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Updated Review On Mucoadhesive Drug Delivery System

Author name: Mohini Manoharrao Murkute[1], Dr. Nishan N. Bobade[2], Shritesh Ramdas Bhoyar[3], Aachal H. Kolhe[4],Hemangi P. Vaishnav[5],

[1,3,4,5,]**M pharm , Vidyabharti college of pharmacy, Amravati, Maharashtra, India.**

[2]**Assistant professor, Department of pharmaceutics, Vidyabharti college of pharmacy, Amravati, Maharashtra, India.**

ABSTRACT:

Tablets intended for buccal membrane delivery that are mucoadhesive are unusual formulations with a number of technological advantages. However, the statistics used in its formulation are not standardised. This article's objective is to assess the data pertaining to the final quality of this technology through a scientific study and meta-analysis. Using a direct compression technique, buccal tablets were made using mucoadhesive polymers such chitosan, HPMC K4M, Na CMC, and soda alginate. Numerous metrics, including hardness, weight uniformity, thickness, percent friability, swelling index, mucoadhesive strength, surface pH, drug-excipient interaction research, drug content uniformity, and in vitro drug release study, were used to describe buccal tablets. Low bioavailability and significant drug depletion from the indefinite quantity type are the results of continual salivation and the swallowing that follows. Therefore, different transmucosal routes like nasal, rectal, vaginal, ocular and oral mucosae are being thought of as alternatives typical to standard to traditional} oral indefinite quantity forms for drug delivery to avoid the on top of disadvantages related to conventional oral delivery (i.e., tablets, capsules, syrups, etc.). of those routes of delivery, the buccal oral membrane has emerged in concert of the target sites for administration of medicine in an exceedingly large choice of indefinite quantity forms, particularly for those drugs targeted for local delivery in the oral cavity and systemic absorption. This review describes the structure of mucosal layer, mechanism of action of mucoadhesion, and evaluation parameters of tablets.

Key words: Buccal Tablets, Polymers, Mucoadhesion / Bioadhesion tablets, buccal administration.

1. INTRODUCTION:

The membrane of the mouth is incredibly totally different from the remainder of the duct and morphologically is a lot of the same as skin. though the porosity of skin is wide thought to be poor, it's not usually appreciated that the oral membrane lacks the nice porosity incontestable by the viscus. The buccal membrane is another for the oral route avoiding chiefly the first-pass metabolism and therefore the excessive degradation by the channel setting. These variations at intervals the willal[alimentary tract]digestive tube{digestive tract[GItract, duct,epithelial duct,canal,channel} can for the most part be attributed to the organization of the epithelia, that serve terribly totally different functions.1 A simple, single-layered epithelial tissue lines the abdomen, gut, and colon, that provides for a least transport distance for absorbents. In distinction, a stratified or multilayered epithelial tissue covers the mouth and passageway and, in common with skin, consists of layers with varied states of differentiation or maturation evident on progression from the basal cell layer to the surface. However, recently there has been interest in exploiting the mouth as a portal for delivering medicine to the circulation.8 Notwithstanding the comparatively poor porosity characteristics of the epithelial tissue, variety of benefits area unit offered by this route of administration. Foremost among these area unit the dodging of first-pass metabolism, easy access to the delivery web site, and therefore the chance of sustained drug delivery preponderantly via the buccal tissues.[8]

STRUCTURE AND FUNCTION OF ORAL MUCOSA:

In the oral cavity, a stratified, squamous epithelium is present. Oral mucosa can be divided into three categories: masticatory, lining, and specialized mucosa. The gingiva and hard palate are covered by the masticatory mucosa. Because it is made up of a keratinized epithelium that is firmly connected to the underlying tissues by a collagenous connective tissue, it can endure the abrasion and shearing forces of the masticatory process. The dorsal surface of the tongue is the only portion not covered by the lining mucosa, which is protected by a less keratinized and more porous epithelium. This mucosa can bend elastically and stretches to meet the demands of speaking and mastication. Human epithelium varies in thickness depending on the area, for example, the floor of the mouth is 190 µm thick and the hard palate is 310 µm thick; buccal,580µm.[3]

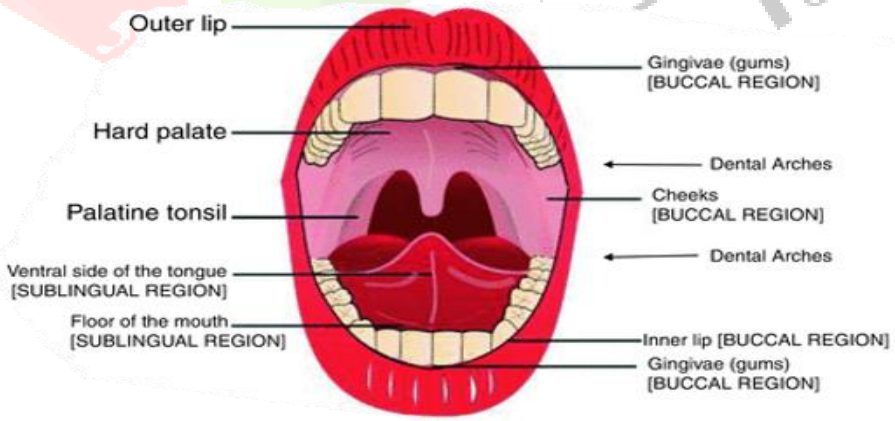

Figure-1: Different anatomical region of buccal cavity

Different permeability qualities caused by regional variations in morphology have a significant impact on the layout and positioning of drug delivery systems. As the keratinocytes move from the buccal layers to the epithelial surface, a differentiation process that results in regional variations takes place. The keratinocytes in

the basal layer are cuboidal or columnar, have a plasma membrane enclosing them, and contain the typical 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 slower for 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.[3]

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

In essence, saliva serves as a lubricant for the tissues of the mouth cavity. The soluble mucins, which may join together to create oligomeric mucins, make up the majority of the mucous secretions. Both viscoelastic and lubricating qualities are offered by these structures. In addition to establishing a permeability barrier atop the epithelia, salivary mucins also lubricate surface tissues and regulate a variety of host defensive mechanisms [33]. colonization of oral microbes in 1857. An adult produces 750 mL of saliva each day, with 60% coming from the submandibular glands, 30% from the parotids, 5% from the sublingual glands, and around 6% from the minor salivary glands.

Role of Saliva

1. Protective fluid for all tissues of the oral cavity.
2. Continuous mineralization / demineralization of the tooth enamel.
3. To hydrate oral mucosal dosage forms.

Role of Mucus

1. Made up of proteins and carbohydrates.
2. Cell-cell adhesion
3. Bioadhesion of mucoadhesive drug delivery systems

Physiological aspects and functions of the oral cavity:

The oral cavity is accountable for the following primary functions:

- As an entrance for absorbing food and water.
- Chewing, chewing, and mixing food.
- Food lubrication and bolus formation.
- Identification of ingested substances by the taste buds of the tongue.
- Initiation of carbohydrate and fat metabolism.
- Absorption of catabolic
- Product absorption and subsequent metabolism.
- Supports speech and breathing processes.
- Slight disinfection of the oral cavity with ingested material and saliva.[5]

Functions of the Mucus layer:

1. Protection: especially due to its hydrophobicity.
2. Barrier: The role of the mucus layer as a barrier in the tissue absorption of drugs and other substrates is well known as it affects drug bioavailability.
3. Adhesion: Mucus has strong adhesive properties and binds tightly to the epithelial cell surface as a continuous gel layer.
4. Lubrication: An important role of the mucus layer is to keep mucous membranes moist. Continued secretion of mucus from goblet cells is required to complement the removal of the mucus layer by digestion, bacterial degradation, and solubilization of mucin molecules.

Modes of Transport Across the Buccal Mucosa Physicochemical:

The properties of drugs are important for passive transport across the oral mucosa. For drug absorption through the buccal mucosa of the oral cavity, the dosage form must dissolve in saliva, thereby releasing the drug into solution. The drug then splits into the mucus that lines the buccal mucosa, at which point it becomes permeable. There are two routes by which passive drug transport occurs across the oral mucosa and reaches locally adjacent structures and the systemic circulation. Transcellular and paracellular routes allow drugs to reach the systemic circulation. Drugs can follow these two pathways simultaneously, but one pathway is favored over the other depending on the physicochemical properties of the molecule (molecular weight, polarity, etc.).

Advantages of Mucoadhesive Oral Drug Delivery

Oral mucosal drug delivery has several advantages:

1. Ease of emergency dosing and termination of therapy.
2. Allows the drug to be localized for an extended period of time.
3. It can be administered to unconscious and trauma patients.
4. Provides an excellent route for systemic delivery of drugs that bypasses first-pass metabolism, thereby providing greater bioavailability.
5. Substantial dose reductions can be achieved by reducing doses, experiencing dose-related side effects, and eliminating peak-trough profiles.
6. Drugs that are labile in the acidic environment of the stomach or that are destroyed by the enzymatic or alkaline environment of the intestine can be administered.
7. Provides a passive drug absorption system.
8. Can be unidirectional to ensure buccal absorption only.
9. Allows local alteration of tissue permeability, inhibition of protease activity, or reduction of immune response. Therefore, selective use of therapeutic agents such as peptides, proteins, and ionized species can be achieved.
10. Flexibility of physical state, shape, size and surface.
11. Maximization of absorption due to intimate contact with the absorbing membrane and reduced diffusion barrier.[6]

Disadvantages of mucoadhesive buccal drug delivery:

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.
5. Eating and drinking may become restricted.
6. There is an ever-present possibility of the patient swallowing the dosage form.
7. 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.[5]

2. FACTORS AFFECTING ORAL ABSORPTION

a. **Membrane factors**:

The oral mucosa's low permeability in comparison to other mucosal membranes is a significant barrier to the successful use of the mouth cavity as a location for systemic medication administration. Understanding the numerous membranes that line the oral cavity's anatomy, physiology, and composition is crucial. It may aid in locating and choosing the best delivery location, which would then have an impact on delivery system design. The oral cavity has regional variations and contains both keratinized and nonkeratinized tissues of varied thickness and composition. Of the entire surface area of the mouth, keratinized and nonkeratinized tissue make up around 50% and 30%, respectively. The buccal (area: 50.2 cm 3, thickness: 500–600 tm) and The sublingual region (thickness: 100-200 tm, area: 26.5 cm 3) is nonkeratinized and mostly composed of polar lipids, including cholesterol sulphate and glucosylceramides. The palatal (thickness: 250 m, area: 20.1 cm) and gingival (thickness: 200 tm) mucosa are keratinized and exhibit a lipid pattern dominated by neutral lipids, such as ceramides.

ENVIRONMENTAL ISSUES:

1. **Saliva**

All of the oral cavity's tissues are protected by saliva, which is often only important for oral health when either its quantity is diminished or its quality deteriorates. These alterations, notably a decrease in salivation, are brought on by a number of systemic illnesses, such as diabetes, as well as by medical interventions like radiation therapy or prescription medications. Saliva shields soft tissues from certain chemicals and abrasion from abrasive surfaces. It permits the enamel of teeth to continue to mineralize after they erupt and helps the enamel demineralize in the early stages of dental caries. By assisting or hindering bacterial adhesion to the surfaces of the oral cavity, it also has a significant antibacterial effect. It may be necessary to take into account the changes that occur in saliva during illness conditions and as a result of therapies since these changes may also impact the effectiveness of medication delivery via this channel.

2. **Salivary glands**

Three pairs of major salivary glands—the parotid, submandibular, and sublingual—each located outside the oral cavity, as well as smaller glands located in the tissues lining the majority of the oral cavity—produce saliva.

A. Transcellular Pathway

As demonstrated in Figure 2, drug transport via the basolateral membrane, intracellular space, and apical cell membrane all contribute to drug penetration into epithelial cells. The transcellular pathway, also referred to as the intracellular pathway, is where drugs are transported between cells. Small molecules can be transported passively (via diffusion or pH partition) through this pathway, while macromolecules can be transported actively (via carrier-mediated diffusion or facilitated diffusion). The complicated process of drug transport across the transcellular route depends on a number of the drug's physical

properties, including as its molecular weight, lipophilicity, hydrogen bond potential, charge, and conformation. Small hydrophobic molecules and lipophilic substances are mostly transported through cells. The quantity of membrane coating granules present in the intracellular spaces has an inverse relationship with transcellular diffusion. Hydrophilic medications will have trouble penetrating the cell membrane due to a low partition coefficient because the cell membrane is lipophilic by nature. The interaction of the absorption-enhancing excipients with the phospholipid bilayer and the integrated proteins can improve the passive transport of hydrophilic substances, including macromolecules like polypeptides and proteins. A few tiny, water-soluble molecules can pass through the aqueous pores in the cell membrane, including amino acids, ions, and sugar.

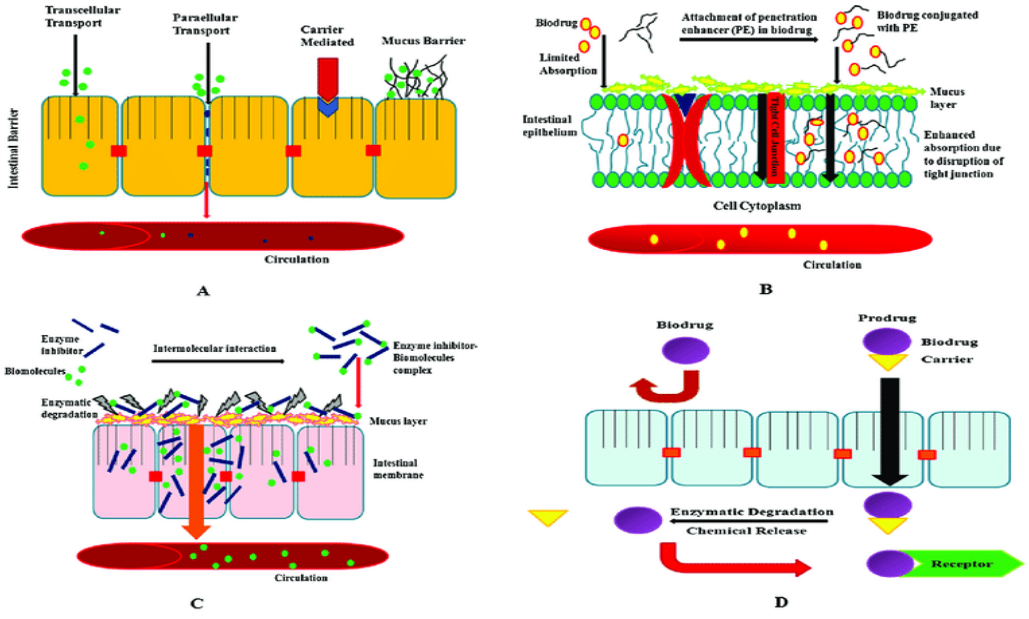

Figure 2: Transport pathways of molecules across buccal tissue

A. Paracellular Pathway

Figure 3 illustrates how drug transport through lipids or in-between epithelial cells can also cause drug penetration through epithelial cells. The paracellular pathway, often referred to as the intercellular pathway, may be divided into two categories: a hydrophilic pathway connected to the polar head groups of lipid bilayers and a hydrophobic pathway that mostly travels through the lipid bilayer. The major barriers to permeability for chemicals delivered via the paracellular pathway are tortuosity and intercellular space. A chemical that is equally soluble in lipid and aqueous mediums can enter cells via paracellular and transcellular routes.

Drug delivery via buccal route: When a dosage form is put in the outer vestibule between the buccal mucosa and gingival, buccal delivery, or medication release, can take place. The following are some benefits and other details of this route that are clarified.

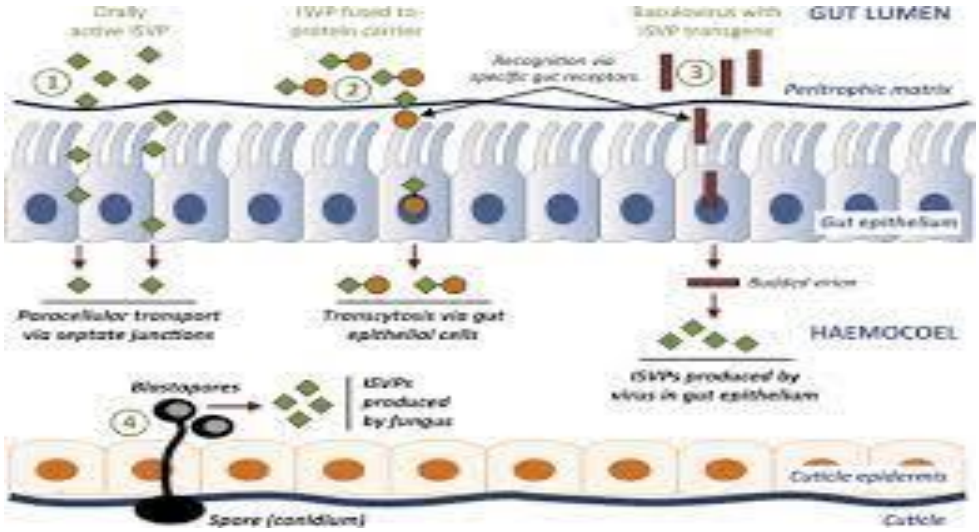

Figure 3: paracellular pathway

Drug delivery via buccal route :

Drug release known as buccal delivery can take place when a dosage form is inserted in the outer vestibule between the buccal mucosa and gingival. The following list of benefits and other features of this route are explained.

3. **IDEAL CHARACTERISTICS OF BUCCAL ADHASIVE DRUG DELIVERY SYSTEM [8]:**
    - Should facilitate the rate of drug absorption
    - Should not cause any inconvenience or irritation to the patient
    - Should stick to the site of attachment for a few hours
    - Should discharge the medication in a controlled manner and
    - Allow medication to be released in a single direction, toward the mucosa.

Advantages of mucoadhesive buccal drug delivery:[9]

Drug administration via the oral mucosa offers several advantages

1. Easy of administration and termination of therapy in emergency.
2. Permits localization of the drug for a prolonged period of time.
3. Can be administered to unconscious and trauma patients.
4. Offers an excellent route for the systemic delivery of drug which by passes first pass metabolism, there by offering a greater bioavailability.
5. By significantly reducing the dose, dose-dependent side effects can be avoided, and the peak-valley profile is eliminated.
6. It is possible to administer medications that are unstable in the acidic environment of the stomach or that are ruined by the enzymatic or alkaline environment of the intestine.It offers a passive system for drug absorption.

7. It is possible to make it one-way to guarantee exclusively buccal absorption.
8. It enables localised changes to tissue permeability, protease activity suppression, or immunogenic response decrease. As a result, it is possible to utilise therapeutic substances such peptides, proteins, and ionised species in a targeted manner.
9. Flexibility in terms of surface, size, form, and condition.Increased absorption rate as a result of reduced diffusion barriers and close contact with the absorbing membrane.

Disadvantages of mucoadhesive buccal drug delivery:[12]

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.
5. Eating and drinking may become restricted.
6. There is an ever present possibility of the patient swallowing the dosage form.
7. 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.

4. EVALUATION TEST

1) Preformulation study

a. Identification of drug

Identification of drug was carried out by melting point determination, infrared spectroscopy, and differential scanning calorimetry (DSC).

- **Melting point method**
- Melting point testing is the best way to authenticate a medication. This approach recorded the temperature at which the sample melted and finished solidifying. MCN's melting point was tested and determined to be between 186 and 188°C. It was verified by the MCN melting point, which was found to be between 182 and 186 °C (Clark's study, Vol. 2, 1282).
- **Fourier transform infrared (FTIR) spectroscopy**
- The drug's solid-state IR spectra was evaluated using potassium bromide dispersion. The bands have been given in cm^{-1}. An FTIR spectrometer-430 was used to produce the miconazole nitrate FTIR spectrum (8400S, Shimadzu, Japan).
- **Melting point determination by DSC**

b. DSC was used to ascertain the drug's melting point. DSC (Cyrus-DSC Wipro GE DX-300, Perkin Elmer, USA) was used to acquire the thermograms for MCN.Drug-excipient interaction study[9].

- **FTIR spectroscopy:**

➢ Infrared spectroscopy is used to predict possible drug-excipients interaction study.

As potassium bromide dispersion, the drug's IR spectra was studied in the solid form.

Pre-washed, dried, and sealed aluminium paper ampoules were used to hold the medication, polymers, and physical combination. The sealed ampoules were stored in a stability chamber for 28 days at 37 0.5 °C (TH 90 G, Thermolab, Thane, India)

5. EVALUATION OF TABLET PROPERTIES:[22,23]

Different quality control parameters of all the batches of mucoadhesive aceclofenac tablets were analyzed by adopting the method described in Indian Pharmacopeia 2018

Weight variation

Twenty tablets (n = 20) from each batch were weighed using electronic balance and their average weight was calculated.

Friability

Each batch's twenty tablets (n = 20) were weighed and placed in the friabilator drum. Tablets were found after the friabilator had completed 100 rotations. After being cleaned of dust, the tablets were weighed. The Eq was used to calculate friability. (1).

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Hardness:

A hardness tester was used to assess the hardness of 20 tablets (n = 20). The tablet was positioned in-between the hardness tester's two probes, one of which is moveable and the other immovable. Then the moveable probe delivered the force. It was noted how much effort it took to shatter the tablet, which was interpreted as the tablet's hardness.

Drug content:

% drug content can be stuied from monographs of Indian pharmacopoiea

Mucoadhesion test

The model mucosal surface for the bioadhesion test was porcine buccal mucosa. The buccal mucosa was taken from the pig just after it was killed, brought to the lab in tyrode solution, and stored at room temperature. Strips of swine buccal mucosa that had been cleaned with tyrode solution were used to calculate the mucoadhesive forces of the tablets (n = 3).

The modified pan balance, as seen in Figure 1, was used to estimate the mucoadhesive forces of the tablets. Cut into the proper sized pieces, the porcine buccal mucosa was then Tyrode solution rinsed. A piece of buccal mucosa (c) was attached to the upper glass vial (b) during the test using a rubber band. The exposed mucosa was 1 cm in diameter. The buccal mucosa vial (b) was kept in the tyrode solution for 10 minutes at room temperature (37 °C). The buccal mucosa vial (b) and another vial (e) were then set on an adjusted height that was equivalent to the tablet's thickness. The pill was added to the lower vial using bilayered adhesive tape.. In order for the buccal mucosa and the adhesive tape to adhere to one another, both vials were moved. The tablets were consistently adhered to the buccal mucosa for 2 minutes using a steady force supplied to the top vial, after which the upper vial was linked to the balance. The right pan's weight was then gradually increased by 0.5 g until two vials separated from one another. The mucoadhesive strength was measured as the total weight (g), to remove [20].

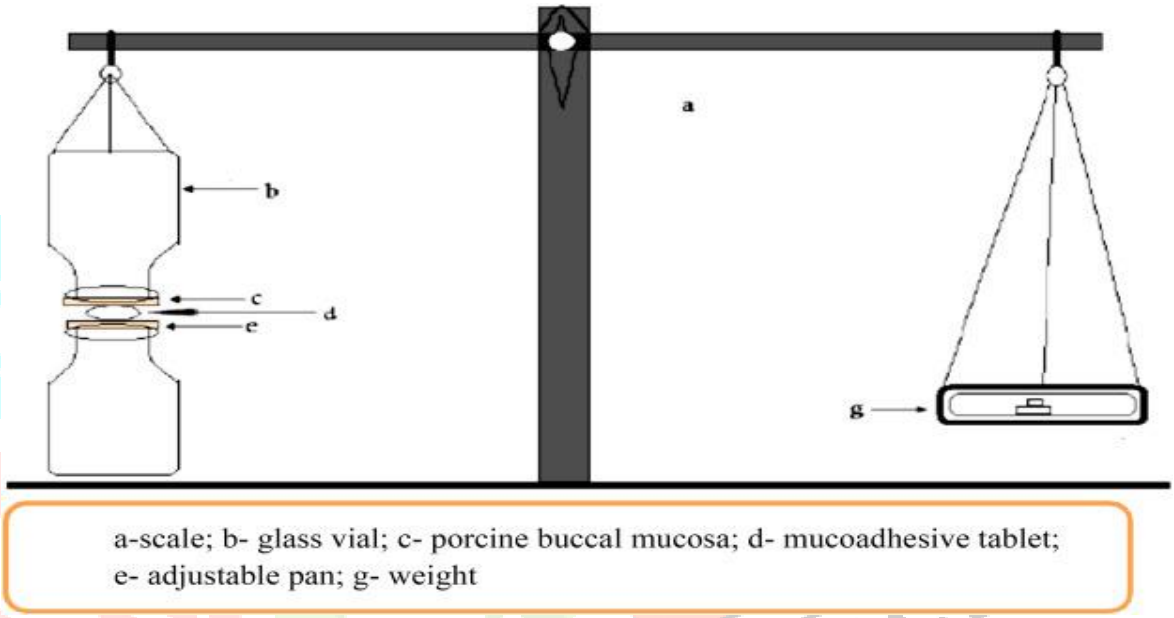

Figure 1. General lay out of modified pan balance used for the determination of mucoadhesion force of newly formulated tablets

Swelling test

Three pills were taken from each batch, weighed separately (W1), and then put in separate Petri plates with 5 mL of pH 6.8 phosphate buffer. They were withdrawn from the petri dish at intervals of 1, 2, 4, and 8 hours, and extra water was wiped away using filter paper. The swelled tablets were reweighed (W2), and the Eq. (3) was used to determine the percentage of hydration for each tablet. [21]

$$\text{Swellining index} = [(W2 - W1)\,/W1\ X100]$$

In vitro dissolution studies

Utilizing the procedure outlined in the Indian Pharmacopoeia 2018 [18], in vitro dissolution was carried out. Studying the release of the medication from the pills was done using a spinning paddle. The disintegration investigation used six pills (n = 6). 900 mL of pH 7.4 phosphate buffer made up the dissolving media. At a speed of 50 rpm, the test was run at 37 °C with a 0.5 °C tolerance. Every hour, a total of 5 mL of samples were taken out and the same volume was replaced with new medium. The buffer was used to dilute the removed samples to 50 mL. Using a UV spectrophotometer set at 273 nm, the samples were filtered and examined. Utilizing the calibration curve of the standard medication, the percentage of drug release was computed The stock solution of aceclofenac was produced in phosphate buffer pH 7.4 at a concentration of 32 mg/mL for the calibration curve. A UV spectrophotometer was used to detect the absorbance at a wavelength of 273 nm after diluting the stock solution to create solutions with concentrations ranging from 0.25 g/mL to 13 g/mL.

Compatibility study

A FTIR spectrophotometer was used to perform infrared (IR) spectroscopy for the medicine excipient compatibility investigation, and the spectrum was acquired in the wavelength range of 1950 to 400 cm1. A sample (of a medicine or a combination of a drug and excipients) was dissolved in potassium bromide and crushed into discs using a hydraulic press at a pressure of 5 tonnes for 5 minutes. The spectrum was acquired when the pellet was positioned in the direction of the light [13].

Surface pH analyses

The pHs of three tablets (n = 3) from each batch were determined. The tablets were placed in distilled water with a pH of 6.8 and allowed to swell for up to two hours. The pH of the tablet's surface was determined using a pH metre. Surface pH analysesThree pills (n = 3) from each batch had their pHs measured. The pills were submerged in distilled water kept at a pH of 6.8 and let up to two hours to swell. A pH metre electrode was used to determine the tablet's surface pH [21].

Determination of release kinetics

To comprehend the rate and mechanism of aceclofenac release from the manufactured batches, dissolution data were fitted to zero-order, first-order, Higuchi, Hixson Crowell, and Korsmeyer-Peppas equations. The mechanism where the medication release rate is unrelated to its concentration is known as a zero-order release rate. The first-order release rate, which plots log cumulative percent medication remaining vs time, defines the release from the system as concentration-dependentHiguchi's model defines the drug's release from an insoluble matrix as a square root of a process based on Fickian diffusion that is time-dependent. The cumulative proportion of drug release is shown against the square root of time in Higuchi's root kinetics. When the surface area and diameter of the particles or tablets change, the Hixson Crowell model is used to describe how the

medicine is released from the system. The statistical indicator R2 indicates how closely the data resemble the fitted regression line. The value that was most desired was one that was close to 1 [13, 22].

Statistical analysis:

Values were expressed as mean ± SD. Post Hoc Tukey test followed by one way-ANOVA was used for statistical analysis of mucoadhesive strength of different batches. P-value less than 0.05 ($p<0.05$) was considered to be statistically significant. For kinetic studies Kinet DS 3.0 software was used.

6. CONCLUSION:

The buccal medication administration method offers a number of benefits for the drug delivery process. The buccal mucosa is rich in both vascular and lymphatic system, allowing for direct medication drainage into systemic circulation while avoiding first-pass hepatic processing and presystemic gastrointestinal evacuation. Additionally, buccal medication delivery is safe and simple since it may be stopped in the event of toxicity. The administration of powerful peptide and protein therapeutic molecules via the buccal cavity is a promising topic for future research with the goal of systemic distribution. Both in-vitro and in-vivo assessment methods for buccal medicines are being developed. Extended versions of the straightforward oral medication administration mechanism, mucoadhesive dosage forms have several benefits over it. The usage of peptides as medications and the recent development of novel formulation types, such as mucoadhesive formulations, may cause this number to rise in the future.

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