International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 749-753 www.ijprajournal.com ISSN: 2456-4494

# Development and Characterization of Ranitidine Loaded Mucoadhesive Delivery System – Review

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Date of Submission: 05-05-2024 Date of Acceptance: 15-05-2024

**ABSTRACT**
Mucoadhesive drug delivery systems are delivery systems which utilize the property of bioadhesionof certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time.
Ranitidine is a commonly used drug in, gastroesophageal reflux disease classified as a histamine h2 receptor antagonist, and belongs to the same drug class as cimetidine and famotidine. This drug helps to prevent and treat gastric-acid associated conditions. In the study gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder characterized by the regurgitation of gastric contents into the esophagus and review of preparation of ranitidine loaded mucoadhesive delivery system of study.
**Keywords:**Ranitidine, GERD, antagonist, mucoadhesive drug delivery systems

## I. INTRODUCTION

Gastroesophageal Reflux Disease
Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder characterized by the regurgitation of gastric contents into the esophagus. It is one of the most commonly diagnosed digestive disorders in the US with a prevalence of 20%, resulting in a significant economic burden in direct and indirect costs and adversely affects the quality of life. GERD is caused by multiple different mechanisms that can be intrinsic, structural, or both, leading to the disruption of the esophagogastric junction barrier resulting in exposure of the esophagus to acidic gastric contents. Clinically, GERD typically manifests with symptoms of heartburn and regurgitation. It can also present in an atypical fashion with extra-esophageal symptoms such as chest pain, dental erosions, chronic cough, laryngitis, or asthma. Based on endoscopic and histopathologic appearance, GERD is classified into threedifferent phenotypes: non-erosive reflux disease (NERD), erosive esophagitis (EE), and Barrett esophagus (BE).(1)

Mucoadhesive Delivery System
Mucoadhesive drug delivery systems are delivery systems which utilize the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane. In the case of polymer attached to the mucin layer of a mucosal tissue, the term "mucoadhesion" is used.Mucoadhesive drug delivery systems can be delivered by various routes [2]:

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

**Polymers used for mucoadhesion**
**a. Synthetic polymers:**
i. Cellulose derivatives (Methylcellulose, Ethyl cellulose, Hydroxyl ethyl cellulose, Hydroxyl propyl cellulose, Hydroxypropyl methylcellulose, Sodium carboxy methylcellulose).
ii. Poly (Acrylic acid) polymers (Carbomers, Polycarbophil).
iii. Poly hydroxyl ethyl methylacrylate.
iv. Polyethylene oxide.
v. Polyvinyl pyrrolidone.
vi. Polyvinyl alcohol.
**b. Natural polymers:**
Tragacanth, Sodium alginate, Guar gum, Xanthum gum, soluble starch, Gelatin, Chitosan [3]

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### 1.1 Ranitidine

Ranitidine is a histamine H2 antagonist used to treat duodenal ulcers, ZollingerEllison syndrome, gastric ulcers, GERD, and erosive esophagitis [6]. Brand Names: Good Sense Acid Reducer, Wal-zan, Zantac Generic Name: Ranitidine Background: Ranitidine is a commonly used drug, classified as a histamine H2 receptor antagonist, and belongs to the same drug class as cimetidine and famotidine. This drug helps to prevent and treat gastric-acid associated conditions, including ulcers, because of its ability to decrease gastric acid secretion. Ranitidine is often referred to as Zantac, and is available in various forms, including tablet, injection, and effervescent tablet preparations. The prevalence of GERD is thought to be 10-20% in western countries. Ranitidine has proven to be an effective treatment for relieving uncomfortable symptoms of gastric acid associated conditions and is therefore widely used in GERD and other gastric-acid related conditions. Type: Small Molecule
Groups: Approved
Weight: 314.4

Chemical Formula: $C_{13}H_{22}N_4O_3S$
**Mechanism of action:** After a meal, the hormone gastrin, produced by cells in the lining of the stomach, stimulates the release of histamine, which then binds to histamine H2 receptors, leading to the secretion of gastric acid. Ranitidine reduces the secretion of gastric acid by reversible binding to histamine (H2) receptors, The relief of gastric-acid related symptoms can occur as soon as 60 minutes after
**administration** of a single dose, and the effects can last from 4-10 hours, providing fast and effective symptomatic relief.
**Absorption:** Ranitidine is rapidly absorbed with peak concentrations reached within 1-3 hours after administration, and varying greatly among patients. Bioavailability is about 50%-60% due to hepatic metabolism. In a pharmacokinetic study of healthy males, the AUC 0-infinity was about 2,488.6 ng × h/mL and the median Tmax was 2.83 hours. Food or antacids have limited effects on absorption. One clinical study found that the administration of a potent antacid (150 mmol) in subjects in the fasted state led to decreased absorption of ranitidine.
**Volume of distribution:** The volume of distribution is higher than body volume, and measures at approximately 1.4 L/kg. It concentrates in breast milk, but does not readily distribute into the cerebrospinal fluid. Protein binding: The plasma protein binding of ranitidine is approximately 15%.
**Metabolism:** The major metabolite in the urine is N-oxide, which represents less than 4% of the dose. Other metabolites of ranitidine include S-oxide (1%) and desmethyl ranitidine (1%). The feces contain the remainder of the excreted ranitidine dose. Liver dysfunction has been shown to cause small, but clinically insignificant, changes in various ranitidine pharmacokinetic parameters.
Route of elimination: This drug is mainly excreted in the urine but also excreted in the feces. About 30% of a single oral dose has been measured in the urine as unchanged drug within 24 hours of ingestion. Half-life: The elimination half-life or ranitidine is about 2.5-3 hours. It may be longer after oral administration versus injection. The plasma half-life is longer for elderly patients population due to a decrease in renal function, and is measured at 3-4 hours.
**Clearance:** Renal clearance is about 410 mL/min according to FDA prescribing information. Another resource mentions a plasma clearance of approximately 600 ml/min. Clearance is decreased in the elderly and those with impaired or hepatic renal function. It is recommended to decrease the dose of ranitidine by one-half in patients with renal impairment. Toxicity: Oral doses of 1,000 mg/kg in mice and rats were not found to be lethal. Intravenous LD50 values in mice and rats were 77 and 83 mg/kg, respectively. Overdose information: There has been limited experience with ranitidine overdose. Reported acute ingestions of up to 18 grams orally were followed by temporary adverse effects similar to the normal adverse effects of this drug, including tachycardia, bradycardia, dizziness, diarrhea, nausea, and vomiting, among other effects. Gait abnormalities and hypotension have also been observed. When an overdose with ranitidine is suspected, remove unabsorbed ranitidine from the gastrointestinal tract if possible, and monitor the patient and provide supportive therapy as required.

## II. AIMS & OBJECTIVES

Aims Development and Characterization of Ranitidine Mucoadhesive Delivery System for the effective management of Gastroesophageal Reflux Disease Objectives

- Formulation development of mucoadhesive tablets of Ranitidine.
- Characterization of developed mucoadhesive tablet formulations.
- In vitro drug release study.

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•Short-term accelerated stability study of the optimized mucoadhesive tablet formulation.

## III. PLAN OF WORK

The proposed plan of work can be outlined as:

I. Literature survey.
II. Drug, chemicals, reagents, and solvents will be purchase from the standard vendor(s).
III. Pre-formulation studies of drug and excipients.

a. Physical properties
b. Melting point
c. Solubility studies
d. Partition coefficient
e. Lambda max determination
f. Drug-polymer interaction study (Fourier Transform Infrared (FTIR) Analysis)
4. Development of mucoadhesive tablet formulations.
5. Characterization of formulations:
a. Tablet thickness and tablet diameter
b. Hardness test
c. Friability test
d. Disintegration test
e. Content uniformity
f. Weight variation test
g. Moisture absorption studies
h. Surface pH study
i. Swelling index studies
j. Mucoadhesive/bioadhesive strength
k. Residence time
l. Drug release m. Stability study (according to ICH guidelines)

## IV. STATISTICAL ANALYSIS OF THE DATA.

### 4. Materials and Methods

Pre-formulation studies According to the techniques/protocols specified by Mahajan et al., 2013, drugs will undergo a thorough analysis of its physical characteristics, melting point, solubility studies, partition coefficient, and drug interactions (FT-IR investigations) [19].

**4.1**Physical properties we will determine the taste, odor, and color to determine the physical characteristics of drugs.

**4.2.Melting point:**by putting a little amount of the medicine in a capillary tube with one end closed, placing it in Thiele's melting point apparatus, and recording the temperature at which the drug melts, the melting point of the drugs will be determined. Three readings' averages will be kept track of.

**4.3. Solubility studies :**The solubility of drugs will be tested in distilled water, a number of buffer solutions (pH 4.0, pH 7.4, and pH 8.0), and methanol. Three identical readings will be used to calculate the average.

**4.4. Partition coefficient:**to calculate the partition coefficient of drugs, n-octanol and water will be utilised in equal parts in a separating funnel. A drug solution will be prepared, and 1 ml will be added to a 50/50 mixture of octanol and stimulated tear solution (pH 7.4) in a separating funnel. The mixture will then be stirred for 10 minutes, let to stand for an hour, and then continued for another 24 hours. Following this, the aqueous and octanol phases will be centrifuged for 10 minutes at 2000 rpm to separate them. Using a UV-Vis Spectrophotometer, the aqueous and octanol phases will be measured at their respective maximums before and after partition in order to estimate the partition coefficient.

**4.5. Determination of wavelength UV-Vis spectrophotometry:** will be used to find drugs. The absorbance properties from 200 nm to 400 nm qualitatively match those of a standard solution that will be similarly prepared and tested at the same time. In terms of quantitative analysis, the absorbances of the equimolar sample and the standard solutions will be at their maximum.

**4.6**. **Fourier transform-infrared spectroscopy (FT-IR)** In order to assess the Drug-polymer interaction study, Fourier transform-infrared (FT-IR) spectroscopy will be employed. The pellets will be scanned in 128 scans with a resolution of 4 cm-1 and a 1 cm-1 interval over a wave number range of 4000-400 cm-1 in an inert atmosphere. Each spectrum's background will be taken away.

**5. Formulation development**themucoadhesive tablet will be formulated using direct compression method. The excipients compatible with Ranitidine will be used. All ingredients passed through a sieve with mesh number 60. The required quantity will be taken for the formulation and it will be mixed thoroughly using a blender. The blended powder will be compressed using a compression machine to produce the tablet [20] (Table 5.1).

**5.1 Content uniformity**: Twenty tablets will be triturated using mortar and pestle and powder equivalent to one tablet will be taken and dissolved in 100 mL phosphate buffer (pH 6.8) and will be heated at 37 ºC for 15 to 20 minutes with stirring. The solution will be filtered and after suitable dilution will be subjected to UV spectrophotometer at lambda max for measurement of drug content.

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**5.2 Weight variation test**: Twenty tablets will be weighed together and separately using analytical balance. The average weight and percent variation of the tablet will be calculated. The weight uniformity will be determined according to USP specification.

4.10. Moisture absorption studies Agar at 5% w/v will be dissolved in hot water and then transferred to a petri dish and will be allowed to be solidified. Prior to the study, six tablets will be placed in a vacuum overnight to remove moisture. They will be weighed initially and then positioned on the top of the agar and incubated at 37 ºC for one hour. At the end of the test, the tablets will be reweighed and the percent moisture absorption will be calculated using the formula: % Friability = Wi / Wf × 100 Where Wf is the final weight and Wi is the initial weight of the tablets

**5.3Surface pH study**The surface pH must be closed to the salivary pH, so that it would not irritate the mucosa. The salivary pH has the range of 6.5 to 7.5. The tablets will be allowed to swell for 2 hours in 1 mL of distilled water. The surface pH of the tablet will be then measured using a digital pH meter. The pH electrode will be placed near the surface of the tablet and will be allowed to equilibrate for 1 minute before reading the measurement.

**5.4Swelling index studies**The swelling study will be performed on petri dishes containing 1% agar gel. Four tablets will be weighed and placed in a petri dish. The petri dishes contained 4 tablets, and each will be placed in an incubator at 37 ºC + 1 ºC. After 0.5, 1, 1.5, 2, 2.5, 3 hours, excess water on the surface will be carefully removed using the filter paper without pressing. The tablets will be reweighed and the swelling index will be calculated using the formula: % Friability = Wi / Wf × 100 Where Wi is the initial weight and Wf is the final weight of the tablet

**5.5 Mucoadhesive/bioadhesive strength**a modified physical balance will be used to measure the strength of mucoadhesiveness. The apparatus consisted of a double beam physical balance in which the right side has a pan, and the left side of the balance has a string that will be hanged and at the bottom of the string will be a suctioned glass slide. This will be the place where the tablets will be placed using an adhesive. The porcine buccal mucosa will be placed on top of an inverted 50 mL beaker which will be placed inside a 500 mL beaker that will be filled with phosphate buffer with pH 6.8 kept at 37 ºC. The buffer amount will be just enough so that it reaches the buccal mucosa surface. Exactly five gram of weight will be placed on the right pan before putting the porcine buccal tablet in place. The weight will be then removed to lower the glass slide with the attached buccal tablet. The tablet will be to be in contact with the porcine buccal mucosa membrane and this will be not disturbed for 5 minutes. After 5 minutes, weights will be added on the right side of the pan to separate the tablet from the membrane. The accumulated weight on the right side will be then noted and subtracted with 5 g. The value will be taken as the measure for the bioadhesive strength of the tablet. The bioadhesive force will be calculated using the formula: N = W × g / 1000 Where N is bioadhesive force, W is the weight required for detachment of the tablet from the porcine buccal mucosa in grams, and g is the acceleration due to gravity at 9.81 m/sec2

**5.6Residence time**The residence time will be tested using a modified USP dissolution apparatus. The dissolution medium will be 500 mL of phosphate buffer with pH of 6.8 maintained at 37 ºC. The porcine buccal mucosa will be attached to a glass slide using an adhesive and will be tied to the paddle of the dissolution apparatus. The tablet will be hydrated using 15 µL of phosphate buffer and will be placed in intimate contact with the porcine buccal mucosa for 30 seconds. It will be then immersed in the dissolution medium and will be rotated at 25 rpm. The time of displacement of the tablet from the mucosal surface will be noted.

**5.7Drug release In-vitro drug release** studies will be tested using USP dissolution test apparatus II, the paddle type with dissolution medium of phosphate buffer with a pH of 6.8. It will be performed at 37ºC + 0.5ºC with a speed of 50 rpm. The sample at 5 mL will be withdrawn at time interval of 15, 30, 45, 60, 90, 120, 150, 180 minutes and will be replaced with 5 mL of fresh phosphate buffer. The amount of drug will be determined at lambda max using UV spectrophotometer.

**5.8Stability study** The tablets will be stored for 3 months and the samples will be tested after a period of 30, 60, and 90 days. The samples will be analyzed using the quality control tests such as hardness, friability, thickness, content uniformity, weight variation, and moisture absorption studies and in vitro tests such as swelling studies, mucoadhesive strength, stability in human saliva, and drug release.

**5.9Statistical analysis**The format of the data will be Mean SD. Data will be evaluated using one-way ANOVA and Dunnett's multiple comparison tests

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using Sigmastat® software. The group means are regarded as significantly significant when the p-value is less than 0.05. Has Institutional animal clearance (IEC) been obtained? Yes/No

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