissue and should possess some site specificit.
- It should allow easy incorporation of the drug andoffer non hindrance to its release.
- The polymer must not decompose on storage or during shelf-life of the dosage form.
- The cost of polymer should not be high.Some of the mucoadhesive polymers along with their mucoadhesive property are summarized below:

Mucoadesive polymer with their Mucoadesive property:(35)

Sr. No	Polymer	Mucoadhesive property
1	Carbopol 934	+++
2	Carboxymethylcellulose	+++
3	Polycarbophil	+++
4	Tragacanth	+++
5	Sodium alginate	+++
6	Hydroxyethyl cellulose	+++
7	Hydroxypropyl methylcellulose	+++
8	Gum karaya	++
9	Guar gum	++
10	Polyvinylpyrrolidone	+
11	Polyethylene glycol	+
12	Hydroxypropyl cellulose	+

Note: +++ excellent, ++ fair, +poor

USES OF BUCCAL DRUG ADMINISTRATION :

Drug administration via buccal mucosa has certain limitations.

1. Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour; can not be administered by this route.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 1404-1417 www.ijprajournal.com ISSN: 2249-7781

2. Drugs, which are unstable at buccal pH can not be administered by this route.
3. Only drugs with small dose requirements can be administered.
4. Drugs may swallow with saliva and loses the advantages of buccal route.
5. Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
6. Eating and drinking may become restricted.
7. Swallowing of the formulation by the patient maybe possible.
8. Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

II. CONCLUSION

Mucoadhesive drug delivery system utilize the property of bioadhesion of certain water soluble polymer which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for an extended period of time. Many potential mucoadhesive systems are being investigated which may find their way into the market innear future. The main objective of using bioadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once daily dosing. Researchers will motivate for the establishment of some more naturally occurring polymer and the scenario of pharmaceutical development will change with fewer side effects due to biodegradability of natural occurring polymer.Development of mucoadhesive buccal drug delivery ofVildagliptin tablets is one of the alternative routes of administration and provide prolongs release. Mucoadhesive buccal tablets could be formulated using the drug, were evaluated for physicochemical parameters i.e., hardness, thickness,weight variation, friability, % ofdrug contents, surface pH, bio adhesive strength, % Swelling index, In-vitro drug release studies and In-vitro drug release kineticstudies. by using drug and polymer in the ratio of 1:1. The in-vitro drug release kinetics studies revealed that all the formulations fit to Peppas order kinetics followed by non-Fickian diffusion mechanism. Hence it can be concluded that the formulation H4 will be useful for buccal administration.

REFERENCE

[1]. Vogler EA. Water and the acute biological response to surfaces. J Biomater Sci Polym 1999;10:1015-1045.
[2]. Jones DS, Woolfson AD, Djokic J, Coulter WA. Development and mechanical characterization of bioadhesive semi-solid, polymeric systems containing tetracycline for the treatment of periodontal diseases. Pharm Res 1996;13:17341738.
[3]. Mizrahi B, Domb A. J. Mucoadhesive polymers for delivery of drugs to the oral cavity. Recent Pat Drug Deliv Formula 2008;2:108-119.
[4]. Salamat-Miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev 2005;57:1666-1691.
[5]. Woodley J. Bioadhesion new possibilities for drug administration. Clin Pharmacokinet 2001;40:77-84.
[6]. Tangri P,Sateesh Madhav NV.Oral mucoadhesive drug delivery system. Int J of biopharmaceutics 2011;2(1):36-46
[7]. 7.2021 IJCRT volume 9,Issue 4 April 2021 ISS: 2320-2882.
[8]. N.K. Jain "Controlled and Novel Drug Delivery", Ist Edition,CBS Publishers and Distributors, India, 2004, 52-74.
[9]. Swarbrick James, Boylan C. James, "Encyclopedia of Pharmaceutical Technology", IInd Edition, Vol. 2, Marcel Dekker, Inc., New York, 1990, 189-210.
[10]. Michael J. Rathbone, "Oral Mucosal Drug Delivery" Drug and Pharmaceutical sciences. IInd Edition , Marcel Dekker Inc., New York.1992.
[11]. Ayyappan T and Kasture P. V, A Review, "Development and in-vitro evaluation of a buccoadhesive of Ondansetron hydrochloride tablet formulation", Indian Drug, 43 (2) (2006), 92-95.
[12]. Anil K. Shingla, Manish Chawla and Amarjit Singh.; "Potential application of carbomer in oral Mucoadhesive controlled drug delivery system: A review"; Drug Development and Industrial Pharmacy, 2000, Vol. 26(9), 913-914.
[13]. Shojaei Amir H, Buccal Mucosa As A Route For Systemic Drug Delivery: A Review;J Pharm Pharmaceut Sci (www.ualberta.ca/~csps) 1998;1 (1):15-30

[14]. Amir H Shojaei, "Buccal mucosa as a route for systemic drug delivery", J. Pharm. Pharmaceut. Sci., 1998, June, 15:30, 15-30.
[15]. Research J. Science and technology 8 (2):April -June 2016.
[16]. Donthi MR, Dudhipala NR, Komalla DR, Suram D, Banala N. Preparation and evaluation of fixed combination of ketoprofen enteric coated and famotidine floating mini tablets by single unit encapsulation system. Journal of Bioequivalence & Bioavailability. 2015; 7(6):279.
[17]. Swamy SK, Reddy LN, Goud BA. Development and in vitro evaluation of bioadhesive buccal tablets of hydralazine hydrochloride. Int. J. Pharm. Educ. Res. 2014; 1:8-16.
[18]. Journal of Drug Delivery and Therapeutics 2021;11(1-s) :35-42, ISSN:2250 1177 CODEN(USA):JDDTAO.
[19]. Ayyappan T and Kasture P. V, A Review, "Development and in-vitro evaluation of a buccoadhesive of Ondansetron hydrochloride tablet formulation", Indian Drug, 43 (2) (2006), 92-95.
[20]. Anil K. Shingla, Manish Chawla and Amarjit Singh.; "Potential application of carbomer in oral Mucoadhesive controlled drug delivery system: A review"; Drug Development and Industrial Pharmacy, 2000, Vol. 26(9), 913-914.
[21]. Rathbone MJ, Tucker IG. Mechanisms, barriers and pathways of oral mucosal drug permeation. Adv. Drug Del. Rev. 1993; 13:1-22.(Chinna Reddy etal/DARU Journal of Pharmacutecial Science 2011-19(6)385-403.)
[22]. Nielsen HM, Rassing MR. TR146 cells grown on filters as a model of human buccal epithelium. Permeability enhancement by different pH value, different osmolarity value and bile salts. Int. J. Pharm. 1999; 185:215-225.
[23]. Utoguchi N, Watanabe Y, Suzuki T, Maeharai J, Matsumoto Y Matsumoto M. Carrier mediated transport of monocarboxylic acids in primary cultured epithelial cells from rabbit oral mucosa. Pharm. Res. 1997; 14:320-324.
[24]. Squier CA, Kremer MJ, Wertz PW. Continuous flow mucosal cells for measuring in vitro permeability of small tissue samples. J. Pharm. Sci. 1997; 86:82-84.
[25]. Brun PPHL, Fox PLA, Vries MED, Bodde HE. In vitro penetration of some βadrenoreceptor blocking drugs through porcine buccal mucosa. Int. J. Pharm. 1989; 49:141-145.
[26]. Reddy AB, Reddy ND. Development of multiple-unit floating drug delivery system of clarithromycin: formulation, in vitro dissolution by modified dissolution apparatus, in vivo radiographic studies in human volunteers. Drug research. 2017 Jul; 67(07):412-8.
[27]. Reddy, N.D., Chinna R. P., Sunil, R., && Madhusudan, R. Y.Development of floating matrix tablets of Ofloxacin and Ornidazole in combined dosage form: in vitro and in vivo evaluation in healthy human volunteers. Int J Drug Deli, 2012; 4:462-469.
[28]. Ramana MV, Nagada C, Himaja M. Design and evaluation of mucoadhesive buccal drug delivery systems containing metoprolol tartrate. Indian Journal of Pharmaceutical Sciences. 2007; 69(4): 515-518.
[29]. Narendar D, K. Someshwar, N. Arjun and Y. Madhusudan Rao. Quality by design approach for development and optimization of Quetiapine Fumarate effervescent floating matrix tablets for improved oral delivery. J Pharm Investigation., 2016; 46(3):253-263.
[30]. Rajitha R, Narendar D, Arjun N, Mahipal D and Nagaraj B. Colon delivery of naproxen: preparation, characterization and in vivoevaluation. IJPSN, 2016; 9(3):1-10.
[31]. Alekya T, Narendar D, Mahipal D, Arjun N, Nagaraj B. Design and evaluation of chronomodulated drug delivery of tramadol hydrochloride. Drug research. 2018 Mar; 68(03):174-80.
[32]. Arjun N, Narendar D, Sunitha K, Harika K, Madhusudan Rao Y and Nagaraj B. Development, evaluation and influence of formulation and process variables on in vitro performance of oral elementary osmotic device of atenolol. Int J Pharm Invest, 2016; 6(4):1-9.

[33]. IJCRT 2104235(international Journal of Creative Research throughts (IJCRT) www.ijcrt.org.
[34]. Swarbrick James, Boylan C. James, "Encyclopedia of Pharmaceutical Technology", IInd Edition, Vol. 10, Marcel Dekker, Inc., New York, 1990, 133.
[35]. Amir H Shojaei, "Buccal mucosa as a route for systemic drug delivery", J. Pharm. Pharmaceut. Sci., 1998, June, 15:30, 15-30.
[36]. Satyabrata B et al., Formulation and in vitro evaluation of mucoadhesive buccal tablets of Timolol maleate, Int J Pharm Biomed Res, 2010, 1(4), 129-134. 37.Ankarao et al., Formulation and evaluation of buccoadhesive bilayered tablets of carvedilol, ijpcbs, 2011, 1(1), 6-11.
[37]. Indian Pharmacopoeia, Controller of Publication, Delhi, Vol. II, 1996, A-144145.
[38]. Nielsen HM, Rassing MR, TR 146 cells grown on filters as a model of human buccal epithelium permeability of water, mannitol, testosterone and betaadrenoreceptor, antagonist: Comparison to human, monkey and porcine buccal mucosa, Ind. J. Pharm. Sci, 2000, 194,155-167
[39]. S.S.Kadam et al/ International Journal of Pharmacutecial Science (1),2014,67-80.