IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 5, Issue 3, January 2025

Mucoadhesive Drug Delivery System

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Abstract*: Mucoadhesive drug delivery systems engage with the mucus layer on the mucosal epithelial surface, interacting with mucin molecules and prolonging the duration of the dosage form at the absorption site. Mucoadhesive drug delivery systems are components of controlled drug delivery systems as well as novel drug delivery systems. Administering drugs through the absorptive mucosa in various readily accessible body cavities such as ocularnasal, buccal, rectal, and vaginal mucosa presents notable benefits compared to peroral administration for systemic effects. Mucoadhesive drug delivery systems extend the duration the dosage form remains at the application or absorption site. They promote close interaction between the dosage form and the underlying absorption surface, thereby enhancing the drug's therapeutic effectiveness.*

Keywords: Mucoadhesive drug delivery

I. INTRODUCTION

Mucoadhesive drug delivery system :

Mucoadhesive drug delivery system interact with the mucus layer covering the mucosal epithelial surface ,and mucin molecules and increase the residence time of dosage form at the site of the absorption.Mucoadhesive drug delivery system is a part of controlled drug delivery system and also novel drug delivery system .Delivery of drug via the absorptive mucosa in various easily accessible body cavities like ocular, nasal, buccal, rectal and vaginal mucosa, offered distinct advantages over peroral administration for systemic effect.

Mucoadhesive drug delivery systems prolong the residence time of the dosage form at the site of application or absorption. They facilitate an intimate contact of the dosage form with the underlying absorption surface and thus improve the therapeutic performance of the drug.

Dosage forms designed for mucoadhesive drug delivery should be small and flexible enough to be acceptable for patients and should not cause irritation. Other desired characteristics of a mucoadhesive dosage form include high drug loading capacity, controlled drug release (preferably unidirectional release). good mucoadhesive properties, smooth surface, tastelessness, and convenient application.

A number of relevant mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides. Including thyrotropin- releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been delivered via the mucosal route, albeit with relatively low bioavailability (0.1-5%), owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the mucosa.

The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period but this is not sufficient to get sustained therapeutic effect. They may be cleared from the site of absorption before emptying the drug content. Instead, the mucoadhesive dosage form will serve both the purposes of sustain release and presence of dosage form at the site of absorption. In this regard, our review is high lighting few aspects of mucoadhesive drug delivery systems.

History

Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology. Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface. The American Society of Testing and Materials has defined it as the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both.

In the previous few years, the mucoadhesive drug delivery system has become popular and gained substantial attention for both local and systemic medication delivery due to exceptional approachability, avoiding first-pass metabolism, large blood supply, safety, and more patient acceptability with enhanced and better treatment.

In 1947 T.R. Jacoby et al., made attempts to formulate bio-adhesive ointment of Penicillin using gum tragacanth for topical purpose which led to an idea for the development of pharmaceutical formulations using mucoadhesive polymers

Muco-adhesion is a process of interaction between the mucus layer and bioadhesive polymer covering the body tissues where wetting. absorption, and interpenetration of the involved biopolymer chains take place.

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 periods of time by interfacial forces. Mucoadhesion is a state in which one of the materials is mucosal membrane (biological) and another is nature or synthetic polymer that are held together for an extended period of time by interfacial force.

Antomy and physiology of mucosa:-

Oral mucosal locale is adhesive in nature and goes about as a lubricant, which is permitting the cells to move comparative with each other with less grating. There are four sites are as follow:

- Buccal cavity
- The sublingual areal
- The palate
- Gingival region

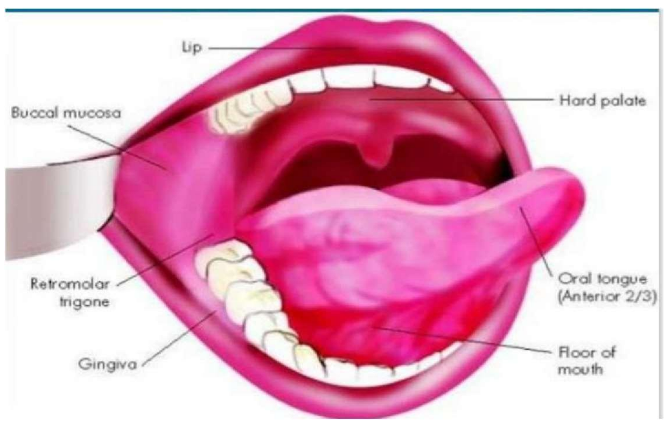

Fig no :-1

Mucoadhesive inner layers called mucosa & inner epithelial cell lining is covered with visco- elastic fluid called mucus. Mucus is translucent and viscid secretion which forms a thin continuous gel adherent to mucosal epithelial surface. Composed of water and mucin. Thickness varies from 40 µm to 300 µm.

Composition:

Water-95%

Glycoprotein and lipids -0.5-5%

Mineral salts-1%

Free proteins-0.5-1%

- The oral cavity is lined by thick dense & multilayered mucous membrane of highly vascularized nature.
- Drug penetrating into the membrane passes through net of capillaries & arteries and reaches the systemic circulation.

There are mainly three functional zones of oral mucosa:-

1) 1-Masticatory mucosa - (25% of the total oral mucosa) covers the gingiva and hard palate. Keratinized epithelium.

DOI: 10.48175/IJARSCT-23115

2) 2-Lining mucosa- (60% of the total oral mucosa) covers the lips, cheeks, soft palate, lower surface of the tongue and the floor of the oral cavity. Non-keratinized mucosa.

3) 3-The specialized mucosa-(15% of the total oral mucosa) is found on the dorsum of the tongue, high selective keratinization

Mucosal druge delivery system :- Ideal characteristics

Provide rapid adherence to the mucosal membrane without changing the physical property of the delivery system.

1. Should not interference with the controlled/sustained release of the active agent.
2. Should be biodegradable and should not produce any toxic by products.
3. Should enhance the penetration of the active agent.
4. The formulation stays longer at the delivery site & improve the bioavailability of API.
5. The specific bioadhesive molecules can allows for the targeting of particular sites or tissues. Use of penetration enhancers allows modification of tissue permeability for absorption of macromolecules, such as peptides and proteins. Ex. Sodium glycocholate,
Sodium taurocholate and L-lysophosphotidyl choline
6. Use of protease inhibitors in the mucoadhesive dosage forms resulted in better absorption of peptides and proteins

Mucoadhesive drug transport structures may be brought via way of diverse routes:-

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

II. LITERATURE REVIEW

1) Andrews, G. P., Laverty, T. P., & Jones, D. S. (2009)
Discusses the development and application of mucoadhesive polymeric platforms for controlled drug delivery, focusing on polymer selection and formulation strategies.

2) Peppas, N. A., & Buri, P. A. (1985)
Provides foundational insights into the mechanisms of bioadhesion and the interfacial interactions between polymers and mucosal tissues.

3) Smart, J. D. (2005)
Explores the basic principles and underlying mechanisms of mucoadhesion, emphasizing factors influencing adhesion strength.

4) Sogias, I. A., Khutoryanskiy, V. V., & Williams, A. C. (2008)
Highlights the properties of chitosan as a mucoadhesive polymer, focusing on its interactions with mucosal surfaces and potential applications.

5) George, M., & Abraham, T. E. (2006)
Reviews the use of alginate and other polyionic hydrocolloids for protein drug delivery through mucoadhesive systems.

6) Lehr, C. M. (2000)
Examines the role of biodegradable polymers, such as pectin and hyaluronic acid, in mucosal drug delivery systems.

7) Shojaei, A. H. (1998)
Discusses the buccal mucosa as a route for systemic drug delivery and the design considerations for mucoadhesive formulations.

8) Bernkop-Schnürch, A. (2005)
Introduces thiolated polymers (thiomers) as a new class of mucoadhesive materials with improved adhesion and drug delivery potential.

9) Hägerström, H., et al. (2003)
Investigates the development of mucoadhesive formulations for oral drug delivery, focusing on bioadhesive strength and drug release kinetics.

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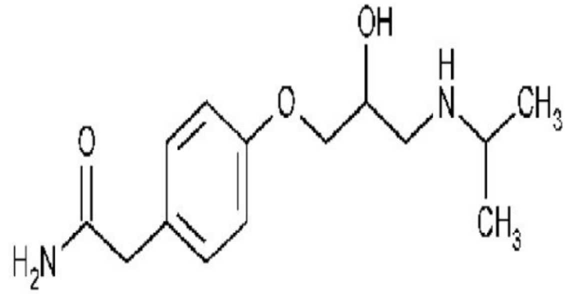
III. DRUG PROFILE



- Drug Name: Atenolol
- The molecular formula of Atenolol is: C14H22N2O3
- The molecular weight of Atenolol is 266.33 g/mol.
- Structural Formula: (±)-4-[2-Hydroxy-3-(isopropylamino)propoxy]phenol
- IUPAC Name: (RS)-2-[4-[2-Hydroxy-3-(propan-2- ylamino)propoxy]phenol

Classification:

- Therapeutic: Beta-blocker, Anti-hypertensive, Anti-anginal
- Pharmacological: Beta-1 selective adrenergic receptor blocker

Indications:

1. Hypertension (essential or renovascular)
2. Angina pectoris (stable or unstable)
3. Arrhythmias (atrial fibrillation, atrial flutter)
4. Myocardial infarction (prophylaxis)
5. Migraine prophylaxis

Mechanism of Action:

1. Selectively blocks beta-1 receptors in the heart
2. Reduces heart rate, contractility, and cardiac output
3. Decreases renin-angiotensin-aldosterone system activity

Pharmacokinetics:

1. Absorption: 50% oral bioavailability
2. Distribution: Widely distributed, high lipid solubility
3. Metabolism: Hepatic (extensive first-pass metabolism)
4. Elimination: Urine (85-100%), feces (0-15%)
5. Half-life: 6-7 hours

Dosage and Administration:

1. Hypertension: 50-100 mg once daily
2. Angina: 50-100 mg once daily
3. Arrhythmias: 25-100 mg once daily

4. Myocardial infarction: 50-100 mg once daily

Contraindications:
1. Severe asthma or COPD
2. Heart failure (uncompensated)
3. Second- or third-degree AV block
4. Pregnancy and lactation
5. Hypersensitivity to Atenolol

Side Effects:
Common:
1. Dizziness
2. Headache
3. Nausea
4. Bradycardia

Less common:
1. Hypotension
2. Heart failure
3. Bronchospasm
4. Masked hypoglycemia

Interactions:
1. Beta-agonists (e.g., salbutamol)
2. Calcium channel blockers (e.g., verapamil)
3. Antiarrhythmics (e.g., amiodarone)
4. Nonsteroidal anti-inflammatory drugs (NSAIDs)

Precautions:
1. Diabetes mellitus
2. Renal impairment
3. Hepatic impairment
4. Thyrotoxicosis

Monitoring Parameters:
1. Blood pressure
2. Heart rate
3. Electrocardiogram (ECG)
4. Renal function tests
5. Liver function tests

Storage and Handling:
1. Store at room temperature (20-25°C)
2. Protect from light and moisture

Aim and objectives
Aim
- Atenolol is a beta blocker medicine, used to treat high blood pressure (hypertension) and irregular heartbeats (arrhythmia).

- If you have high blood pressure, taking atenolol helps prevent future heart disease, heart attacks and strokes.
- It can also be used to prevent chest pain caused by angina.
- Atenolol works by slowing down your heart rate, making it easier for your heart to pump blood around your body.
- Atenolol is sometimes prescribed to prevent migrainesand help with anxiety.
- This medicine is only available on prescription.
- It comes as tablets or as a liquid that you swallow. It can also be given as an injection, but this is usually done in hospital.
- Atenolol can also be mixed with other medicines such as nifedipine (brand name Tenif). It it's mixed with chlortalidone it's called co-tenidone or by the brand names Tenoret or Tenoertic.

Objectives:

- Identify the FDA-approved indications and off-label uses for atenolol, including hypertension, angina, and acute myocardial infarction.
- Screen patients for asthma, bronchospasm, or obstructive airway diseases to assess the use of atenolol or consider alternative therapies.
- Assess patients for adverse drug reactions and recognize potential complications, such as masked symptoms of hypoglycemia and thyrotoxicosis.
- Collaborate within the interprofessional healthcare team to coordinate comprehensive care for patients using atenolol, ensuring regular renal function, heart rate, and blood pressure monitoring

Principle

Principle of mucoadhesive drug delivery system is based on mucoadhesion and bioadhesion – Immobilization of drug delivery systems at the biological surface by the process of adhesion is referred to as “bioadhesion”.

Bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. When these adhesive interactions are confined to the mucus layer lining of mucosal surface, this is called as “mucoadhesion”.

The interfacial molecular attractive forces between the two surfaces of the biological substrate and the natural or synthetic polymers allows the polymer to adhere to the biological surface for an extended period of time.

Provide site specific action by localization of the drug delivery system in a particular region. Close contact with the mucosa increases of the residence time of the pharmaceutical dosage form in a specific region.

Plan Of Work :

A. Literature survey .
B. Selection and procurement of Drug and Excipients.
C. Preformulation of study of Drug and Excipients .
1. Angle of repose
2. Bulk density
3. Tapped density
4. Hausner’s ratio
5. Carr’s index
D. Preparation of mucoadhesive drug delivery system.
E. Evaluation of mucoadhesive delivery system.
1. Thickness
2. Hardness
3. Fraibility
4. Weight variation
5. Disintegration test

6. Dissolution test

IV. MATERIAL AND METHOD

Materials

Atenolol was obtained as a gift sample from Cipla Ltd., Mumbai. Carbopol 934P, Ethyl cellulose, hydroxypropyl methylcellulose K100M were obtained from Rajesh Chemicals, Mumbai. Sodium alginate low viscosity (5.5±2 cp of 1% solution at 250C) was obtained from Loba chemicals, Mumbai. All other ingredients used in formulations were of analytical grade.

Methods

Preparation of buccoadhesive tablets7

All the ingredients including drug, polymers and excipients weighed accurately according to their batch size. All the ingredients except magnesium stearate were mixed in an ascending order and blended for 20 minutes. After uniform mixing of ingredients, magnesium stearate was added and again mixed for 2 min. The prepared blend of each formulation was subjected to flow properties of granules. 100 mg of powder bed was pre-compressed, on the single station tablet- punching machine (Cadmach Ahemdabad,

India) at a pressure of 0.5 ton for 30 seconds to form single layered flat-faced tablets of

8 mm diameter. Then, 50 mg of ethyl cellulose powder was added, and final compression was done at a pressure of 3.5 tons for 30 seconds to get bilayer tablet. Composition of bilayer tablets is given in table 1.

Physical properties of tablets

It includes hardness, thickness, weight uniformity of tablets in a similar manner as stated for conventional oral tablets.

Swelling studies7

Three tablets from each formulation were placed in empty baskets and the total weight of basket with tablet noted (W1). The tablets containing baskets were fixed to a sixstation dissolution apparatus.

Baskets immersed in a 500 ml dissolution medium (phosphate buffer pH6.6), at 370C and at 50 rpm. At regular interval of one hour, the baskets were detached from the dissolution apparatus and blotted with tissue paper to remove excess surface water. Then the weight of basket containing swollen tablet was taken and reported as

(W2). The graph of swelling index Vs time was plotted for each formulation Swelling Index (SI) = W2 −W1100 W1

Were, tablet

W1- dry weight of tablet. W2 - wet weight of swollen Surface pH8

The surface pH of the buccal tablets was determined in order to find out the possibilities of any side effects in vivo. The tablets used for the determination of swelling index were used for determination of their surface pH using pH meter. The tablet is allowed to equilibrate for 1 minute with glass electrode. The study was carried out in triplicate.

Ex- vivo mucoadhesive strength measurement7

A modified balance method was used for determining the ex-vivo mucoadhesive strength. Fresh sheep buccal mucosa was obtained from the local slaughterhouse and used within 2 hours after receiving.

The mucosal membrane was separated by removing underlying fat and adipose tissues with the help of surgical scissor. The membrane was cut into pieces and washed with distilled water and then with phosphate buffer pH 6.8 at 370C. Mucosa was fixed on the glass vial immediately using rubber band, which was filled with phosphate buffer. The vial with buccal mucosa was stored at 370 C for 5 minutes. Then vial with a section of mucosa was connected to the balance in inverted position.

Another vial was placed on a height adjustable pan. The backing layer of mucoadhesive tablet was glued to the flat surface of vial. Then the height of pan was adjusted so that mucosal surface of vial comes in intimate contact to adhesive layer of tablet. Two minutes contact time was given to ensure intimate contact between mucosal surface and the tablet. 5 gm weight was applied as preload. Then the weight was kept rising in the pan until tablet get detached from mucosal surface. The bioadhesive force was expressed as the force of adhesion (N) and was determined from the minimal weight required to detach the tablet from mucosal tissue using following equation10.

Force of adhesion (N) = weight in grams x G / 1000 Were,
W is weight required for detachment of two vials in grams, G is acceleration due to gravity

Equipment

Reaction and Synthesis Equipment:

1. Reactors (stainless steel or glass-lined)
2. Heat exchangers (cooling or heating systems)
3. Agitators (mechanical or pneumatic)
4. Condensers
5. Distillation columns

Purification and Separation Equipment:

1. Filters (plate and frame or centrifuges)
2. Centrifuges
3. Decanters
4. Chromatography columns (HPLC or GC)
5. Crystallizers

Drying and Milling Equipment:

1. Dryers (vacuum or nitrogen)
2. Mills (hammer or pin mills)
3. Sifters
4. Blenders
5. 5Granulators

Quality Control and Testing Equipment:

1. HPLC (High-Performance Liquid Chromatography)
2. GC (Gas Chromatography)
3. IR (Infrared Spectroscopy)
4. NMR (Nuclear Magnetic Resonance Spectroscopy)
5. UV-Vis Spectrophotometers

Packaging and Filling Equipment:

a. Tablet presses
b. Capsule filling machines
c. Powder filling machines
d. Labeling machines
e. Packaging lines

V. EXPECTED OUTCOME

1. Improved bioavailability: Enhanced absorption of the active ingredient through the mucous membrane, leading to higher bioavailability and efficacy.
2. Prolonged release: Controlled release of the active ingredient over an extended period, reducing the frequency of administration and improving patient compliance.
3. Targeted delivery: Specific targeting of the active ingredient to the site of action, reducing systemic side effects and improving therapeutic outcomes.
4. Enhanced patient compliance: Simplified administration regimens and reduced dosing frequency, leading to improved patient compliance and adherence.

5. Reduced side effects: Minimized systemic exposure to the active ingredient, reducing the risk of side effects and improving overall safety.

6. Improved therapeutic outcomes: Enhanced efficacy and reduced treatment failures, leading to improved therapeutic outcomes and quality of life

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