

# To Design and Develop Mucoadhesive Buccal Tablet of Vildagliptin: Review

**Dr. Bharat.V. Jain<sup>1</sup>, Miss. Kiran Jijabro Patil<sup>2</sup>, Dr. Sandip.R. Pawar<sup>3</sup>, Mr. Tanveer .Y. Shaikh<sup>4</sup>**

*Smt.Sspcop, Chopda, 425107, Maharashtra, India*

## Abstract

***Drug actions are improved by new drug delivery system, like mucoadhesive system. This method remains in close interaction with the absorption tissue, the membrane; release the medicine at the action site resulting in enhancement in both local and systemic effects. Oral route is that the most ancient furthermore as chosen by patient being suitable to require. However, perioral route has short comings like hepatic first pass breakdown and enzymatic degradation in Gastro Intestinal Tract which can remain a hindrance to the absorption of most proteins and peptides groups of medicine. The mucosa of the rima oris presents a formidable barrier to drug penetration, and one technique of optimizing drug delivery is by the use of adhesive dosage forms and also the mucosa contains a ridiculous blood supply and it's relatively permeable. Laminated devices are developed to attain sustained drug release.***

**Keyword: Mucoadhesive, Vildagliptin, Anti-Diabetic.**

## 1.INTRODUCTION

The Mucoadhesive drug delivery systems which apply the property of bio adhesion of assured polymers which develop adhesive on hydration and from now will be used for aiming a drug to a specific region of the body for extended periods of your time. During which two materials, a minimum of one amongst which is biotic, are held together by means of interfacial forces. The attachment can be between a man-made substantial and biotic substrate, like adhesion between a polymer and a biological membrane. Within the situation of polymer committed to the mucin layer of a mucosal tissue, the term "mucoadhesion" is employed.

Mucoadhesive drug delivery methods are delivered by many routes:-

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

### 1.1 Mucoadhesive Oral Drug Delivery Systems

This route is that the most desired route for the delivery of several drug. Drug delivery via the membranes of the oral fissure will be subdivided as:

- Sublingual delivery: this can be systemic delivery of medicine over the mucosal membranes lining the ground of the mouth.
- Buccal delivery: this is often drug administration through the mucosal membranes lining the cheeks (buccal mucosa).
- Local delivery: this is frequently drug delivery into the rima. Inside the oral mucosal cavity, the buccal area offers a horny route of administration for controlled systemic drug delivery

Buccal delivery is that the administration of medication through the mucosal membrane lining the cheeks. While the sublingual mucosa is thought to be further permeable than the buccal mucosa, the concluding is that the preferred route for systemic transmucosal drug delivery. This can be because the buccal mucosa has an expanse of smooth muscle and comparatively immobile mucosa, which makes it a more desirable region for retentive systems.

### **1.1.1 Advantages of Oral Mucoadhesive Drug Delivery Systems:**

- Extends the residence period of the dosage form at the site of absorption, therefore increases the bioavailability.
- Outstanding accessibility, quick onset of action.
- Quick absorption because of massive blood supply and good blood flow rates.
- Drug is secure from degradation in the acidic environs in the git.
- Enhanced patient compliance.

### **1.1.2 Disadvantages of Mucoadhesive Drug Delivery Systems:**

- Existence of local ulcerous effects due to extended interaction of the drug possessing ulcer genic property.
- One of the main limits in the improvement of oral mucosal delivery is the absence of a good model for in vitro screening to find drugs appropriate for such administration.
- Eating and Drinking is prohibited.

### **1.2. Structure and Function of Oral Mucosal Membrane:**

The outmost layer of oral mucosa is stratified squamous epithelium and below it, there's a basement membrane called lamina propria which is followed by the submucosa. It similarly covers many sensory receptors with the taste receptors of the tongue. Lamina propria, accommodates collagen fibres a supporting layer of connective tissues, vessel and smooth muscles. The epithelium may accommodate one layer (stomach, small and enormous intestine, bronchi) or multiple layers (oesophagus, vagina). Tissue have wet surface because of mucus which could be a viscous, gelatinous secretion and this mucus composed of glycoproteins, lipids and inorganic salts, and up to 95% water. Mucin (Glycoproteins) is the foremost main constituents of mucus and it's also accountable for gelatinous structure, cohesion, and anti-adhesive properties. Mucin contains three dimensional networks with sizable amount of loops. The most purposes of the mucus are to shield and lubricate the supportive epithelial layer.

#### **1.2.1 Permeability:**

The permeability of the buccal cavity is estimated to be 4-4000 times superior to the skin. In general, the permeability's of the oral cavity decrease within the order of sublingual greater than buccal, and buccal superior than palatal. This order relies on the comparative depth and degree of keratinization of those tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and also the palatal in-between in thickness. The penetrability barrier property of the oral cavity is mainly thanks to intracellular constituents resulting from the so termed "membrane coating granules" (MCGS). Latest evidence has exposed that passive diffusion is that the prime mechanism for the transport of medicine across the buccal mucosa while carrier mediated carriage has been reported to possess a little role. In buccal mucosa double routes of transportation are initiate one involves the transport of compounds through the intercellular space among the cells (Para cellular) and other involves passage into and across the cells. Alternative obstacle to drug permeability athwart buccal epithelium is enzymatic degradation

#### **1.2.2. Role of Saliva:**

- a. Protecting fluid for entirely tissues of the oral Mucosa.
- b. Constant mineralization and demineralization of the tooth coating.
- c. To hydrate oral mucosal dosage forms.

#### **1.2.3 Role of Mucus:**

- a. Made up of proteins and carbohydrates.
- b. Cell-cell linkage
- c. Lubrication
- d. Bio linkage of mucoadhesive drug delivery systems

### **1.3 Buccal Drug Delivery and Mucoadhesive Property:**

1. For the event of Buccal drug delivery methods, mucoadhesion of the method is that the important criteria. For correct and good mucoadhesion, mucoadhesive polymer are utilized in many various dosages form like drugs, patches, adhesive tape, films,

semisolids and powders. Several studies showed that addition of varied polymers to drug delivery systems like gums, increased the duration of attachment of the formulations to the mucous surface and also increased the efficacy.

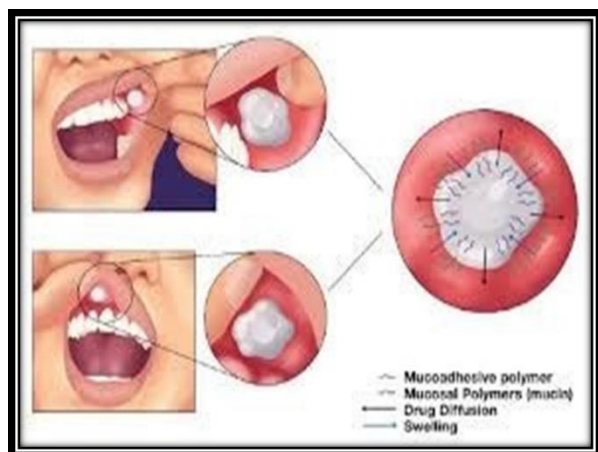


Fig. No.1. Design of Buccal Mucoadhesive Tablets

2. The polymers should possess following general physiochemical features so on function mucoadhesive polymers–

- Mainly anionic hydrophilicity with many hydrogen bond-forming groups.
- Polymer and its degradation products must be non-toxic, non-irritant and free from leachable contaminations.

3. Must have decent spreadability, wetting, swelling, solubility and biodegradability assets.

4. pH must be biocompatible and will possess decent viscoelastic properties..

### 1.4 Theories of Mucoadhesion

There are 6 overall concepts of adhesion, which are amended for the examination of mucoadhesion: -

#### 1.4.1 The electronic theory

Suggests that electron transmission occurs upon contact of adhering surfaces thanks to variances in their electric structure. This can be proposed to end in the

creation of an electrical dual layer at the interface, with consequent adhesion because of attractive forces.

#### 1.4.2 The wetting theory

It involves the flexibility of a fluid to extent suddenly on a surface as a precondition for the event of adhesion. The similarity of a liquid for a surface are often found by techniques like contact angle goniometry to live the contact angle of the fluid on the surface, through the overall rule existence that the lesser the contact angle, the larger the affinity of the liquid to the solid.

#### 1.4.3 The adsorption theory

Terms the addition of adhesives on the premise of hydrogen bonding and van der Waals' forces. It's been planned that these forces are the most contributors to the adhesive interaction. A subset of this, the chemisorption's theory, assumes a contact across the interface occurs as results of strong covalent bonding.

#### 1.4.4 The dispersion theory

This process is derived by concentration gradients and is plagued by the accessible molecular chain lengths and their mobility's. The penetration of interpenetration depends on the dispersion coefficient and therefore the time of contact. Satisfactory depth of penetration produces a semi-permanent adhesive bond.

#### 1.4.5 The mechanical theory

However, rough exteriors also provide an improved zone accessible for interaction together with an improved viscoelastic and plastic degeneracy of energy through joint failure, which are assumed to be most imperative in the bond process than a machine-driven effect

#### 1.4.6 The fracture theory

The fracture theory differs a bit from the opposite five there in it relays the adhesive power to the forces required for the detachment of the 2 involved surfaces after adhesion

### 1.5 Mechanisms of Mucoadhesion

The mechanism of mucoadhesion is often distributed in 2 steps,

1. Contact stage
2. Consolidation stage

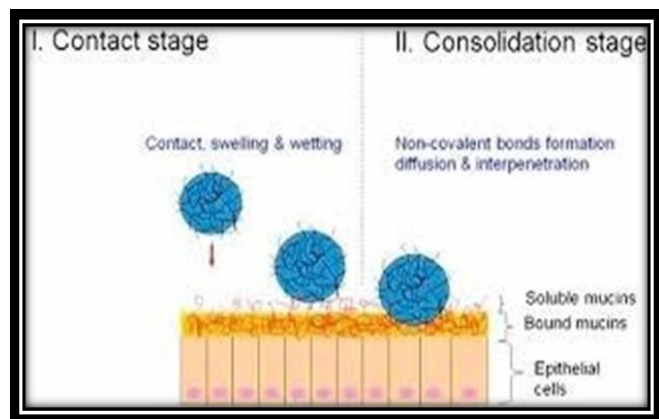


Fig.No 2 Mechanism of Mucoadhesion

The main phase is considered by the interaction among the mucoadhesive and consequently the tissue layer, with dispersion and swelling of the preparation, initiating its deep interaction with the mucus film. In specific cases, like for optical or vaginal preparations, the delivery system is automatically involved over in other cases, the deposition is encouraged by the aerodynamics of the organ to the membrane, the system is run, like for the nasal route. Inside the alliance step, the mucoadhesive constituents are triggered by the present of moisture. Moisture plasticizes the system, permitting the mucoadhesive particles to disturb free and to meet up by weak van der Waals and hydrogen bonds.

Basically, there are 2 theories explanation the consolidation stage:

1. The dispersion theory
2. The dehydration theory

Rendering to diffusion concept, the mucoadhesive particles and also the glycoproteins of the mucus equally interrelate by means of interpenetration of their chains and consequently the structure of secondary bonds. For this to need place the mucoadhesive method has types favoring both chemical and mechanical collaborations. Per dehydration theory, materials that are able to readily gelfie in an aqueous environment,

when placed involved with the mucus can cause its dehydration thanks to the difference of pressure level.

## 1.6 Mechanism to Increase Drug Delivery through Buccal Route:

### 1.6.1 Absorption enhancer:

The epithelium that lines the buccal mucosa could be a most important barrier to the absorption of medicine. Materials the help the permeation over buccal mucosa are denoted as absorption enhancers. However, the choice of enhancer and its efficiency depends on the physicochemical possessions of the drug, site of administration, nature of the additives and other excipients. In certain cases usage of enhancers together has revealed synergistic result than the separate enhancers the efficiency of enhancer in one site isn't same within the other site due to variances in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein connections are structural and functional properties. The foremost common absorption enhancers are zone, fatty acids, bile salts and surfactants like sodium dodecyl sulphate. Solutions/gels of chitosan were also found to push the transport of mannitol and fluorescent-labelled dextran's across a tissue culture perfect of the buccal epithelium though Glyceryl monoolete were reported to increase peptide absorption by a co-transport mechanism.

### 1.6.2 Mechanism:

Mechanisms by which diffusion enhancers are assumed to enhance mucosal absorption are as follows.

### 1.6.3 Changing mucus rheology:

Mucus prepare viscoelastic coat of varying thickness that distresses drug absorption. Further, saliva cover the mucus coatings also delays the absorption. Some infusion enhancers' act by decrease the viscosity of the mucus and saliva disables this barrier.

### 1.6.4 By Overcoming Enzymatic Barrier:

These acts by inhibiting various peptidase and proteases existing in buccal mucosa, thus overcoming the

enzymatic barrier. Additionally, changes in membrane fluidity also alter the enzymatic action indirectly.

**1.6.5 Increasing the thermodynamic activity of drug:**

This ends up in increased thermodynamic activity resulting better absorption. Surfactants like anionic, cationic, non-ionic and bile salts rise permeability of medication by perturbation of intercellular lipids while chelators perform by interfering with the calcium ions, fatty acids by growing fluidity of phospholipids and charged polymers by ionic interaction with charge on the mucosal exterior. Chitosan exhibits several favourable properties like biodegradability, bioavailability, and antifungal/antimicrobial properties additionally to its latent bio adhesion and absorption enhancer.

**Table.1. Examples of some of permeation enhancers:**

Sr.NO	Permeation enhancers:
1	Cyclodextrin
2	Lauric acid
3	Polyoxyethylene
4	Polysorbate 80
5	Sodium glycodeoxychlorate
6	Sodium lauryl sulphate
7	Sodium taurochlorate

**1.7 Formulation and Design:**

**1.7.1 General criteria for selection of drug candidate**

- Buccal bonding agent drug delivery systems with the scale 1–3 cm<sup>2</sup> and a regular dose of 25 mg or fewer are preferable.
- The maximum time of buccal delivery is approximately 4–8 hr.
- Drug necessity undergo 1st pass effect or it should have local effect in mouth cavity.

- Drugs with biological half-life 2-8 hr will generally be decent candidates for continuous release dosage forms.
- Local medication irritation caused at the the positioning of application is to be considered while choosing the drug.

**1.7.2 Pharmaceutical considerations:**

Good care has to be applied while developed a safe and effective buccal adhesive drug delivery device. Causes inducing drug release and penetration over buccal mucosa, organoleptic factors, and effects of additives wont to progress drug release pattern and absorption, the consequences of local drug irritation caused at the site of application are to be considered while plan a formulation.

**1.7.3 Muco adhesive polymers:**

Is an overall term inclined to define a really long particle containing of structural units and repeating units linked by covalent chemical bonds. The time springs from the Greek words: polys significance many, meaning parts. The important functions that differentiates polymers from other particles is that the repetition of the various matching, similar, or complementary molecular subunits in these chains. These subunits, the monomers, are small particles of little to moderate relative molecular mass, and are connected to every further during a chemical action called polymerization.

**1.7.4 Ideal Characteristics:**

Polymer and its deprivation products must be non-toxic, non-irritant and free from leachable contaminations.

- Should require good spread ability or wetting, swelling and solubility and biodegradability properties.
- Polymer must be decently available and its cost mustn't be high.
- Should exhibit local enzyme inhibition and penetration improvement properties.
- Should demonstrate acceptable Period.
- Should have optimum Mass.

**Table 2: Commercially available buccal adhesive formulations**

Commercial Name	Bio adhesive polymer	Dosage form
Buccastem	PVP, Xanthum gum, Locust bean gum	Tablet
Suscard	HPMC	Tablet
Gaviscon liquid	Sodium alginate	Oral liquid
Orabase	Pectin, gelatin	Oral paste
Corcodyl gel	HPMC	Oromucosal gel
Corlan pellets	Acacia	Oromucosal pellets
Fentanyl Oralet	CP 934, Sodium CMC	Lozenge

## 2. DRUG PROFILE

### 2.1 VILDAGLIPTIN

Vildagliptin is an orally anti-hyperglycemic agent used for the treat non-insulin dependent diabetes mellitus (NIDDM).

**2.1.2 Physico-chemical properties:**

**2.2.3 Physical state:** crystalline powder

**2.2.4 Color:** A White or slightly yellow color powder

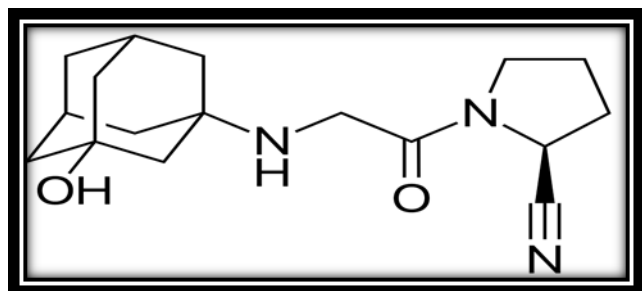
**2.2.5 Solubility:** Vildagliptin is Non-Hygroscopic soluble in organic solvents such as Ethanol DMSO and easily soluble in water

**2.2.6 Melting point:** 150° c

**2.2.7 Chemical name:** (S)-1- [N-(3-Hydroxy -1-adamantyl)glycyl] pyrrolidine-2-carbonitrile

**2.2.8 Molecular Formula** -C<sub>17</sub> H<sub>25</sub> N<sub>3</sub> O<sub>2</sub>

**2.2.9 Structure:**



**2.2.10 Molecular weight:** Average: 303.4

**2.2.11 Pka:** 14.71

**2.2.12 PH** -7.2

### 2.3 Pharmacokinetics of Vildagliptin:

#### 2.3.1 Absorption:

In a abstaining state, vildagliptin is quickly absorbed subsequent oral administration. Peak plasma concentrations are detected at 1.7 hrs. Following administration. Plasma concentrations of vildagliptin rise in an about dose-proportional manner. Absolutely the bioavailability is 85%

#### 2.3.2 Distribution:

The Protein binding of Vildagliptin is low (9.3%)

#### 2.3.3 Protein binding:

The plasma Protein binding of vildagliptin is 9.3% Vildagliptin allocates equally among plasma and red blood corpuscle

#### 2.3.4 Metabolism:

Nearby 69% of orally take vildagliptin is removed via metabolism not arbitrated by cytochrome P450 enzymes. Supported the outcomes of a rat study, DPP-4 contributes moderately to the hydrolysis of vildagliptin. Vildagliptin is break down to pharmacologically inactive cyano (57%) and amide (4%) hydrolysis products within

the kidney. LAY 151 (M20.7) could be a major inactive metabolite and an acid that's formed via hydrolysis of the cyano moiety: it accounts for 57% of the dose. Other mingling metabolites testified are an N-glucuronide (M20.2), an N-amide hydrolysis product (M15.3), two oxidation products, M21.6 and M20.9.9

**2.3.5 Route of Elimination:**

Vildagliptin is removed via metabolism. Subsequent oral administration, about 85% of the radiolabelled vildagliptin dose was eliminating waste in urine and about 15% of the dose was improved in feces. of the improved dosage in urine, around 23% accounted for the unaffected parent compound.

**2.3.6 Half-life:**

The Half-life after IV administration is 2Hrs

The Half Life after Oral Administration 3 Hrs

**2.3.7 Dose:** 50-100mg Daily once

**2.4 Pharmacodynamics:**

Established on the pharmacological properties, vildagliptin may be a second generation sulphonylureas which as a hypoglycemic agent. It encourages  $\beta$  cells of the islet of Langerhans within the pancreas to release insulin. It similarly improves peripheral insulin sensitivity. Overall, it potentiates insulin release and expands insulin dynamic

**2.5 Mechanism of Action:**

Glucagon-suchlike peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are incretin hormones that regulate glucose situations and maintain glucose homeostasis. it's estimated that the exertion of GLP-1 and GIP contribute over 70 to the insulin response to an oral glucose challenge. They stimulate insulin stashing in a veritably glucose-dependent manner via G-protein- coupled GIP and GLP-1 receptor signalling. also to their goods on insulin stashing, GLP-1 is also involved in promoting island neogenesis and isolation, likewise as cheapening pancreatic beta- cell apoptosis. Incretin hormones also plyextra-pancreatic goods, like

lipogenesis and myocardial function.<sup>3</sup> In type II DM, GLP-1 stashing is bloodied, and thus the insulinotropic effect of GIP is significantly lowered

**2.6 Contra-Indications:**

vildagliptin should be avoided if case have known history of mislike with drug or any of its constituents  
 2.7 Risk Group:

**2.7.1 Pregnancy:** Pregnant women shouldn't take vildagliptin.

**2.7.2 Breast-feeding:** Breast-feeding women shouldn't take vildagliptin.

**2.7.3 Children:** The care and efficiency of using this drug haven't been established for children

**2.7.4 Side-effects:** Headache Sweating ,Dizziness,backpain,weakness

**2.8 Drug -Interactions**

Amitriptyline	Amitriptyline may reduction the hypoglycemic Condition of Vildagliptin.
Amitriptylinoxide	Amitriptylinoxide may decline the hypoglycemic Condition of Vildagliptin.
Amoxapine	Amoxapine may reduction the hypoglycemic Condition of Vildagliptin.
Clomipramine	Clomipramine may decline the hypoglycemic Condition of Vildagliptin

**3. CONCLUSION**

In the present design of Vildagliptin mucoadhesive buccal medicines was equipped and estimated. As vildagliptin undergoes expansive first pass metabolism its bioavailability when given through Conventional route is 30 and (80x4) boluses. So, so as to boost its

bioavailability, to drop the dosing frequency and to bypass the primary pass metabolism the study has been planned to organize vildagliptin buccal tablets. The gift sample of vildagliptin was analyzed by colorimetric and spectrophotometric methods. The sample of Vildagliptin possesses analogous color, odor, and taste and texture given in officers. The temperature of carried sample was analyzed by capillary Fusion Method and located 180°C. The qualitative solubility of vildagliptin makes up my mind by colorimetric solvent systems.

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