FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF PANTOPRAZOLE

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Abstract

Gastroretentive drug delivery systems (GRDDS) are designed to prolong the gastric residence time of drugs, thereby enhancing their bioavailability and therapeutic efficacy. The present study focuses on the formulation and evaluation of gastroretentive floating tablets of Pantoprazole, a proton pump inhibitor widely used in the treatment of peptic ulcers and gastroesophageal reflux disease. Floating tablets were prepared using hydrophilic polymers such as HPMC K4M and HPMC K15M, along with gas-generating agents like sodium bicarbonate and citric acid to achieve buoyancy. The prepared formulations were evaluated for various physicochemical parameters including thickness, weight variation, hardness, friability, drug content, floating lag time (FLT), and total floating time (TFT). In vitro dissolution studies were carried out in 0.1 N HCl to assess the drug release profile. The results indicated that the optimized formulation exhibited satisfactory floating behavior with minimal lag time and prolonged floating duration, along with sustained drug release over an extended period.

The study concludes that gastroretentive floating tablets of Pantoprazole can be successfully formulated to improve gastric retention and provide controlled drug release, thereby enhancing therapeutic effectiveness and patient compliance.

Keywords: Pantoprazole, Gastroretentive Drug Delivery System (GRDDS), Floating Tablets, HPMC, Floating Lag Time (FLT)

1. INTRODUCTION

Oral delivery of drugs is still the most commonly used delivery method because it is convenient, patients are willing to comply, it is cost-effective, and simple to prepare. Nevertheless, the traditional types of oral dosage preparation are usually characterized by various shortcomings, including limited gastric retention, inadequate absorption of the drug, and irregular plasma concentration of the drug. These issues are especially critical to drugs that are mainly absorbed in the upper section of the gastrointestinal tract (GIT) or are unstable within the intestinal environment. In order to address these shortcomings, sophisticated drug delivery modalities like gastroretentive drug delivery systems (GRDDS) have been invented.

Drug delivery systems are gastroretentive, aimed to increase the residence time of dosage forms in the stomach to increase the absorption of drugs and increase bioavailability. Among the different methods, floating drug delivery system (FDDS) have attracted much attention because it is capable of achieving a longer duration of floating on the gastric fluids. These systems are dilute in comparison to gastric contents and rely on the use of gas-generating agents or swellable polymers to obtain flotation. Floating systems, by staying in the stomach, offer a controlled release of drugs, decreasing the number of doses, and enhancing effective therapy.

Pantoprazole is a proton pump inhibitor common in the treatment of acid related diseases including peptic ulcer, gastroesophageal reflux disease (GERD) and Zollinger-Ellison syndrome. It works by blocking the H +K- +ATPase enzyme in the gastric parietal cells irreversibly, thus decreasing the amount of gastric acid secretion. Although Pantoprazole has therapeutic significance, there are some shortcomings of the drug such as the short biological half-life, stability determined by pH, and low bioavailability because of rapid gastric emptying. Thus, the creation of a gastroretentive preparation of Pantoprazole can dramatically increase its therapeutic effect on the basis of a longer retention period in the stomach and a stable release of the drug.

Floating tablet is one of the promising methods of gastroretentive Pantoprazole delivery. These systems usually incorporate hydrophilic polymers like hydroxypropyl methylcellulose (HPMC) which swell in the presence of gastric fluid to create a gel barrier that releases the drugs. Further,

effusive substances like sodium bicarbonate and citric acid produce carbon dioxide gas that becomes trapped in the moist matrix allowing the tablet to float. The effect of swelling and gas production together leads to the increased retention of gases and the slow release of drugs in the stomach.

To create floating tablets, polymers, gas-generating agents, and excipients should be carefully chosen to provide the best buoyancy, mechanical strength, and release properties. Floating lag time, total floating duration, hardness, friability, drug content and in-vitro dissolution profile are key parameters of evaluation used to measure the performance of the developed formulation. Moreover, stability researches should be conducted to make sure that the formulation will retain its quality and effectiveness stored.

In this regard, the current research will develop and test gastroretentive floating pills of Pantoprazole using appropriate polymers and excipients. The aim is to gain a long-term gastric retention, controlled delivery, and a better bioavailability. The research also determines the physicochemical characteristics, floating, and stability of the formulation developed with the aim of determining its appropriateness as an effective gastroretentive drug delivery system.

2. EXPERIMENTAL METHODS

2.1 Materials

Pantoprazole sodium was received as a gift sample of Sun Pharmaceutical Industries Ltd., Mumbai, India. Hydroxypropyl methylcellulose (HPMC K4M and HPMC K15M) was also purchased in Colorcon Asia Pvt. Ltd., Goa. Sodium bicarbonate and citric acid were obtained in Loba Chemie Pvt. Ltd., Mumbai. Polyvinylpyrrolidone (PVP K-30) was sourced at BASF India ltd., Mumbai. SD Fine-Chem Ltd., Mumbai provided lactose. Magnesium stearate and talc were obtained Himedia Laboratories Pvt. Ltd., Mumbai.

The remaining reagents were of analytical reagent (AR) grade. Throughout the study, distilled water was used.

2.2 Preformulation Studies

2.2.1 Melting Point Determination

A digital melting point apparatus was used to determine the melting point of Pantoprazole sodium. The powdered drug was packed in a capillary tube and heated slowly (1-2 °C/min). The quantity of melting range observed was compared against the standard values to ascertain drug identity and purity.

2.2.2 Determination of λmax

Pantoprazole sodium was put in stock solution in 0.1 N HCL and scanned at 200-400nm in a UV-visible spectrophotometer. The wavelength with the highest absorbance (λmax) was noted and utilized in the rest of the analysis.

2.2.3 FT-IR Analysis

Potassium bromide (KBr) was added to the drug sample and the mixture was pressed into pellets and subjected to FT-IR spectroscopy between 4000 and 400 cm -1. The spectrum was compared to the standard reference to identify functional groups and drug identity.

2.2.4. Drug-Excipient Compatibility Study (DSC)

DSC of pure drug and drug-excipient mixtures (1:1 ratio) was carried out. Samples were heated between 30 ºC and 300 ºC at 10 ºC/min in the presence of nitrogen. Any interaction was considered in thermograms.

2.3 Powder Blend (Pre-compression Parameters) Evaluation.

2.3.1 Angle of Repose

Findings obtained through the funnel method. The angle (0) was determined by:

$$\tan\theta = \frac{h}{r}$$

2.3.2 Bulk and Tapped Density

The method used to measure bulk density and tapped density was the use of a graduated cylinder.

$$\text{Bulk Density} = \frac{\text{Weight of powder}}{\text{Bulk volume}}$$

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

2.3.3 Index of Carr and Ratio of Hausner

Computed with the help of standard equations:

$$\text{Carr's Index } (\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

The formulation of Floating Tablet will be as follows:

Direct compression was used to make floating tablets. The ingredients were all sifted through sieve no. 60 and blended together. The last stage was the addition of lubricants. The blend was compressed using a rotary tablet machine.

Table 1: Composition of Floating Tablets (mg/tablet)

Ingredient	**Qty**
Pantoprazole	20
HPMC K4M	40

2.4

Sodium bicarbonate	20
Citric acid	10
PVP K-30	10
Lactose	185
Mg stearate	5
Talc	10

Evaluation of Tablets (Post-compression)

2.4.1 Thickness

A Vernier caliper was used to measure the thickness of the tablet in order to make the tablets the same size. Each batch was randomly chosen on ten tablets and the thickness of each was measured. The mean thickness and the standard deviation were computed. The thickness remains constant; it means that the die is filled uniformly and compressed correctly in the process of making tablets.

2.4.2 Weight Variation

To determine the variation of weight, 20 tablets were weighed on an analytical balance one at a time. The calculation of the average weight was done and the individual weights were compared with the mean to find the percentage deviation. This test determines the evenness of the powder mix and adherence to pharmacopeial levels.

2.4.3 Hardness

The Monsanto or Pfizer hardness tester was used to measure the strength of the tablets in terms of their mechanical strength. Each batch of tablets was tested on six tablets and the force to break each tablet was recorded. Sufficient hardness means that the tablets will not break during handling, packaging, and transportation.

2.4.4 Friability

The friability was determined by a Roche friabilator at 25 rpm with 4 minutes (100 revolutions) of rotation. A sample of weights of tablets was placed under mechanical shock and reweighed after dusting. The percentage weight loss was determined. A friability value of less than 1 percent implies good mechanical resistance of the pills.

2.4.5 Drug Content

The UV- Visible spectrophotometric method was used to determine drug content. Tablets were dissolved and a measured dose of one dose of the tablet was dissolved in a proper solvent (0.1 N HCl) filtered and diluted accordingly. The absorbance was read at the set λmax and a calibration curve was used to determine the concentration of the drug. The test also assures that the drug is evenly distributed in the pills.

2.5 Floating Behavior Study

2.5.1 Floating Lag Time (FLT)

The time in which the tablet will rise to the surface of the dissolution media (0.1 N hydrochloric acid) and start floating is what is termed as floating lag time. In this test, a tablet is put in a beaker of 0.1 N HCl at 37 + 0.5 o C and time elapsed until the tablet comes to the surface is recorded using a stopwatch. A low floating lag time would mean that the carbon dioxide gas is generated very fast and that the polymer matrix hydrated fast, which is what is required to be an effective gastroretentive drug delivery system.

2.5.2 The time spent in total floating (TFT)

Total floating time is the total time in which the tablet stays on the surface of the dissolution medium without breaking or sinking. Once the tablet starts floating, the time of which it stays continuously in the air is visually measured and noted down. The long floating time is necessary

to ensure that the tablet spends as long time in the gastric region as possible, increasing the absorption of the drug and its therapeutic effect.

2.6 In-Vitro Dissolution Study

Performed using USP Type II apparatus in 0.1 N HCl (900 ml) at 37 ± 0.5°C and 50 rpm. Samples were sampled at intervals which were predetermined and analyzed spectrophotometrically.

2.7 Stability Studies

Conducted as per ICH guidelines at 40°C ± 2°C / 75% RH ± 5% for 3 months. Tablets were considered on an interval basis.

3. RESULT AND DISCUSSION

3.1 Preformulation Studies

Preformulation tests are necessary to investigate the physicochemical characteristics of the drug and to verify its feasibility to be put into formulation. The melting point of Pantoprazole sodium observed in the current study was found to be in the range of 138-140C, which is similar to the reported standard value. This is a low melting point that shows a high level of purity and ensures that no impurities or degradation products are present. The similarity of the measured melting temperature with the literature values confirms the identity and appropriateness of the drug to undergo further formulation.

The spectrophotometric analysis of the UV-Visible showed that the Pantoprazole sodium had a maximum absorbance (maximum absorbance) of 288 nm in 0.1 N hydrochloric acid. The observation is consistent with the data that has been reported in the past and this confirms that the drug is stable and has a good solubility in acidic conditions. The existence of a sharp and clear peak means that the drug is obeying Beer-Lambert law at the chosen concentration range, and thus valid and reliable quantitative analysis in future researches like drug content estimation and dissolution testing.

The FT-IR spectral analysis of the pure drug was used to establish the existence of the typical functional groups that were related to Pantoprazole sodium. The measured peaks were in good

agreement with the standard reference spectra, which showed that the drug did not undergo degradation during work or storage and that the chemical structure of the drug was not destroyed. This assurance in the integrity of the functional groups also promotes authenticity and quality of the drug sample that was used to conduct the study.

To examine the compatibility of the drug and the chosen excipients, Differential Scanning Calorimetry (DSC) analysis was conducted. Pure Pantoprazole sodium DSC thermogram showed a sharp endothermic peak at crystalline melting point, indicating that the compound was crystalline. Thermograms of drug-excipient mixtures were found to have no major difference in peak position, peak disappearance or appearance of new peaks. This implies that the drug does not interact with the excipients chemically. Therefore, the chosen polymers (HPMC K4M and K15M), gas-generating agents, and other excipients were known to be compatible with the drug and, thus, could be used in the formulation development.

3.2 Powder Blend (Pre-compression Parameters) Evaluation.

Powder blend properties should be reviewed so that die filling is uniform and all tablets of the same batch have the same quality. The repose angle was determined to be 26.8 0.4 degrees which is a good indication of the flowability of the powder blend. In most cases, a repose angle lower than 30 degrees is regarded as good flow characteristics. The value obtained indicates that there is little interparticle friction and adhesive forces, which permit the powder to flow freely. This is of special concern in direct compression processes, where uniform flow has a direct effect on weight uniformity and dose accuracy.

The bulk density of the powder blend was determined to be 0.44 ± 0.02 g/ml and tapped density was 0.52 ± 0.01 g/ml. Bulk density is the behavior of particles at loose packing conditions, whereas tapped density is the maximum packing when the particles are tapped using mechanical means. The difference between these values observed shows that the powder has a high compressibility and rearrangement capability when tapped. The standard deviation and the difference between the two values are relatively low which implies that the distribution of the particle size is homogenous and that it mixes well.

Compressibility properties like Carr index and Hausner ratio can then be deduced by these density values that in turn reinforce the good flow and packing properties. All in all, the findings suggest

that the powder blend has reasonable flowability and compressibility which results in its applicability in direct compression into tablets.

3.3 Post-compression parameters

the floating tablets are evaluated to determine their effectiveness in reducing the occurrence of pressure ulcers on patients.

The floating tablets were also tested on several parameters of physical parameters to determine quality, uniformity, and mechanical strength. The tablets were observed to have the same thickness with a mean thickness of 3.2 mm. The low range of change in thickness implies that there was consistency in filling die and uniform compression force in the process of making the tablet. The homogenous thickness is necessary to ensure effective packaging, aesthetic appeal, and consistency of doses.

The weight fluctuation test revealed an average tablet weight of 299 mg which is quite close to the theoretical weight of 300 mg. The slight variation in the weight of each tablet reflects an excellent flow characteristic of the powder blend, and homogenous filling of the die. Tablets were all of pharmacopeial quality, which once again validated the quality of the formulation process.

The tablets were determined to have a hardness of 5.0 + 0.3 kg/cm 2 which is a sufficient grade of mechanical strength. This is the best hardness, because it means that the tablets will not break during handling and transportation, and at the same time, the drugs are able to release properly. Too much hardness would slow down the release of the drug and too little would cause the pills to break up. The values obtained are evidence of a balanced formulation.

The friability of the tablets was estimated at 0.55% which is significantly low as compared to the acceptable limit of 1%. This low friability means that the tablets are resistant to abrasion and mechanical stress, which proves their strength. According to the results, the parameters of the formulation and compression were optimized to make durable tablets.

The uniformity of the drug content was between 91.5 and 94.2, which means that there is even distribution of the drug in the tablets. Such homogeneity indicates effective mixing and blending of the drug and excipients, which avoid segregation during processing. Stability in drug content is critical towards proper dosage and therapeutic effect.

3.4 Floating Behavior

A key parameter to gastroretentive drug delivery systems is the floating behavior of the tablets. The floating lag time (FLT) was 30 ± 2, which showed that it became in contact with buoyancy quickly. The reason of this rapid floating is the interaction of the sodium bicarbonate and citric acid in the acidic medium, which produces carbon dioxide gas. The gas gets trapped in the hydrated polymer framework, lowering the thickness of the tablet and allowing it to float.

It was found to be more than 12 hours in total floating time (TFT), indicating long-lasting buoyancy. This long floating time will guarantee that the tablet will be kept longer in the gastric area, which will increase drug absorption and bioavailability. A mixture of hydrophilic polymers and gas producing agents was successful in providing sustained floating behavior.

3.5 In-vitro Drug Release Study

The drug release profile of in-vitro had a regulated and prolonged release profile up to 12 hours. The drug release began with 14% release at 0.5 hours which means that there was an initial release phase since the drug was on the surface of the tablet. This was then gradually and slowly released to reach 52 percent at 4 hours and 90 percent at 12 hours.

This prolonged release action may be explained by the fact that HPMC polymers form a gel layer when hydrated. This gel coating restrains the diffusion of the drug into the dissolution media and determines the rate of release. Further erosion and swelling of the polymer matrix also help in the long-term release of the drug.

The desirable property of this release is that it is able to achieve a constant drug concentration in the systemic circulation, decrease the dosing frequency, and enhance patient compliance. The findings clearly show that the formulation has been able to attain the long-term drug release that is appropriate in gastroretentive systems.

3.6 Stability Studies

The three-month stability studies that were carried out under accelerated conditions (40 o C + 2 o C / 75 per cent RH + 5) indicated that the formulation was stable. No changes in the appearance of the tablets were observed, which means that the formulation can withstand the stress conditions of the environment like temperature and humidity.

The tablets also exhibited a slight reduction of hardness to 4.8 kg/cm 2, but this is acceptable and will not influence the performance of the pills. The drug content was reduced slightly by 93.3% to 92.2% which means that the drug did not degrade much and it has a good chemical stability.

The floating lag time had slightly risen to 35 seconds instead of 30 seconds, yet this was within good ranges, which meant that the gas-generating capacity was maintained. The overall floating time was also not affected (>12 hours), and this indicated that the buoyancy could be sustained even after storage.

The 12 hours drug release in-vitro was slightly lower at 88 percent than 90 percent indicating that the controlled-release mechanism was not significantly affected. In general, the slight alterations that have been noticed fall within acceptable ranges and they do not affect the quality or performance of formulation.

4. CONCLUSION OF FINDINGS

The overall analysis of preformulation, powder blend, tablet properties, floating behavior, drug release, and stability tests clearly shows that the formulation developed is strong, effective, and can be used to deliver gastroretentive drugs. The effervescent agents coupled with hydrophilic polymers effectively also realized rapid floating, extended gastric retention, and 12-hour sustained drug release. Moreover, the formulation was relatively stable in accelerated conditions that validate its long-term usage.

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