Development of Gastroretentive Mucoadhesive Solid Dosages Form Containing Amoxicillin Trihydrate and Ranitidine HCL for the Treatment of Helicobacter pylori Infections

Sushmita Mishra1*, Shalini Sharma1, Sandeep Sahu2, Amrita Chourasia3

ABSTRACT
Mucoadhesion can be explored in the design of a drug delivery system. Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface and mucin molecules, thus increasing the residence time of the dosage form at the site of absorption. The drugs having local action or possessing maximum absorption in the gastrointestinal tract (GIT) require an increased duration of stay in GIT. Gastro retentive mucoadhesive solid dosages form containing amoxicillin trihydrate and ranitidine HCL were formulated to prolong the residence time of the dosage form at the site of application or absorption, and it results in intimate contact of the dosage form with the underline absorption surface. FDA approves this combination for the treatment of Helicobacter pylori Infections. The formulation results in efficient absorption, enhanced bioavailability of the drugs due to a high surface-to-volume ratio and an improved therapeutic performance of the drug. The prolonged drug release resulted in reduced drug administration frequency and improved patient compliance. The optimized formulation was evaluated for various parameters i.e. hardness, friability, thickness, weight variation, drug content, dissolution study and swelling index.

Keywords: Gastric Retention Formulations (GRFs), Mucoadhesive, Amoxicillin Trihydrate, Ranitidine HCL, Helicobacter pylori,

INTRODUCTION
Oral route is undoubtedly most favored route of administration, but hepatic first-pass metabolism, drug degradation during absorption, mucus covering GI epithelia, and high mucus turnover are serious concerns of oral route. In recent years, gastrointestinal tract (GIT) delivery emerged as a most important route of administration. Bioadhesive retentive system involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the GIT. Using bioadhesives would be achieved increase GI transit time and increase in bioavailability. Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 μm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially, depending on the species, the anatomical location and pathological states. However, it has general composition.

Due to their considerable therapeutic advantages, oral controlled release (CR) dosage forms (DFs) have been developed for the past three decades. However, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal tract, i.e. stomach and small intestine.

Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, but the coupling of mucoadhesive properties to tablet has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer. Mucoadhesive tablets can be tailored to adhere to any mucosal tissue, including those found in stomach, thus offering the possibilities of localized and systemic controlled drug release. The application of mucoadhesive tablets to the mucosal tissues of gastric epithelium is used for the administration of drugs for localized action. Mucoadhesive tablets are widely used because they release the drug for prolong period, reduce frequency of drug administration and improve patient compliance.

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of solid dosages form used for treating *Helicobacter pylori* infection. *H. pylori* is very sensitive to amoxicillin both *in-vivo* and *in-vitro*. Amoxicillin works by inhibition of bacterial cell wall synthesis, leading to cell death. Amoxicillin has topical intraluminal activity at the level of the gastric mucosa, as well as systemic activity. The advantage of amoxicillin is that *H. pylori* does not develop resistance to it, and it can be used again in another antibiotic regimen. Ranitidine is a histamine 2-receptor-antagonist (H2RA). Ranitidine works by reducing the amount of acid your stomach produces. The agent has been developed for the treatment of patients with duodenal ulcer with or without infection with *H. pylori*. Combining Ranitidine HCL with amoxicillin trihydrate has resulted in an eradication rate of 72 to 80% compared to th The food and drug administration recently approved this combination. As mentioned earlier, the combination of Ranitidine HCL with amoxicillin trihydrate has been shown to be effective in eradicating *H. pylori* infection. Therefore, we have planned in the development of gastro retentive mucoadhesive tablet containing Amoxicillin Trihydrate and Ranitidine HCL which may result in improved patient compliance, easy to administration, increased residence time resulting in enhanced absorption and increased therapeutic efficacy of the drug with reducing frequency of drug administration.

**Material and Methods**

The chemicals used were of laboratory reagents grade and were used as they were procured. Amoxicillin trihydrate and ranitidine hydrochloride were procured from Sun Pharmaceuticals Industries Limited, Indore. Rest of the chemicals, Guar Gum (GG), Micro Crystalline Cellulose (MCC), polyvinyl pyrollidone K-30 (PVP), Talc and magnesium stearate were procured from Central Drug House Pvt. Ltd. The distilled water was used in all experiments.

**Instruments used in the studies were UV Spectrophotometer Shimadzu 1800, FT-IR, Electronic Weighing balance, Hardness tester, Friability test apparatus and Standard USP or IP dissolution apparatus.**

**Procedure**

**Preformulation study**

Pre formulation study of both drug i.e. amoxicillin trihydrate and ranitidine HCL, are performed its include solubility, melting point, FTIR, Angle of repose, Bult and Tap density.

**Calibration curves of both drugs are performed by UV visible spectrophotometer.**

**Calibration curve data of Ranitidine HCL**

**Preparation of standard stock solution**

An accurately weighed quantity of ranitidine (10 mg) was dissolved in 100 mL of water to prepare a stock solution of 100 µg/mL of ranitidine.

**Determination of absorption maxima (λ max)**

Standard solution containing 10 µg/mL of ranitidine was scanned for the absorption maxima between 200 to 400 nm. Two absorption maxima were obtained i.e. one at 315 nm and the other at 231 nm.

**Calibration curve data of Amoxicillin Trihydrate**

**Preparation of standard stock solution**

An accurately weighed quantity of amoxicillin (10 mg) was dissolved in 100 mL of ethanol to prepare a stock solution of 100 µg/mL of amoxicillin.

**Determination of absorption maxima (λ max)**

Standard solution containing 10 µg/mL of amoxicillin was scanned for the absorption maxima between 200 to 400 nm. Two absorption maxima were obtained i.e. one at 228 nm and the other at 331 nm.

**Formulation of Mucoadhesive Tablets**

Wet Granulation Method: Mucoadhesive tablets of ranitidine and amoxicillin were prepared by wet granulation technique using different concentrations of Guar gum and microcrystalline cellulose. All the ingredients were passed through sieve no. 85# and were mixed uniformly. Granulation was carried out with sufficient quantity of binder solution (PVP k30- 5% in water). Wet mass passed through sieve no. 12# and dried at 45 to 55°C for 1-hour. Dried granules were sized by sieve no. 18# and add magnesium stearate and t alc. Then tablet punching machine was used to compress tablets containing 150 mg ranitidine and 250 mg amoxicillin at an average weight of 800 mg per tablet.

**Post-compression parameters of mucoadhesive tablet:**

**Appearance**

Twenty tablets of each formulation were taken to check any discoloration or surface roughness in the tablet formulation.

**Weight variation test**

To study weight variation tablets were weighed using an electronic balance and the test was performed according to
the Indian Pharmacopoeia.

**Hardness**
The hardness of five tablets was determined using the Monsanto hardness tester and the average values were calculated.

**Thickness**
The Thickness of the tablets was determined using manual Vernier Caliper. Five tablets were used, and average values were reported.

**Friability**
The friability of 20 tablets was measured by Roche friability by rotating for 4 minutes at 25 rpm up to 100 revolutions. Accurately weighed 20 tablets were placed into Roche friability for 100 revolutions then dedusted and weighed again.

\[
\% \text{ Friability} = \frac{W_0 - W}{W_0} \times 100
\]

\(W_0=\) Initial weight of tablet
\(W=\) Weight of tablet after revolution

**Procedure to study Drug release of different formulation**

**Dissolution Time**
*In-vitro*, release study Standard USP or IP dissolution apparatus have been used to study *in-vitro* release profile using both basket and rotating paddle. *In-vitro* release rate study of the mucoadhesive tablet was carried out using the Apparatus 2 (Basket apparatus) method. Place the tablet in a dry basket at the beginning of each test. Lower the Basket before rotation operates the apparatus immediately at 50 rpm. Medium used for release rate study was 900 mL 0.1 N HCl during the course of study whole assembly was maintained at 37±0.5°C. Withdraw a 5 mL of sample at specific time interval and replaced with 5 mL of fresh dissolution medium. The withdrawn samples were diluted with dissolution medium and then filtered with whatman filter paper and assayed.

**Procedure to study Swelling index of different formulation**

**Swelling Studies**
The degree of swelling of mucoadhesive polymer is an important factor affecting adhesion. For conducting the study, a tablet was weighed and placed in a petridish containing 5 mL of 0.1 N HCl buffer pH 1.2 in 6 hours at regular intervals of time (1, 2, 4, and 6 h), the tablet was taken carefully by using filter paper. The swelling index was calculated using the following formula.

\[
\text{Swelling Index (S.I)} = \frac{(Wt-Wo)}{Wo} \times 100
\]

Where S.I = swelling index.

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<th>Table 1: Composition of mucoadhesive tablet</th>
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<td><strong>Composition</strong></td>
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<tr>
<td>Amoxicillin trihydrate</td>
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<tr>
<td>Ranitidine HCL</td>
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<td>GG</td>
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<td>MCC</td>
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<td>PVP</td>
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<td>Talc magnesium stearate</td>
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<td><strong>Total weight (mg)</strong></td>
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<th>Table 2: Pre-compression parameters of amoxicillin trihydrate</th>
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<th>Table 3: Pre-compression parameters of ranitidine HCL</th>
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<td><strong>Formulation</strong></td>
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<th>Table 4: Evaluation of physical parameters of different mucoadhesive tablets</th>
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\(W_t=\) weight of tablet a filter swollen at time \(t\),
\(W_0=\) weight of the initial tablet

**Results and Discussions**
Mucoadhesive tablets of ranitidine and amoxicillin were prepared by wet granulation technique using different
concentration of Guar gum and microcrystalline cellulose. Five formulations from F1 to F5 are prepared, total weight of tablet is 800 mg. (Table 1).

**Evaluation of Mucoadhesive Tablet**

Evaluation of mucoadhesive table are performed by different parameters like % drug content, % water absorption, mucoadhesive strength. (Table 5)

%water absorption studies done by Agar at 5% w/v was dissolved in hot water and then transferred to a petri dish and was allowed to be solidified. Prior to the study, six tablets were placed in a vacuum overnight to remove moisture. They were 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 were reweighed and the percent moisture absorption was calculated using the formula:

\[
\text{% Moisture Absorption} = \left( \frac{W_f}{W_i} \right) \times 100
\]

Where Wf is the final weight and Wi is the initial weight of the tablets

**Mucoadhesive/bioadhesive strength**

A modified physical balance was 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 was hanged and at the bottom of the string was a suctioned glass slide. This was the place where the tablets were placed using an adhesive. The porcine buccal mucosa was placed on top of an inverted 50 mL beaker which was placed inside a 500 mL beaker that was filled with phosphate buffer with pH 6.8 kept at 37 ºC. The buffer amount was just enough so that it reaches the buccal mucosa surface. Exactly five gram of weight was placed on the right pan before putting the porcine buccal tablet in place. The weight was then removed to lower the glass slide with the attached buccal tablet. The tablet was to be in contact with the porcine buccal mucosa membrane and this was not disturbed for 5 minutes. After 5 minutes, weights were added on the right side of the pan to separate the tablet from the membrane. The accumulated weight on the right side was then noted and subtracted with 5 g. The value was taken as the measure for the bioadhesive strength of the tablet. The bioadhesive force was calculated using the formula:

\[
N = \frac{W \times g}{1000}
\]

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 (Fatima et al., 2015; Lodhi et al., 2013; Prasad et al., 2010). Figure 1 shows the modified physical balance.

<table>
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<th>Table 5: Evaluation parameters of different mucoadhesive tablets</th>
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<th>Table 6: Drug release of different formulations</th>
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<td><strong>Time in Hours</strong></td>
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USP dissolution test apparatus II, the paddle type with dissolution medium of phosphate buffer with a pH of 6.8. It was performed at 37 °C + 0.5 °C with a speed of 50 rpm. The sample at 5 mL was withdrawn at time interval of 15, 30, 45, 60, 90, 120, 150, 180 minutes and was replaced with 5 mL of fresh phosphate buffer.

**CONCLUSION**

Mucoadhesive dosage forms have a high potential of being use full means of delivering drugs to the body for topical or local administration. The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates. The various advantage of the oral mucoadhesive drug delivery systems like prolongation of the residence time of the drug which in turn increases the absorption of the drug are important factors in the oral bioavailability of many drug.

Mucoadhesive tablets in general have the potential to be used for controlled release drug delivery; mucoadhesive tablets has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs, more intimate contact with the mucus layer. Mucoadhesive tablets are widely used because they release the drug for prolonged period, reduce the frequency of drug administration and improve patient compliance.

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Combined ranitidine HCL with amoxicillin trihydrate has resulted in an eradication rate of 72 to 80% compared to triple antibiotic therapy. The food and drug Administration recently approved this combination. As mentioned earlier, the combination of ranitidine HCL with amoxicillin trihydrate has been shown to be effective in eradicating *H. pylori* infection.

Therefore, we have planned in the development of gastro retentive mucoadhesive tablet containing amoxicillin trihydrate and ranitidine HCL which may result in improved patient compliance, easy to administration, increased residence time resulting in enhanced absorption and increased therapeutic efficacy of the drug with reducing frequency of drug administration.

**References**


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