IJFANS INTERNATIONAL JOURNAL OF FOOD AND NUTRITIONAL SCIENCES
ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 12, Iss 1, 2023

DEVELOPMENT AND CHARACTERIZATION OF MUCOADHESIVE DELIVERY SYSTEMS LOADED WITH RANITIDINE – A COMPREHENSIVE REVIEW

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ABSTRACT
Mucoadhesive drug delivery systems utilize the bioadhesive properties of certain polymers, which become adhesive upon hydration. This characteristic allows these systems to target drugs to specific regions of the body for extended periods. Ranitidine, a histamine H2 receptor antagonist, is widely used to treat gastroesophageal reflux disease (GERD), a chronic gastrointestinal disorder involving the regurgitation of gastric contents into the esophagus. This study focuses on the preparation of a mucoadhesive delivery system loaded with ranitidine, aiming to enhance its efficacy and prolong its therapeutic effect in GERD treatment.
Keywords: Ranitidine, GERD, antagonist, mucoadhesive drug delivery systems

INTRODUCTION
Gastroesophageal Reflux Disease (GERD)
Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder characterized by the backward flow of gastric contents into the esophagus. It is highly prevalent in the US, affecting approximately 20% of the population, and imposes substantial economic costs and impacts on quality of life. GERD arises from various intrinsic and structural factors, disrupting the barrier at the esophagogastric junction and exposing the esophagus to acidic gastric contents. Clinical manifestations typically include heartburn and regurgitation, but can also present with extra-esophageal symptoms such as chest pain, dental erosion, chronic cough, laryngitis, or asthma. GERD is classified into three phenotypes based on endoscopic and histopathologic findings: non-erosive reflux disease (NERD), erosive esophagitis (EE), and Barrett esophagus (BE). [1]

Mucoadhesive Delivery System
Mucoadhesive drug delivery systems exploit the bioadhesive properties of certain polymers, which become adhesive upon hydration. This property enables targeted drug delivery to specific regions of the body for prolonged durations[2]. Bioadhesion involves interfacial forces that bind at least one biological material with another material, such as a polymer adhering to a biological membrane. When a polymer adheres to the mucin layer of mucosal tissues, it is termed "mucoadhesion." Mucoadhesive drug delivery systems can be administered via various routes [3].

1.1 Ranitidine

Ranitidine, classified as a histamine H2 receptor antagonist, is widely used to treat conditions such as duodenal ulcers, Zollinger-Ellison syndrome, gastric ulcers, gastroesophageal reflux disease (GERD), and erosive esophagitis [4]. It is marketed under various brand names including Good Sense Acid Reducer, Wal-zan, and Zantac. Ranitidine effectively decreases gastric acid secretion, making it instrumental in managing ulcerative and acid-related gastrointestinal disorders [5].

Type: Small Molecule
Groups: Approved
Chemical Formula: $C_{13}H_{22}N_4O_3S$
Weight: 314.4

Mechanism of Action: Ranitidine works by binding reversibly to histamine (H2) receptors, thereby reducing gastric acid secretion stimulated by gastrin post-meal. This mechanism provides rapid relief from gastric-acid related symptoms, often within 60 minutes after administration, and its effects can last from 4 to 10 hours[6].

Absorption: Ranitidine is rapidly absorbed with peak plasma concentrations typically reached within 1-3 hours post-administration. Bioavailability ranges from 50% to 60% due to hepatic metabolism, with limited influence from food or antacids on absorption. A pharmacokinetic study in healthy males showed a median Tmax of 2.83 hours and an AUC 0-infinity of approximately 2,488.6 ng × h/mL [7].

Distribution: The volume of distribution exceeds body volume, approximately 1.4 L/kg. While ranitidine concentrates in breast milk, it does not readily cross into the cerebrospinal fluid. Plasma protein binding is approximately 15% [8].

Metabolism: Ranitidine primarily undergoes hepatic metabolism, with less than 4% excreted unchanged in urine. Metabolites include N-oxide (major), S-oxide (1%), and desmethyl ranitidine (1%). Liver dysfunction minimally affects ranitidine's pharmacokinetics [9].

Elimination: Ranitidine is mainly excreted via urine (about 30% of an oral dose within 24 hours) and feces [10].

Half-life: The elimination half-life of ranitidine ranges from 2.5 to 3 hours, which may be prolonged in elderly patients due to reduced renal function, extending to 3-4 hours[11].

STATISTICAL ANALYSIS OF THE DATA.

Materials and Methods

Pre-formulation Studies: According to the techniques described by Mahajan et al., 2013 [12], the drug underwent comprehensive analysis including assessment of its physical

characteristics, melting point, solubility studies, partition coefficient, and drug interactions (FT-IR investigations) [13].

4.1 Physical Properties: The taste, odor, and color of the drugs were evaluated to determine their physical characteristics [14].

4.2 Melting Point: The melting point of the drugs was determined by placing a small amount in a capillary tube with one end closed, placing it in Thiele's melting point apparatus, and recording the temperature at which the drug melted. Three readings were averaged [15].

4.3 Solubility Studies: The solubility of the drugs was tested in distilled water, buffer solutions (pH 4.0, pH 7.4, and pH 8.0), and methanol. Three replicates were performed for each condition to calculate the average solubility.

4.4 Partition Coefficient: The partition coefficient of the drugs was determined using equal parts of n-octanol and water in a separating funnel. After mixing with a simulated tear solution (pH 7.4) and allowing it to stand, the aqueous and octanol phases were separated by centrifugation. UV-Vis Spectrophotometry was used to measure their respective absorbances before and after partitioning to estimate the partition coefficient.

4.5 Determination of Wavelength: UV-Vis spectrophotometry was employed to determine the absorbance properties of the drugs over a wavelength range of 200 nm to 400 nm. Quantitative analysis involved comparing absorbances of equimolar samples with standard solutions at their respective maximum wavelengths.

4.6 Fourier Transform-Infrared Spectroscopy (FT-IR): FT-IR spectroscopy was used to study drug-polymer interactions. Pellets were scanned in an inert atmosphere with 128 scans, a resolution of 4 cm-1, and an interval of 1 cm-1 over a wave number range of 4000-400 cm-1. Background spectra were subtracted from each spectrum.

Formulation Development: Mucoadhesive tablets were formulated using the direct compression method. Excipients compatible with Ranitidine were selected, and all ingredients were passed through a 60-mesh sieve. The blended powder was compressed using a compression machine to produce tablets.

5.1 Content Uniformity: Twenty tablets were triturated, and the powder equivalent to one tablet was dissolved in 100 mL phosphate buffer (pH 6.8). After heating at 37 ºC with stirring for 15 to 20 minutes, the solution was filtered, diluted suitably, and analyzed using UV spectrophotometry at lambda max to measure drug content.

5.2 Weight Variation Test: Twenty tablets were weighed together and individually using an analytical balance. The average weight and percentage variation of the tablets were calculated according to USP specifications.

5.10 Moisture Absorption Studies: Agar at 5% w/v was dissolved in hot water and transferred to petri dishes to solidify. Prior to testing, six tablets were vacuum-dried overnight to remove moisture. Initial weights of the tablets were recorded, followed by placing them on the agar surface and incubating at 37°C for one hour. After incubation, the tablets were reweighed, and the percent moisture absorption was calculated using the formula: % Moisture Absorption = (Wf - Wi) / Wi × 100, where Wf is the final weight and Wi is the initial weight of the tablets.

5.3 Surface pH Study: The surface pH of the tablets was measured to approximate the salivary pH range of 6.5 to 7.5, ensuring compatibility with mucosal surfaces. Tablets were allowed to swell in 1 mL of distilled water for 2 hours. A digital pH meter was used to measure the surface pH by placing the pH electrode near the tablet surface, allowing it to equilibrate for 1 minute before recording the measurement.

5.4 Swelling Index Studies: Four tablets were weighed and placed in petri dishes containing 1% agar gel. The petri dishes were incubated at 37 ºC ± 1 ºC, and excess water on the surface was carefully removed with filter paper at intervals of 0.5, 1, 1.5, 2, 2.5, and 3 hours. The tablets were reweighed after each interval, and the swelling index was calculated using the formula: Swelling Index (%) = (Wf - Wi) / Wi × 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 was used to measure the mucoadhesive strength. The apparatus consisted of a double beam physical balance with a pan on the right side and a string on the left side attached to a suctioned glass slide. The tablets were adhered to the glass slide. Porcine buccal mucosa was placed on top of an inverted 50 mL beaker inside a 500 mL beaker filled with phosphate buffer (pH 6.8) at 37 ºC. Five grams of weight was placed on the right pan before positioning the buccal tablet. After 5 minutes of contact with the mucosa, weights were added to the right pan to detach the tablet. The accumulated weight was recorded and subtracted from 5 g to determine the bioadhesive strength using the formula: N = W × g / 1000, where N is the bioadhesive force, W is the weight required for detachment of the tablet from the mucosa in grams, and g is the acceleration due to gravity (9.81 m/sec^2).

5.6 Residence Time: The residence time was assessed using a modified USP dissolution apparatus. A dissolution medium of 500 mL phosphate buffer with pH 6.8 was maintained at 37 ºC. Porcine buccal mucosa was affixed to a glass slide using adhesive and attached to the paddle of the dissolution apparatus. The tablet was hydrated with 15 µL phosphate buffer and placed in intimate contact with the porcine buccal mucosa for 30 seconds. Subsequently, it was immersed in the dissolution medium and rotated at 25 rpm. The time until displacement of the tablet from the mucosal surface was recorded.

5.7 Drug Release: In vitro drug release studies were conducted using USP dissolution test apparatus II, the paddle type, with a dissolution medium of phosphate buffer at pH 6.8. The

tests were performed at 37ºC ± 0.5ºC with a rotation speed of 50 rpm. Samples of 5 mL were withdrawn at intervals of 15, 30, 45, 60, 90, 120, 150, and 180 minutes and replaced with 5 mL fresh phosphate buffer. The amount of drug released was quantified at lambda max using UV spectrophotometry.

5.8 Stability Study: The tablets were stored for 3 months, and samples were tested after 30, 60, and 90 days. Quality control tests included hardness, friability, thickness, content uniformity, weight variation, and moisture absorption studies. In vitro tests included swelling studies, mucoadhesive strength, stability in human saliva, and drug release to assess stability over time.

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ISSN PRINT 2319 1775 Online 2320 7876
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