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# ENALAPRIL DISSOLUTION PROFILES IN PREOPERATIVE AND POSTOPERATIVE MODEL OF GASTRIC BYPASS SURGERY

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**Abstract: Introduction:** Enalapril, an antihypertensive drug commonly used in populations with arterial hypertension, is also a therapeutic option for obese patients. However, the process of bariatric surgery, a prevalent intervention in obesity, introduces a significant challenge. This surgery involves a restriction in nutrient absorption, which can complicate the dissolution and absorption of orally administered drugs, including antihypertensives like Enalapril. **Objective:** To compare the dissolution profile of Enalapril 20mg tablet presentations marketed in Colombia, simulating pre- and post-bariatric surgery conditions using an in vitro model. **Materials and Methods:** A biopharmaceutical dissolution profile study of 4 brands of Enalapril was performed by simulating the gastrointestinal conditions of pre- and post-surgical patients undergoing bariatric surgery according to the specifications established in the United States Pharmacopeia 38 for dissolution profiles modifying the pH to emulate the pre-surgical and post-surgical environment. The behavior of each drug in the different media was compared. **Results:** The methodology, validated using UV-Vis spectroscopy for both acidic and basic media, demonstrated a high level of accuracy with a percentage recovery of 97.53±0.43; 97.67±0.39 for acidic and basic media, respectively. The study confirmed that Enalapril not only met but exceeded the %Q standards set in USP38, a testament to its quality. Importantly, all brands exhibited identical behavior in both pH and volume. Notably, the innovator drug showed no discernible differences from the other brands. **Conclusions:** This research, with its robust methodology, unequivocally demonstrated that there was no significant difference between the dissolution profiles for each enalapril brand marketed in Colombia, regardless of the pH of the pre-surgical and simulated post-surgical environment. This finding is of utmost importance for the pharmaceutical industry, as it suggests the interchangeability of these brands.

**Keywords:** Enalapril, Gastric Bypass, Dissolution Profile.

## INTRODUCTION

Obesity has been recognized as a severe threat to global health; by 2022, more than 1 billion people will be obese, of which 43% are adults. Obesity is associated with many comorbidities, such as hypertension, as well as unfortunate outcomes leading to shorter life expectancy[1, 2]. Since diet and exercise alone cannot achieve the desired weight loss, other effective long-term treatments for obesity are needed.(2) Because of this, surgical intervention such as bariatric surgery is considered one of the treatment options. In 2016, approximately 700,000 bariatric surgeries were performed worldwide (an increase of 46 % compared to 2013).(3)

The development of morbid obesity as an underlying pathology is associated with comorbidities, such as type II diabetes mellitus, hypertension, cardiovascular disease, asthma, and sleep apnea; these significantly affect patients' quality of life and raise the cost of pharmacotherapeutic treatment of patients (4).

One of the main treatments for morbid obesity is bariatric surgery (5), which generates modifications in the gastric anatomy-physiology by decreasing the size of the stomach, (6) producing a decrease in the number of parietal cells, thus increasing the luminal pH (7); Patients who have undergone this surgery are at risk of nutrient deficiency. Several factors, such as pH and absorption sites, should be considered when providing these patients with adequate supplementation, drug solubility, and surface area(8). Without passing through large portions of the small intestine, Roux-en-Y procedures drastically reduce the absorption surface area (9). The gastrointestinal tract conditions are unique because the volume is reduced between 40 mL to 60 mL, which flows in plus or minus 60 seconds, depending on the individuals physiology, directly into the upper jejunum.

On the other hand, Padwal et al. 2010, identified significant alterations in the processes of release, adsorption, distribution, metabolism, and excretion of drugs within which the release is affected in patients who underwent bariatric surgery since the enzymes produced in the stomach in charge of disintegrating the tablet (amylase, lipases, and proteases) are produced in deficient quantities (10).

Undoubtedly, the reduction of the enzymatic production and the increase of the luminal pH leads to a decrease in the assimilation of nutrients from the diet, and this promotes alterations that could decrease the disintegration of the tablet, which gradually affect all the pharmacokinetic parameters of the drugs used by patients for the treatment of diseases associated with obesity, among which arterial hypertension stands out due to its high prevalence at present. After Roux-en-Y surgery, the patient must continue taking antihypertensive drugs, among others. However, these medications are not formulated with pharmaceutical technology for structural swwmodifications of the gastrointestinal tract. Therefore, this work evaluates Enalapril dissolution profile, taking into account the change in volume and pH adapted to the post-surgical and pre-surgical conditions of patients undergoing Roux--en-Y bariatric surgery (8).

According to the previous paragraph, it becomes important to analyze the drug under simulated post-surgical conditions because Enalapril could have problems in disintegration and dissolution that gradually affect all pharmacokinetic parameters due to physiological and anatomical affectations of the new gastrointestinal tract, reflected in therapeutic failures and increased adverse reactions.

Since one of the objectives of the present work was to study Enalapril in an in vitro medium that simulates the gastrointestinal conditions of patients who have undergone gastric bypass, it should be emphasized that the systemic bioavailability of a drug depends on the absorbed fraction and the intestinal or hepatic metabolism that may occur. This absorbed fraction corresponds to the drug that passes from the intestinal lumen into the bloodstream. This passage of the drug from the site of administration to the blood involves its absorption, defined in turn by the processes of dissolution and permeation of the drug.

Therefore, this study allows us to describe the dissolution and disintegration of the tablet-type pharmaceutical forms of 4 presentations of Enalapril of different brands registered in Colombia using simulated gastric dissolution media with pH 1.2 and intestinal pH 6.8, in addition to a gastric medium with volume reduction.

## MATERIALS AND METHODS

### SELECTION OF THE STUDY POPULATION AND SAMPLE

In the present study, three commercial brands of Enalapril 20 mg generic and innovator distributed in the cities of Cartagena, Barranquilla, and Santa Marta were used; these were randomly selected in the different drugstores of the cities, with the precaution that the tablets were within their shelf life and with current Health Registration.

Enalapril was chosen because it is a first--choice antihypertensive; the side effects reported are not relevant (11), (12). It is also included in the Colombian Compulsory Health Plan and is widely used in hypertensive patients with bariatric surgery.

To avoid analytical bias, each lot was randomly identified with the letters G, L, M, and R. During the studies, the products were stored on closed shelves protected from light at 25 °C and 60 % relative humidity.

## MATERIALS INSTRUMENTATION

An Ultraviolet (UV)-VISIBLE 1700 spectrophotometer - Shimadzu (Kyoto, Japan) was used to read the samples. The dissolving equipment LID 6 (Vanguard Pharmaceutical Machinery). Orion 3-STAR pH meter (Benchtop). Samples and standards were weighed on an analytical balance - Ohaus. A Pure Pro System produced the water used. The volumetric material is class A, and a 100-1000 µL micropipette was used.

## REAGENTS

Reagents such as Potassium monobasic phosphate (99%), Sodium hydroxide (NaOH), Sodium chloride, and fuming hydrochloric acid (37 %, analytical grade) were of the Merck brand. The secondary standard of Enalapril, the Specialized Laboratory of Analysis of the University of Antioquia, supplied 99%.

## METHODOLOGY OF ANALYSIS FOR BIOPHARMACEUTICAL TESTS

### Dissolution with simulated media

The dissolution profile of 4 presentations of Enalapril was determined in a standard model (Pre-Operative) whose pH was 1.2 and in a post-surgical model (Post-Operative) of Gastric Bypass bariatric surgery, which had a pH of 6.8 (13).

- **Acidic media (mimicking pre bariatric surgery) simulated gastric fluid:** 2 g of NaCl were dissolved in 7.0 mL hydrochloric acid (HCl) and brought to 1000 mL. The pH was adjusted to 1.2 in each medium preparation for each brand individually (13).
- **Less acidic media (mimicking post bariatric surgery) simulated intestinal fluid:** 6.8 g of monobasic potassium phosphate was dissolved in 250 mL of water. 77 mL of 0.2 N NaOH and 500 mL of water were mixed, and the resulting solution was adjusted with 0.2 N NaOH or 0.2 N HCl, brought to pH 6.8, and volumetrized with water to 1000 mL (13).
- **Reduced dissolution volume** (200 ml instead 900 ml) mimicking the physical reduction of GIT following the bariatric surgery.

### Model of the dissolution profile

- **Simulated gastric and intestinal medium with volume of 900 mL (mimicking pre bariatric surgery):** For each simulated dissolution medium condition (gastric and intestinal), four generic and innovator brands of Enalapril 20 mg were evaluated in triplicate. Apparatus I (basket) of the LID-6 VPM Dissolving Apparatus was used, using 900 mL of each dissolution medium at a temperature of 37.0 +/- 0.5 °C and agitation speed of 50 rpm, taking aliquots of 5 mL at different times during 30 minutes, to subsequently filter and quantify in a UV-VISIBLE Shimadzu 1700 Spectrophotometer at 215 nm and finally the concentrations of dissolved drug (%Q) vs. the time of the dissolution profile were plotted for each of the different commercial brands under study (13).
- **Simulated intestinal medium with a volume of 200 mL ( mimicking post bariatric surgery)**: Four generic and innovator brands of Enalapril 20 mg were evaluated in triplicate. Apparatus I (basket) of the LID-6 VPM Dissolving Apparatus was used, with 200 mL of the dissolution medium at a temperature of 37.0 +/- 0.5 °C and agitation speed of 50 rpm, taking aliquots of 5 mL, at different times during 30 minutes, each aliquot taken was made a dilution which constituted taking 1 mL of the solution in 4mL of intestinal medium for later, filtering and quantification in a UV-VISIBLE Spectrophotometer

Shimadzu 1700 at 215 nm and finally the concentrations of dissolved drug (%Q) vs. time of the dissolution profile were plotted for each of the different commercial brands under study (13).

For the quantification of Enalapril in dissolution media by UV-VIS spectroscopy, a calibration curve was prepared with the secondary standard of Enalapril 99% purity supplied by the Drug Analysis Laboratory. The points of the curve will be at concentrations of 2.5, 5, 10, 15, 20, 30, and 40 ppm, respectively.

In the test, 5 mL samples were simultaneously taken from each dissolution beaker at 1, 3, 5, 7, 10, 15, 20, and 30 minutes in the six dissolver beakers. The amount of dissolved drug was quantified by linear regression from the calibration curve.

### STATISTICAL ANALYSIS

The calculated active principle (AP) values of the generic and branded Enalapril drugs subjected to dissolution profile tests in acidic and basic media were analyzed by inferential statistics applying a student's t-test, accepting statistically significant differences between the concentration data in each of the media at a p-value> 0.05.

Moreover, we undertook a comprehensive analysis of the AP concentration data of the different brands of Enalapril in each medium, both acidic and basic. This was done through a one-way ANOVA, followed by a Tukey post-test for multiple comparisons. Figure 1 was made in Excel software. This meticulous approach allowed us to evaluate the differences between the dissolution profile values of each brand in gastric and intestinal medium, leaving no aspect of the drug's behavior unexplored.

## RESULTS

The quantification and validation criteria of the technical qualities of the methodology for the dissolution analysis of the samples of the antihypertensive Enalapril from 4 different pharmaceutical laboratories were performed in the UV-Vis spectroscopy equipment in a Shimadzu 1700 equipment of the LAM (Laboratory of Drug Analysis) in the Faculty of Pharmaceutical Sciences of the University of Cartagena, the criteria for the validation were based on the established in the USP 38 (13).

### DISSOLUTION PROFILES IN GASTRIC AND INTESTINAL MEDIA

The dissolution profiles were performed according to the procedures described in the methodology. Figures 1 panel A and B, show the behavior of each commercial brand of Enalapril 20mg in the two simulated dissolution media with a volume of 900mL and a reduced volume of 200mL. The pH of the gastric medium was 1.2, and the intestinal pH was 6.8.

### AREA UNDER THE CURVE (AUC)

The AUC is a pharmacokinetic parameter that expresses the total amount of drug dissolved in the simulated medium. This value was calculated by obtaining the results shown in Table 1. The averages of the AUC area of the dissolutions in gastric medium 900 ml, intestinal medium 900 ml, and intestinal medium with volume reduced to 200 mL obtained are 2434, 2326, and 2396, respectively. Drug G in gastric medium 900 ml presented a result of 2761, the highest AUC value obtained in all media, followed by drug L in gastric medium 900 ml with 2578. There were not significant differences.


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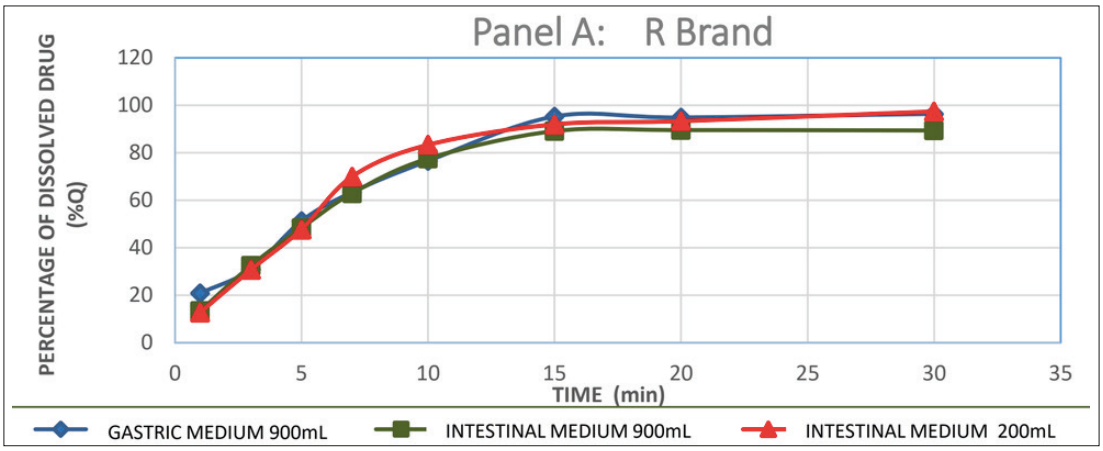


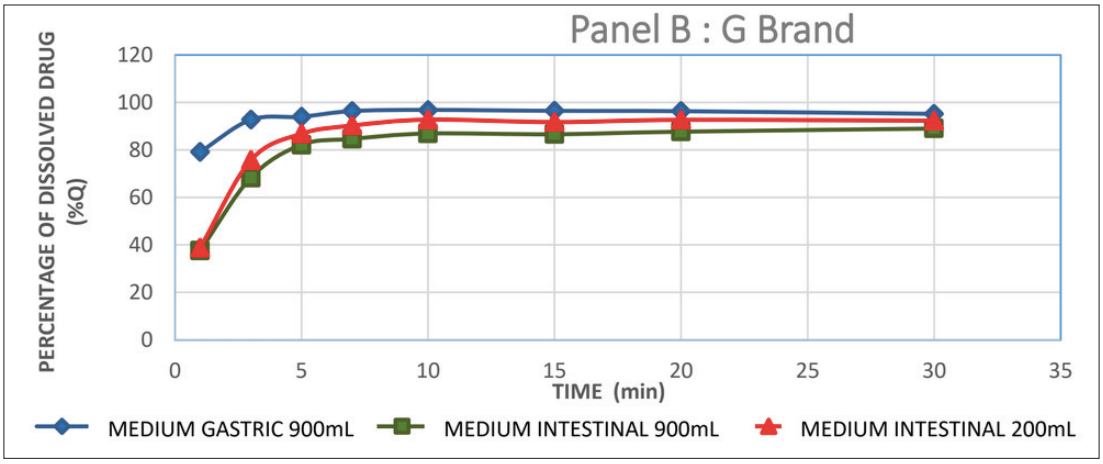


Figure 1. Dissolution profiles of enalapril brand R (see panel A) and brand G (see panel B) in the different simulated media expressed as %Q.

| Brand | GASTRIC MEDIUM 900 mL | INTESTINAL MEDIUM 900 mL | INTESTINAL MEDIUM 200 mL |
|---|---|---|---|
| **G** | 2761 | 2433 | 2577 |
| **L** | 2578 | 2519 | 2545 |
| **M** | 2078 | 2146 | 2137 |
| **R** | 2319 | 2207 | 2325 |

Table 1. Area Under the Curve (AUC) of each brand of Enalapril 20 mg in the respective gastric and intestinal simulated media.

*P > 0,05

| Brand | GASTRIC MEDIUM 900mL | INTESTINAL MEDIUM 900mL | INTESTINAL MEDIUM 200mL |
|---|---|---|---|
| G | 98,0181159 | 94,28405348 | 96,1739455 |
| L | 92,93566408 | 94,22105854 | 92,85062922 |
| M | 77,47949292 | 76,25222025 | 79,90654206 |
| R | 82,98443371 | 85,13305052 | 82,31545406 |

Table 2. Dissolution efficiencies in each of the different simulated gastric and intestinal media.

*P > 0,05

**PERCENTAGE DISSOLUTION EFFICIENCY**

Dissolution efficiency (DE) is the capacity of the drug to be released in the appropriate medium in the corresponding time; in this work, it was taken as the ratio between the AUC of the dissolution up to 30 minutes and the total area of a rectangle describing 100% of the dissolution at this time. The percentages of dissolution efficiency for each of the different pre- and post-surgical simulation media are shown in Table 2, where each mark is identified with its corresponding letter, which was the object of study in the present work.

## DISCUSSION

Enalapril is a prodrug that belongs to the angiotensin-converting enzyme (ACE) inhibitor class of medications. Its action is inhibited by the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, thereby reducing blood pressure and improving heart function. Enalapril is well-absorbed in the gastrointestinal tract, primarily in the small intestine. Previous studies have investigated the dissolution properties of enalapril tablets, which is an important factor in their bioavailability.(10)

In this study, firstly validation of the analytical method yielded significant results. The linearity for the enalapril dissolution profile method in the gastric medium showed a linear regression coefficient value of r = 0.9988 and the coefficient of determination R2 = 0.9994. Similarly, the linear regression coefficient for the intestinal medium was r = 0.9994, and the coefficient of determination R2 = 0.9993 (See Figure S1 and S2 supplementary materials). These results, which are within the acceptance criteria established by USP 38(14), indicate the linearity of the method. The precision for each simulated medium studied obtained average recovery percentages of 97.53% and 97.6666%, respectively, which were within the limits established for spectrophotometric methods (97-103%) and coefficients of variation (CV) of 0.021 and 0.0236, according to the Criteria he %CV should be ≤3%. This demonstrates the precision of the method for each medium. The precision data obtained confirmed the method's excellent reproducibility. The application of the optimized and validated method to the analysis of Enalapril brands as the coefficient of variation (RSD) values were not more significant than 3%, demonstrating that the method's precision study is suitable for chemical and spectrophotometric methods (13) .

For the dissolution profiles shown above, it is known that the tolerance described according to USP 38 establishes that the Q value must be greater than 80 before reaching 30 minutes, which indicates that a product will be considered fast dissolving, as established by the United States Pharmacopoeia (14).

Theoretically, the products are expected to have similar behavior and no differences in dissolution profiles. After analysis using the dissolution profile, all commercial brands of Enalapril were observed and contrasted with the dissolved drug value (Q) at 30 minutes in simulated gastric and intestinal media (7). The dissolution profiles of the tablets in the study presented a value above 80% dissolved drug (%Q) in gastric and intestinal media during the trial. Based on this, pH variation does not significantly affect drug release and dissolution, as none of the values were below specifications.

Among the products evaluated, those typed with the letters L and G presented %Q higher than 80 after 3 minutes in the gastric medium, unlike M and R, which reached %Q 80 after 20 minutes. In the 900 mL simulated intestinal medium, M and L marks reached a %Q of 80 after 5 minutes. After 15 minutes, all brands reached the minimum %Q in the intestinal medium with a volume of 200 mL. It is observed how brand G manages to reach the %Q value 5 minutes after the start of the study, followed by brand L; at 10 minutes, both brands G, L, and

R reached %Q values, and at 15 minutes, all brands reached %Q values, which shows that there may be significant differences in their release or dissolution. However, the required %Q values are reached at the end of the study.

It is crucial to emphasize that the variability of pharmaceutical products on the market can significantly impact biopharmaceutical parameters. This is likely due to differences in excipients and formulation adjuvants, as our research with Enalapril products has demonstrated. These findings underscore the importance of standardized testing methods and formulation practices, providing a clear path to ensure consistent drug performance.

Table 1 shows the results of the four brands of Enalapril and the comparisons between simulated media in a 900 ml volume of simulated gastric and intestinal media and simulated intestinal media with a 200 ml volume reduction. The four brands and their different media had similar values, showing no variation in their dissolution capacity in any given medium.

On the other hand, brands G and L presented the highest % of D and E, which exceeded 90% in all three media. These have good dissolution efficiencies in both media, which is essential for the bariatric patient as pH variation due to parietal cell depletion does not significantly affect the dissolution of the Enalapril drug. However, their dissolution profiles are unequal, with no significant differences. Brand R obtained percentages higher than 80, and brand M obtained the lowest % dissolution efficiency. Although brands M and R have the lowest DE, this indicates that their release was slightly slower than G and L. This may be due to the excipients in each brand in each study tablet, but in general, they all complied. With the requirements of USP 38 (14) Therefore, according to the results found in the present study, the pH of the simulated in vitro medium does not condition the solubility of these drugs in bariatric patients.

Drug dissolution is affected by pH. Drugs more soluble at acidic pH are absorbed in the stomach, and those soluble in alkaline environments are absorbed in the small intestine. In addition, some drugs rely on enzymes in the small intestine to aid their absorption. In patients who have had gastric bypass surgery, the remaining small stomach pouch produces a smaller amount of HCl than the entire stomach, possibly decreasing the absorption of drugs that rely on acidic environments for solubility or absorption. (14)

On the other hand, the possibility of therapeutic failures in the use of enalapril, although the results show that there is no statistically significant difference in the dissolution of the drugs in the pre-surgical and post-surgical media, the research of Utria (15) shows that when changing the drug using other ACE inhibitors such as Captopril based on USP 38, lower dissolution profiles are obtained in some brands marketed in Colombia, increasing the possibility of therapeutic failures in post-bariatric patients with hypertension, however, these alterations in the results are not statistically significant, lower dissolution profiles are obtained in some brands marketed in Colombia, increasing the possibility of therapeutic failure in post-bariatric patients with hypertension. However, these alterations in the results are not the same as those of other brands.

## CONCLUSION

This investigation, with its robust methodology, demonstrated unequivocally that there was no statistically significant difference between the dissolution profiles for each brand of enalapril marketed in Colombia, regardless of the pH of the simulated pre-surgical and post-surgical environment.

There was no difference between the AUCs of the different media for the different brands marketed in Colombia, indicating that the drugs dissolve well in both media.

These findings, of significant importance for the pharmaceutical industry, suggest the interchangeability of these brands, potentially impacting the way these medications are manufactured and prescribed.

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