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## Review on Acyclovir an Mucoadhesive Buccal Tablet

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### Abstract

As an alternative to Parentral injections Pharmaceutical researcher and scientist are trying to explore transdermal and the transmucosal route over the last few years. To overcome the deficiency associated with the other route of administration buccal region of oral cavity is an alternative target for the administration of choice of drug. By buccal route the drug are directly pass through into systemic circulation, less hepatic metabolism and high bioavailability. It can be concluded that by formulating mucoadhesive tablets of acyclovir its complete release can be ensured prior to absorption window and hence the problem of incomplete drug release and erratic absorption could be solved by increasing the retention of drug in GIT for a longer duration. Considering this research article shows the procedure of preformulatory aspects regarding mucoadhesive dosage form of Acyclovir.

**Keywords:** Acyclovir, Buccal drug delivery, First pass Metabolism, Mucoadhesion, Carbopol-934P, HPMC K100M, Mucoadhesive tablet.

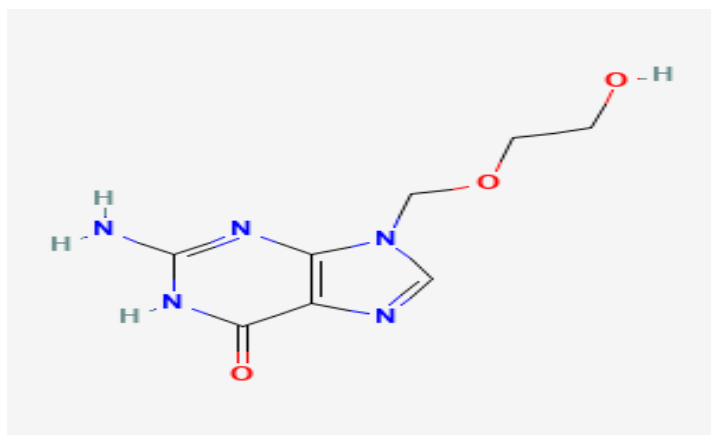
### Introduction

For systemic delivery, the oral route has been the preferred route of administration for many systemically active drugs due to the ease of administration, patient compliance and flexibility of formulation. Considering the other routes of drug delivery which has low patient compliance such as rectal, Vaginal, sublingual and nasal drug delivery for controlled release, the buccal mucosa has rich blood supply and it is relatively permeable. The buccal have ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability.

Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended period of time by interfacial forces. In pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion. In the early 1980s; academic research groups working in the ophthalmic field pioneered the concept of mucoadhesion as a new strategy to improve the efficacy of various drug delivery systems. Since then, the potential of mucoadhesive polymers was shown in ocular, nasal, vagina and buccal drug delivery systems leading to a significantly prolonged residence time of sustained release delivery systems on this mucosal membranes. In addition, the development of oral mucoadhesive delivery systems was always of great interest as delivery systems capable of adhering to certain gastrointestinal (GI) segments would offer various advantages.

Acyclovir [9-(2-hydroxyethoxymethyl)guanine] a synthetic purine nucleoside analog derived from guanine is the most widely used antiviral agent. It is effective in the treatment of herpes simplex virus (HSV), mainly HSV-1 and HSV-2 and Varicella Zoster Virus. According to the biopharmaceutical classification system, Acyclovir is categorized as a Class-III<sup>rd</sup> drug i.e. having high solubility and less permeability. The pharmacokinetic parameters of acyclovir, following oral administration, are generally highly variable. It has an average plasma half-life of about 3 hours on average in adults with normal renal function. Its absorption in the GIT is slow, variable and incomplete. The bioavailability of acyclovir after oral administration ranges from 10-30%. Approximately 80% of an oral dose is never absorbed and excreted through feces. Also the frequency of administration of acyclovir is high: being 200mg five times a day up to 400mg five times a day depending upon the type of infection.

### Chemical Nature



#### 1) Structure

2) **InChi key** : MKUXAQIIEYXACX-UHFFFAOYSA-N Computed by InChI 1.0.6 (PubChem release 2021.05.07)

3) **Molecular Formula** :

Molecular formula of Acyclovir is C<sub>8</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub>.

4) **Molecular Weight** : Molecular weight of Acyclovir is 225.20.

5) **IUPAC Name** : 2-amino-9-(2-hydroxyethoxymethyl)-1H-purin-6-one.

6) **Protein Binding** : 9-33% Protein bound in Plasma.

7) **Class** : Class-III Drug (High Solubility & Less Permeability)

8) **Half-life** : Clearance of Acyclovir varies from 2.5-3 hours depending upon Creatinine Clearance of Patient.

Plasma Half-Life of Acyclovir during Hemodialysis is about 5 hours.

9) **Solubility** : Slightly soluble in water, at 22-25°C and solubility ranges from 1.2 to 1.6mg/ml. very slightly soluble in ethanol (96%). Dissolve in dilute solutions of mineral acid and alkali hydroxide.

10) **Toxicity** : Acyclovir is Low toxic Potential.

11) **PH** : The Ph of reconstituted solution is approximately 11(Basic).

12) **Volume of Distribution** : Volume of Distribution of Acyclovir is 0.6L/Kg.

13) **Melting point** : Melting point of Acyclovir is 256.5°C.

14) **Maximum wavelength** : Maximum wavelength of Acyclovir is  $\lambda_{\max}$  256.5nm.

15) **Beer's Lambert range** : Beer's Lambert range of Acyclovir is 2-20ug/ml.

16) **Summary** : Aciclovir (ACV), also known as acyclovir, is an antiviral medication. It is primarily used for the treatment of herpes simplex virus infections, chickenpox, and shingles. Other uses include prevention of cytomegalovirus infections following transplant and severe complications of Epstein-Barr virus infection. It can be taken by mouth, applied as a cream, or injected. Acyclovir is a Guanosine analog used to treat herpes Simplex, Varicella Zoster, herpes Zoster.

17) **Establishment** : Acyclovir Patented in 1974 & approved for medical use in 1981.

18) **Brand Name** : Sitavig, Xerese, Zovirax

**19) Markated Formulations :** Acivir-400 DT Tablets (Cipla.Ltd), Herpes 5% Cream (Torrent Pharma Ltd), Acivir 500 Infusion (Cipla Ltd), Ocuvir Skin Cream (FDC Ltd).

Mucoadhesive Drug Delivery System in Oral Cavity : Drug delivery via the membranes.

**Mucoadhesive Drug Delivery System in Oral Cavity:** Drug delivery via the membranes of the oral cavity can be subdivided as follows:

- **Sublingual Delivery:** drugs are delivered through mucosal membrane lining the floor of mouth into systemic circulation.
- **Buccal Delivery:** drugs are delivered through mucosal membrane into systemic circulation by placing drug in between cheeks and gums.

**Local Delivery:** drugs are delivered into the oral cavity. Classification of Buccal Bioadhesive Dosage Forms:

1. Buccal Bioadhesive Tablets.
  2. Buccal Bioadhesive semisolids.
  3. Buccal Bioadhesive patch and films.
  4. Buccal Bioadhesive Powders.
- **Buccal Bioadhesive Tablets:** Buccal bioadhesive tablets are dry dosage forms that are to be moistened after placing in contact with buccal mucosa. Double and multilayered tablets are already formulated using bioadhesive polymers and excipients. These tablets are solid dosage forms that are prepared by the direct compression of powder and can be placed into contact with the oral mucosa and allowed to dissolve or adhere depending on the type of excipients incorporated into the dosage form. They can deliver drug multi- directionally into the oral cavity or to the mucosal surface.
  - **Buccal Bioadhesive Semisolid Dosage Forms:** Buccal bioadhesive semisolid dosage forms consist of finely powdered natural or synthetic polymers dispersed in a polyethylene or in aqueous solution example: Arabase.
  - **Buccal Bioadhesive Patches and Films:** Buccal bioadhesive patches consists of two ply laminates or multilayered thin film that are round or oval in shape, consisting of basically of bioadhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhesive films are formulated by incorporating the drug in alcohol solution of bioadhesive polymer.
  - **Buccal Bioadhesive Powder Dosage Forms:** Buccal bioadhesive powder dosage forms are a mixture of bioadhesive polymers and the drug and are sprayed onto the buccal mucosa the reduction in diastolic B.P after the administration of buccal tablet and buccal film of Nifedipine.

## Advantages of Buccal Drug Delivery System

The residence time of dosage form at the site of absorption is prolonged, hence increases the bioavailability.

Rapid onset of action.

High blood supply and good blood flow rate cause rapid absorption.

In the acidic medium of GIT drug is protected from degradation.

Improved patient compliance.

Nor painful neither irritations.

## Disadvantages of Buccal Drug Delivery System:

Prolonged contact of the drug possessin gulcerogenic property.

For the *in vitro* screening of drugs the oral mucosal delivery is lack of good model. This is the major drawback of this drug delivery.

Patient acceptability in terms to taste, irritancy and mouth feel is to be checked.

As compared to the sublingual membrane the buccal membrane is low permeability.

Also has smaller surface area.

The dissolution of drug due to continuous secretion of saliva (0.5-2 l/day).

**Overview of Buccal Mucosa:** Oral mucosa is dividing into two part epithelium and basement membrane and connective tissue.

- **Epithelium:** The epithelium serves as a protecting covering for the tissue and a barrier to the entry of foreign particle. It has thickness 500-800 $\mu$ m and consists of 40-50 layers of stratified sqamous epithelial cell.
- **Basement membrane and connective tissue:** Basement membrane is a boundary between the basal layer of epithelium and connective tissue. It consists of extracellular materials. The organisation which determines the mechanical stability, resistance to deformation, extendibility of tissue is made up of bulk of connective tissue.

## Mechanism of Mucosal Adhesion:

Several theories purposed the mechanism of mucoadhesion by the interaction of polymer and mucus. The mechanism of mucoadhesion is divided into two steps, first is contact step and second is consolidation step. In the first step the mucus layer come in contact with mucoadhesive and mucous membrane and the formulation swell and spread over mucus membrane. In the second consolidation step the moisture activates the mucoadhesive material, this plasticizes the system, this allow to mucoadhesive molecules to break free and link up by weak Vander walls and hydrogen bonds. The diffusion and dehydration theory explain the consolidation step.

The diffusion theory is the mutually interacting of mucoadhesive molecules and glycoprotein of mucus and building of secondary bonds by interpenetration of their chains (**Fig. 1**).

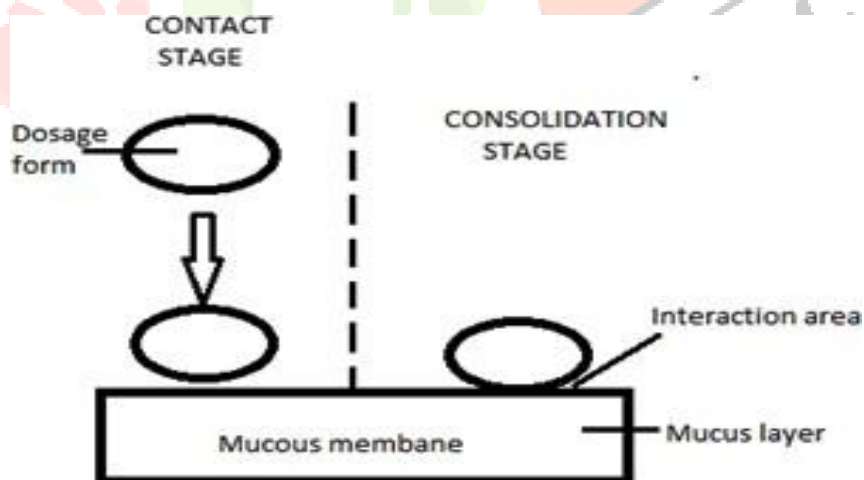


FIG. 1: TWO STEP OF MUCOADHESION PROCESS

According to the dehydration theory the material get gelify when it come in contact with the mucus in the aqueous environment. The drawing of water into the formulation due to concentration gradient until the osmotic balance is reached. This process increases the contact time of mucous membrane with the mixture of formulation and mucus. So it is not the interpenetration of macromolecules chains, it is the water motion that lead to the consolidation of the adhesive bond. The dehydration theory is not applicable for highly hydrated forms or solid formulations (Fig. 2).

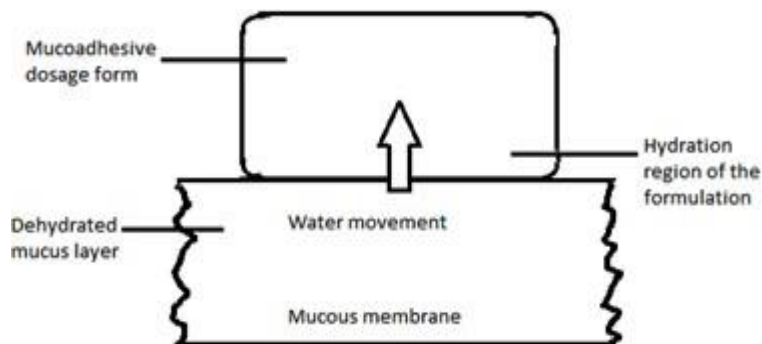


FIG. 2: DEHYDRATION THEORY OF MUCOADHESION

### Ideal characteristics of Buccal Adhesive Polymers:

- Polymer and its degradation products should be non-toxic, non-irritant and non-absorbable in the gastrointestinal tract.
- The polymer should have good properties like wetting, swelling, solubility and biodegradability properties.
- The polymer should show sufficient mechanical strength by adhere quickly to the buccal mucosa.
- The polymer should show sufficient tensile and shear strengths at the bioadhesive range.
- Polymer should not be of high cost and must be easily available.
- The polymer must have bioadhesive properties in both dry and liquid state.
- The polymer should have properties like penetration enhancement and local enzymatic inhibition.
- The polymer does not decompose during the shelf-life of dosage form and during storage.
- Should have narrow distribution and optimum molecular weight.
- The polymer should not have degree of suppression of bond forming group but should have sufficient cross-linkage.
- Should not produce the secondary infection in the dental caries.

### Frequently used Polymers in Formulations.

Ingredients	Category
Acyclovir	Antiviral
Carbopol-934P (CP)	Emulsifying, Stabilizing, Suspending, Thickening, agent.
HPMC K100M	Thickening, Coating Polymer, Bioadhesive, Binder, Coating, Suspending, Viscosity Increasing agent.
Dibasic calcium phosphate (DCP) (5%)	Diluents.
Talc (1%)	Lubricants.
Spray dried lactose (SPD)	Filler, Binders.
Moth bean Starch	Antioxidant.
Starch	Diluents, Disintegrant, Binder
Sodium Starch Glycolate	Disintegrant, Suspending, Gelling, agent.
Fumed Silicon Dioxide	Thickening, Anticaking, agent.
Microcrystalline Cellulose	Texturizer, Anti-Caking agent, Emulsifier, Extender, Bulking, agent.
Sodium saccharine	Sweetening agent.
Polyvinylpyrrolidone	Excellent Binder.
Carbopol-940	Lubricants, Gelling agent
HPMC K4M	Thickening, Binder
HPMC K15M	Thickening, Binder, Suspension aid in Coating.

The Property of tablet not only depends upon Concentration But also behavior of Polymer used.

### Preparation of mucoadhesive tablets

Table 1 enlists the composition of different mucoadhesive formulations prepared using varying amounts of polymers (i.e. CP and HPMC K100M). Dibasic calcium phosphate (DCP) was added as the pore forming agent, while spray dried lactose (SDL) acted as the diluent, with D the excipients were homogeneously blended and (450 mg, 10 mm diameter), using a single punch tablet compression machine.

- 1) Dry granulation.
- 2) Weight granulation.
- 3) Direct Compression.

## Evaluation of formulations Physical evaluation

Twenty tablets from each formulation were evaluated for uniformity in tablet weight and thickness. Since the tablet weight is 450 mg, 13 tablets from each formulation were examined for friability, using the Roche friabilator (Lab Hosp.) and hardness using a Monsanto type hardness tester.

Colour, Odour, Taste, Appearance, Bulk Density, Tap Density, Friability, Angle of repose, Hausner's Ratio, Carr's Index, Drug content, Dissolution Study.

## Content uniformity

Five tablets from each formulation were powdered individually and a quantity equivalent to 100 mg of acyclovir was accurately weighed and extracted with a suitable volume of 0.1N HCl. Each extract was suitably diluted and analyzed spectrophotometrically at 254 nm.

## In vitro drug release studies

Dissolution studies were performed on all the formulations prepared, in triplicate, employing United States Pharmacopoeia (USP)-23 paddle methods (Electrolab, TDT-06P Mumbai) and 0.1 N HCl as the dissolution medium at 50 rpm and  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ . A 0.5-mL aliquots of each test sample were withdrawn periodically at suitable time intervals and the volume was replaced with an equivalent amount of the plain dissolution medium. The samples were analyzed spectrophotometrically at 254 nm.

## Ex-Vivo mucoadhesion studies

The working of a double beam physical balance formed the basis of the bio-adhesion test apparatus fabricated (Figure 1). The right pan of a physical balance was removed and replaced with a steel cylinder hanged with a lightweight thread. The height of this total set-up was adjusted to accommodate a glass container below it, leaving a head space of about 0.5 cm in between. A steel block was fabricated with an upward protrusion on one of its face. This was kept inside the glass container, which was then placed below the right hand set-up of the balance. The two sides were then balanced.

The sheep mucus membrane was excised and washed (equilibrated at  $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$  for 30 min in phosphate buffer saline medium before the mucoadhesion evaluation study) and tied tightly with the mucosal side upwards, using a thread over the protrusion in the steel block. The block was then lowered into the glass container, which at  $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ , such that the buffer just reaching the surface of mucosal membrane and keeping it moist. This was then kept below the right hand set-up of the balance. The tablet was then stuck to the cylinder, using cyanoacrylate glue and the balance beam raised, A constant weight of 10 g was then placed over the steel block for the total contact period of 5 min. Mucoadhesive strength was then assessed by adding weights on the left pan till the tablet separated from the mucosal surface, in terms of the weight (in g) required to detach tablet from the membrane.



### Mucoadhesion test

### Conclusion :

The buccal drug delivery provides a several advantages for the delivery of drug. The buccal mucosa is rich in both vascular and lymphatic system through which drugs are directly drainage in systemic circulation and first-pass metabolism in liver and pre- systemic elimination in gastrointestinal tract are avoided. Additionally buccal drug can be terminated in case of toxicity thereby provide a safe and easy method for administration of drugs. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery and attractive alternative for delivery of potent peptide and protein drug molecules. For the evaluation of the buccal drugs both techniques of *in-vitro* or *in-vivo* are developed. Mucoadhesive dosage forms are the extended forms of the simple oral drug delivery system with large number of advantages over it. However with the recent developments of new formulation types such as mucoadhesive preparations and the use of peptides as drugs this number may increase in the future.

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