# Formulation And Evaluation of Mucoadhesive Tablet of Ranolazine

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**Abstract: Ranolazine, a promising drug for the management of chronic angina, poses challenges in achieving sustained release and localizing its effect at the target site due to its short half-life and frequent dosing regimen. This study aimed to develop mucoadhesive tablets of ranolazine to enhance its bioavailability, prolong its release, and improve patient compliance. The tablets were formulated using various polymers, including hydroxypropyl methylcellulose (HPMC), Carbopol, and sodium alginate, to achieve the desired mucoadhesive properties. The formulations were characterized for drug content, swelling index, mucoadhesive strength, in vitro drug release, and ex vivo mucoadhesion time. The optimized formulation exhibited satisfactory characteristics, with prolonged drug release over 12 hours, strong mucoadhesive properties, and enhanced bioavailability. In conclusion, mucoadhesive tablets of ranolazine hold promise as a potential dosage form for improving therapeutic outcomes and patient adherence in the treatment of chronic angina.**

**Keywords: Hardness, friability, thickness, weight uniformity, drug content, drug release, swelling study, in-vitro drug release and in-vitro mucoadhesive strength.**

## 1.INTRODUCTION

In comparison, transmucosal delivery systems exhibit a faster delivery than do transdermal delivery systems. Also, delivery occurs in a tissue that is more permeable than skin and is less variable between patients, resulting in minimal inter subject variability[7]. The absorptive mucosae include buccal, sublingual, palatal, gingival, nasal, pulmonary, rectal, vaginal and ocular routes. On the other hand, in case of nasal delivery, availability of very small surface area for absorption as well as the large variability in mucus secretion could significantly affect drug absorption. Further, severe sensitivity to drugs causes significant irreversible damage to the mucosa. In pulmonary delivery, despite the enormous surface area available for absorption, the major challenge is the reproducible placement of drug in the alveolar region due to the mucociliary clearance, hence not suitable for sustained delivery[8-9]. Among all transmucosal sites, buccal cavity was found to be the convenient and easily accessible site for the local or systemic delivery of drugs. Because of its expanse of relatively immobile smooth muscle, abundant vascularization, direct access to the systemic circulation through the internal jugular vein that bypasses hepatic first pass metabolism, makes it highly promising for delivery of drugs exhibiting poor oral bioavailabilities. Facile removal of formulation, better patient acceptance and compliance are some other prominent meritorious advantages of buccal adhesive systems. In order to improve bioavailability of administered drug across the buccal mucosa, several bioadhesive tablet systems have been the subject of a growing intere

Novel drug delivery systems (NDDS):
NDDS refer to innovative approaches designed to deliver medications to specific targets within the body, enhancing their therapeutic efficacy while minimizing side effects. These systems aim to overcome barriers such as poor solubility, limited bioavailability, and non-specific distribution of drugs in the body. Here are some key points about NDDS:

Types of NDDS:
There are various types of novel drug delivery systems, including:
Liposomes: Lipid-based vesicles that can encapsulate drugs, improving their solubility and targeting specific cells or tissues.
Nanoparticles: Particles ranging from 1 to 1000 nanometres in size, which can carry drugs and deliver them to targeted sites.
Microspheres/Microparticles: Solid or semisolid particles with diameters typically ranging from 1 to

1000 micrometres, used for sustained release of drugs.
Implants: Devices implanted into the body that slowly release drugs over an extended period.
Transdermal patches: Patches applied to the skin that deliver drugs through the skin barrier into the bloodstream.
Targeted drug delivery systems: Systems designed to deliver drugs specifically to certain cells, tissues, or organs, minimizing systemic exposure and side effects.

1. *Advantages Novel drug delivery systems:*
- Enhanced drug efficacy.
- Improved patient compliance due to reduced dosing frequency.
- Targeted delivery reduces systemic toxicity.
- Controlled release of drugs over extended periods.

2. *Challenges and Limitations:*
- Complex formulation processes.
- Regulatory approval can be challenging due to safety concerns.
- Costlier compared to conventional drug delivery methods.
- Limited scalability for mass production.
- Potential for immune response or toxicity with certain formulations.

3.*Applications of Novel drug delivery systems*
- Cancer therapy: Targeted drug delivery to tumour cells can minimize damage to healthy tissues.
- Chronic diseases: NDDS can provide sustained release of drugs for conditions like diabetes, hypertension, and arthritis.
- Central nervous system disorders: NDDS can bypass the blood-brain barrier for more effective treatment of conditions like Alzheimer's disease and Parkinson's disease.
- Infectious diseases: Targeted drug delivery can enhance the effectiveness of antimicrobial agents.
- Gene therapy: NDDS can deliver genetic material to specific cells for therapeutic purposes.

*4.Future Directions:*
- Continued research into biocompatible and biodegradable materials for NDDS.
- Development of personalized drug delivery systems based on individual patient characteristics.
- Integration of nanotechnology and biomaterials for more precise and efficient drug delivery.
- Exploration of combination therapies delivered through NDDS for synergistic effects and improved outcomes.

Adhesion:
Adhesion, in a broad sense, refers to the attraction or sticking together of two different surfaces. This phenomenon is prevalent in various fields, including physics, chemistry, biology, and engineering. Here's an overview of adhesion:

Factors Affecting Adhesion:
Surface Roughness: Rough surfaces provide more contact points for adhesion, enhancing mechanical interlocking.
*Surface Energy*: Surfaces with higher surface energy tend to exhibit better adhesion, as they promote the spreading and wetting of adhesive materials.
Chemistry of Surfaces: The chemical composition of surfaces influences the formation of chemical bonds and adhesion.
*Temperature*: Adhesion is often affected by temperature, with some adhesives performing better at certain temperature ranges.
*Moisture:* Presence of moisture can affect adhesion, particularly for adhesives that require curing or drying.

Advantages of mucoadhesion tablet:
*1.Enhanced Drug Absorption*: Mucoadhesive tablets adhere to the mucosal lining of the oral cavity or gastrointestinal tract, allowing for prolonged contact with the mucosa. This prolonged contact enhances drug absorption by increasing the residence time of the dosage form at the absorption site, leading to improved bioavailability of the drug.
Non-Invasive Route of Administration: Mucoadhesive tablets are typically administered orally, buccally (between the cheek and gum), or sublingually (under the tongue), providing
*2. non-invasive route of drug delivery*. This is particularly advantageous for patients who may have difficulty swallowing conventional tablets or capsules, such as pediatric or geriatric patients.
*3.Avoidance of First-Pass Metabolism*: By bypassing the gastrointestinal tract and liver, mucoadhesive tablets can help avoid first-pass

metabolism, which can lead to higher systemic drug concentrations and more predictable pharmacokinetics.

*4.Improved Patient Compliance*: Mucoadhesive tablets often have a convenient dosing regimen and can be formulated to provide controlled or sustained release of the drug, reducing the frequency of administration and improving patient compliance.

*5.Localized Drug Delivery:* Mucoadhesive tablets can be designed to target specific sites within the oral cavity or gastrointestinal tract, allowing for localized drug delivery. This is advantageous for the treatment of conditions such as oral mucosal diseases, periodontal diseases, gastrointestinal disorders, and local infections.

*6.Reduced Systemic Side Effects*: By delivering drugs directly to the site of action, mucoadhesive tablets can reduce systemic exposure and minimize systemic side effects associated with high drug concentrations in the bloodstream.

*7.Flexibility in Formulation*: Mucoadhesive tablets can be formulated using a variety of polymers and excipients to achieve desired drug release profiles, mucoadhesive properties, and stability characteristics.

ANGINA:

Angina, also known as angina pectoris, is a medical condition characterized by chest pain or discomfort that occurs when the heart muscle doesn't receive enough oxygen-rich blood. This typically happens because the coronary arteries, which supply blood to the heart, become narrowed or blocked. Angina is often a symptom of underlying coronary artery disease (CAD).

Here's some key information about angina:

1.Types of Anginas:

- Stable Angina: This is the most common type of angina. It occurs predictably during physical exertion or emotional stress and typically lasts a few minutes. Rest or medication usually relieves the symptoms.
- Unstable Angina: Unstable angina is more unpredictable and may occur at rest or with minimal exertion. It is considered a medical emergency because it can signal a heart attack is imminent.
- Variant (Prinz metal's) Angina: This type of angina is caused by a temporary spasm in the coronary arteries, leading to reduced blood flow to the heart. It often occurs at rest and can be severe.

2.Symptoms:

- Chest pain, pressure, or discomfort, often described as tightness, squeezing, or a heavy weight on the chest.
- Pain or discomfort may also be felt in the neck, jaw, shoulders, arms, or back.
- Shortness of breath.
- Nausea.
- Fatigue.
- Sweating.
- Treatment of angina

## II)LITERATURE REVIW

1. *Gharge V, Gurjar M (2015):* The drug loaded beads were prepared by adsorbing drug on the florite, by rapid solvent evaporation and further was used to prepare calcium alginate beads by inotropic gelation method, using 32 factorial designs. Developed formulations were evaluated for yield, entrapment efficiency, image analysis, surface topography, mechanical strength, apparent density, buoyancy studies and dissolution studies. Developed formulations showed instantaneous floating with very slow drug release in acidic medium. Quantity of porous carrier and concentration of sodium alginate solution significantly affected the performance of beads
2. *M. Shashanka, N. Shivani*, The objective of present study was to develop matrix type tablet therapeutic systems of Ranolazine using natural polymers as matrix formers. Ranolazine buccal tablet were developed by using solvent casting technique. Various physicomechanical parameters like weight variation, thickness, folding endurance, drug content, moisture content, moisture absorption parameters like mucoadhesive strength, force of adhesion, and bond strength were evaluated.
3. *Vinay C H and Mohammed Gulzar Ahmed* The Mucoadhesive buccal tablets were prepared by direct compression method using Carbopol 934, HPMC K4M, sodium CMC as mucoadhesive polymer. The compatibility studies of drug and excipients were performed by FT-IR spectroscopy. After examining the flow properties of the powder blends the results are found to be within prescribed limits and indicated good flowing property, hence it was subjected to tablet compression. The tablets were evaluated for post compression parameters

like weight variation, hardness, thickness, friability, drug content uniformity, Surface pH, in-vitro studies like swelling, mucoadhesive strength and drug release.

4. *Rudra gouda Patil* he objective of the study was to develop mucoadhesive buccal tablet of furosemide. Tablets of Furosemide were prepared by wet granulation method using mucoadhesive polymers like Carbopol 934P, Guar Gum, Chitosan, Hydroxy Ethyl Cellulose, in different ratios. Buccal tablets were evaluated by different methods for parameters such as thickness, hardness, weight uniformity, drug content uniformity, swelling index, surface pH, ex vivo mucoadhesive strength, ex vivo residence time, in vitro drug release, ex vivo drug permeation, stability studies. The tablets were evaluated for in vitro release in pH 6.8 phosphate buffer for 12 hr in standard dissolution apparatus. Mohaddessin strength was increased with increase in the concentration of Carbopol. In order to determine the mode of release, the data was subjected to Zero order, first order, Higuchi and Peppas diffusion model. Short-term stability studies on the promising formulate
5. *Dhananjay Audurti* Short-term stability studies on the promising formulations indicated that there were no significant changes in drug content, ex-vivo mucoadhesive strength and in vitro dissolution characteristics. IR spectroscopic studies indicated that there were no drug-excipient interactions. The prepared buccal tablets of furosemide could stay in the buccal for a longer period of time, which indicate a potential use of mucoadhesive tablets of furosemide for treating Hypertensive patients.

## III) AIM AND OBJECTIVE

*Aim*: To formulation and evaluation of mucoadhesive tablet for an Anti- anginal drug Ranolazine with a six- seven hour delay in release after oral administration. So that the dose administered at bedtime, drug is released after the initial delay such that maximum plasma level occurs in the early morning hours, when the patient is most at risk.

*Objectives:*

1) Reformulation studies
2) Selection of the appropriate excipients
3) Formulation of mucoadhesive tablet
4) To evaluate and characterize the prepared formulations
5) To evaluate the prepared Floating Pulsatile tablet.
6)To find out best formulation amongst all prepared tablet

## IV.EXPERIMENTAL WORK:

*Organoleptic properties determination of melting point:*

Melting point of Telmisartan was determined by capillary method. Fine powder of Telmisartan was filled in capillary tube (previously sealed at one end). The capillary tube inserted in sample holder of melting point apparatus and a thermometer is also placed in the apparatus.

*UV-Visible Spectroscopy:*

The absorption maxima of the standard solution of drug in phosphate buffer ph 7.5, was determined by scanning between 200-4

Thermal analysis:

*Differential Scanning Calorimetric (DSC) Study:*

physical and chemical change within a sample as a function of temperature. It is used for assessment of purity, polymorphism, degradation and excipient compatibility. DSC studies were performed using a Mettle DSC 1 (Mettle Toledo, Germany). The instrument was calibrated with an indium standard. Accurately weighed sample (5-10mg) were placed in closed, pierced, flat bottom aluminum pans. DSC scan were recorded at a constant heating rate of 10°C/min. rom 30 to 350°C. Nitrogen gas was pumped at a flow rate of 80ml/min.

Micrometric Properties:

The term bulk density refers to a measure used to describe a packing of particles. It is (gm/ml) and was determine using a balance and measuring cylinder. An accurately weighed Amount of powder should be introduced in 100 ml measuring cylinder. Note the initial volume, then the cylinder should be tapped 100 times on a plane hard surface and Tapped density is determined by placing a graduated cylinder containing same mass of powder on a mechanical tapper tapped volume of packing should be recorded. Bulk Density (BD) and Tapped Density (TD) should be calculated by using following formula.

Bulk Dersity= Weight of the powder / Buk volume

Tap Density= weight of the powder / Tapped volume

Carr's Index:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more foldable it is. As such, it is a measure of the relative inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions, and a greater difference between the bulk and tapped densities will be observed.

*Determination of Angle of Repose:*

angle of repose is the tan inverse of angle between height (h) of pile of powder and the radius (r) of the base of conical pile. It can be obtained between the freestanding surface of the powder heap and the horizontal plane. The fixed funnel that is secured with its tip at a given height h, above graph paper, placed on the flat horizontal surface. Powder is carefully poured through funnel until the apex of conical pile just touches the tip of funnel. Different ranges of flow ability in terms of angle of repose are given bellow:

| Sr.no | Flow property | Angle of repose(degrees) |
|---|---|---|
| 1 | Excellent | 25-30 |
| 2 | Good | 31-35 |
| 3 | Fair-aid not needed | 36-40 |
| 4 | Passable may hang up | 41-55 |
| 5 | Poor must agilate, vibrate | 46-55 |
| 6 | Very poor | 56-65 |
| 7 | Very very poor | >66 |

Table no.1 parameter of flow property and angle of repose

Flow properties of powder according to cars index are as follows:

| Sr no. | Car"s index(%) | Flow |
|---|---|---|
| 1 | 5-15 | Excellent |
| 2 | 12-16 | Good |
| 3 | 18-21 | Fair to passable |
| 4 | 23-35 | Poor |
| 5 | 33-38 | Very poor |

Table no.2 Flow properties of powder according to cars index are as follows:

Formulation of Ranolazine

| | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| Ranolazine | 500 | 500 | 500 | 500 |
| Acacia gum | 20 | 40 | 40 | 20 |
| Pvp | 10 | 40 | 26 | 46 |
| Microcrystalline cellulose | 168 | 118 | 132 | 112 |
| Magnesium stearate | 2 | 2 | 2 | 2 |
| Total weight | 700 | 700 | 700 | 700 |

Table no.3 Formulation of Ranolazine

Evaluation Parameter of Mucoadhesive Tablet:

*In-Vitro Disintegration Time:*

The U.S.P. device to test disintegration uses 6 glass tubes that are 3" long; open at the top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2º C such that the tablet remain 2.5cm below the surface of liquid on their upward movement and not closer than 2.5 cm fromthe bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles perinate. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet.. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified.

Evaluation Parameter of mucoadhesive Tablet:

- Weight variation
- Thickness
- Hardness
- Friability

*1: weight variation:*

Weight variation refers to the fluctuation or change in an individual's body weight over time. It can be influenced by various factors such as diet, exercise, metabolism, hormonal changes, medications, and overall lifestyle. Some degree of weight variation is normal and expected, but significant or rapid changes may indicate underlying health issues or imbalances.

*2: Thickness :*

Thickness typically refers to the distance between two opposite surfaces of an object or material. It's a fundamental measurement used in various contexts, from manufacturing to construction to science.

*3: Hardness:*

Hardness refers to the resistance of a material to deformation, scratching, or indentation. It is an important mechanical property that determines the material's ability to withstand wear, abrasion, and impact.

*4: Friability:*

The results of friability testing help ensure that tablets can withstand the stresses encountered during manufacturing, packaging, shipping, and handling without excessive crumbling or breaking. Tablets with high friability may have issues such as difficulty in handling, inaccurate dosing, or reduced shelf life.

In Vitro Buoyancy Studies:

The in vitro buoyancy was determined by floating lag time, as per the method described by Rosa et al. The tablets were placed in a beaker containing 100 mL of 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time for which the dosage form. constantly remained on the surface of medium was determined as the total floating time.

## V) RESULT AND DISCUSSION

5.1 Physical Properties, Solubility, Melting Point

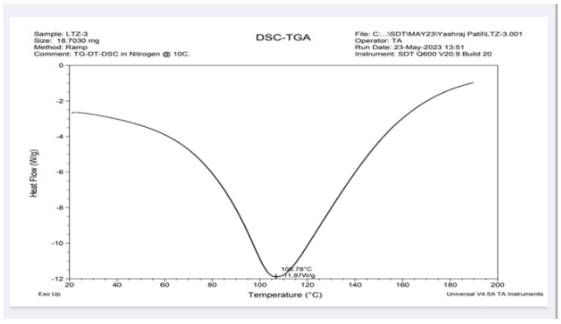
| Sr no | experiment | result |
|---|---|---|
| 1 | Physical properties<br>A] COLOUR<br>B] ODOUR | <br>a) orange<br>b) bitter |
| 2 | SOLUBILITY<br>a) sparingly soluble<br>b) slightly soluble<br>c)practically insoluble | <br>a)tetrahydrofuran<br>b)etyel acetate<br>c) water, ethanol |
| 3 | Melting point | The reported melting point of ranolazine is in the range of 164-166ºC. the observed melting point is 165ºC. |

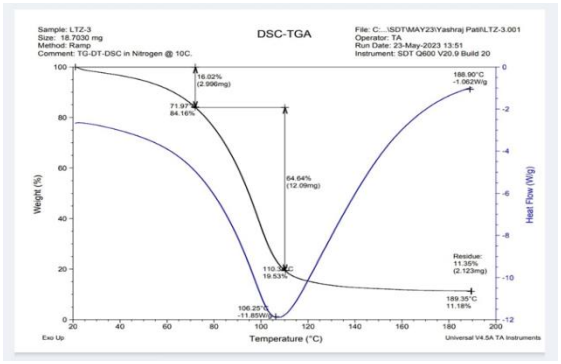
preformulation is the first step in rational development of any pharmaceutical dosage form of a new drug. Reformulation study focuses on Physiochemical Property of new drug compound that can affect drug performance and development of effective dosage form.

The reported melting point of pure drug ranolazine is the range of 164-166ºC. and the observed melting point at165ºC. It confirmed that given powdered drug is in pure in nature and it confirmed that given power is ranolazine.

5.2 Thermal analysis:

Differential scanning calorimetery(DSC) study:



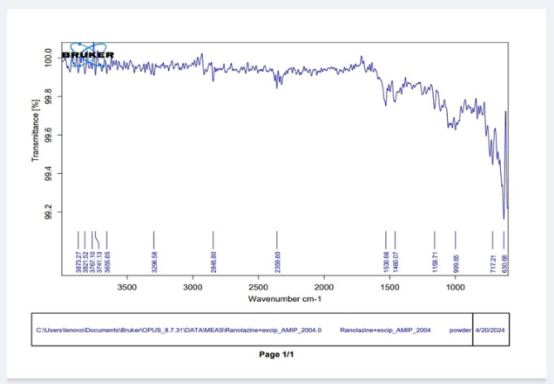




DSC studies were performed using a Mettle DSC 1 (Mettle Toledo, Germany). The instrument was calibrated with an indium standard. Accurately weighed sample (5-10mg) were placed in closed, pierced, flat bottom aluminum pans. DSC scan were recorded at a constant heating rate of 10°C/min from 30 to 350°C. Nitrogen gas was pumped at a flow rate of 80ml/min. appearance any new peak and change in peak shape were noted. The melting points, peak maximaDSC was used to assess the thermal behaviour of the drug ranolazine. In the fig. 1 DSC Thermo gram of ranolazine shows a single sharp characteristic endothermic peak (T peak=271.37°C) corresponding to the melting point of ranolazine.

And a single peak indicates that the drug sample is free from impurities.

*5.3 Calibration curve of Ranolazine :*

calibration curve of ranolazine typically involves plotting its concentration against some measurable response, often absorbance or fluorescence, in order to quantitatively determine its concentration in a sample. This curve helps in accurate measurement, ensuring the reliability of analytical methods used.




*Pre compression and post compression parameter:*

The FTIR (Fourier Transform Infrared Spectroscopy) spectrum of pure ranolazine would display characteristic peaks corresponding to its functional groups and molecular structure. Common functional groups in ranolazine include aromatic rings, amines, and ethers. The spectrum typically shows peaks around 3000-2800 cm^-1 for C-H stretching vibrations, around 1600-1500 cm^-1 for aromatic C=C stretching, and around 1300-1000 cm^-1 for C-O and C-N stretching vibrations.

5.4 Evaluation Parameter of Mucoadhesive Tablet:

| Batch code | Disintegration time (hrs) | Drug content |
|---|---|---|
| C1 | 199±1.10 | 97±0.046 |
| C2 | 162±1.24 | 97±0.57 |
| C3 | 130±1.18 | 98±0.88 |
| C4 | 97±0.40 | 97±1.19 |
| C5 | 60±0.78 | 99±0.35 |

5.5 Pre compression parameter :

| Batch code | Bulk density (g/ml) | Tapped Density (g/ml) | Hausners Ratio | Carrs Index (%) | Angle Of repose Θ |
|---|---|---|---|---|---|
| C1 | 0.37±0.06 | 0.42±0.005 | 1.12±0.04 | 11.63±1.08 | 22.2±0.41 |
| C2 | 0.42±0.05 | 0.47±0.07 | 1.15±0.03 | 13.6±1.19 | 23.02±1.10 |
| C3 | 0.35±0.09 | 0.41±0.08 | 1.12±0.09 | 11±0.60 | 30.14±0.24 |
| C4 | 0.43±0.07 | 0.48±1.08 | 1.15±0.03 | 14.30±0.36 | 22.17±0.29 |
| C5 | 0.44±0.007 | 0.49±0.05 | 1.10±0.06 | 11±0.55 | 26.14±0.39 |

The tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, hardness, friability, and drug content the result was shown instable.

1) *Hauser's Ratio*:

In the result of Hauser's ratio of various batches was shown in table . It shows that all batch show excellent flow properties. All Batches were in the range of 1.10±0.06 to 1.15±0.03

*2) Carr's Index:*

Carr's index was carried out and result was shown in table . It was found that all batches shown good and excellent flow properties. All batches were in the range of 11±0.55to 14.30±0.36

3) *Angle of Repose*:

The angle of repose of core tablet was carried out and the result was shown in table no 05. It shown that batch C1 and C2 has excellent flow properties and batch C3, C4, C5 shown good flow properties. Angle of repose was found to be in the range of 22.17±to 30.14±

*5.6 Dissolution study of Mucoadhsive tablet:*

| Time (Hrs) | A1 | A2 | A3 | A4 | A5 |
|---|---|---|---|---|---|
| 1 | 65.7±0.02 | 68.77±0.006 | 63.25±0.0016 | 61.4±0.0017 | 76.4±0.00022 |
| 2 | 67.8±0.0014 | 70.8±0.0013 | 65.88±0.0034 | 62.8±0.0054 | 80.8±0.00027 |
| 3 | 70.7±0.0013 | 72.8±0.006 | 70.88±0.0013 | 657±0.0013 | 82.4±0.0015 |
| 4 | 72.9±0.003 | 76.6±0.0062 | 73.9±0.010 | 68.7±0.0007 | 85.9±0.0005 |
| 5 | 77.8±0.0021 | 79.56±0.004 | 76.8±0.0082 | 70.3±0.0027 | 92.9±0.0013 |
| 6 | 79.6±0.0014 | 83.88±0.004 | 79.3±0.00068 | 72.8±0.0035 | 94.57±0.0029 |
| 7 | 88.1±0.0012 | 84.8±0.0046 | 80.36±0.002 | 74.5±0.0033 | - |

| | | | | | |
|---|---|---|---|---|---|
| 8 | 90.5±0.006 | - | 83.77±0.0083 | 78.5±0.010 | - |
| 9 | - | - | 88.7±0.0034 | 80.58±0.0053 | - |
| 10 | - | - | 90.77±0.0024 | - | - |
| 11 | - | - | 92.78±0.0017 | - | - |

## VI) CONCLUSION

The formulation and evaluation of mucoadhesive tablets are crucial for ensuring their effectiveness in targeted drug delivery. Through careful formulation, including selection of polymers and excipients, and comprehensive evaluation methods such as mucoadhesion strength, swelling behavior, drug release kinetics, and in vitro/in vivo studies, the efficacy and safety of these tablets can be optimized. Additionally, considering patient comfort and convenience in administration should be a priority to enhance patient compliance and therapeutic outcomes.

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