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Review Article

FORMULATION AND EVALUATION OF BILASTINE FLOATING TABLETS

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ABSTRACT

Rhinitis and urticaria are common allergic conditions that can be treated with bilastine, a second-generation antihistamine. The short half-life of the drug makes consistent dosing difficult for patients despite its efficacy. We conducted this study in order to evaluate the formulation and the therapy efficacy of bilastine floating tablets, with the goal of prolonging gastric residence time and enhancing drug bioavailability, thereby reducing the frequency of dosing and improving the effectiveness of the therapy. As a gas-generating agent, hydroxypropyl methylcellulose (HPMC) and sodium bicarbonate were incorporated into the floating tablets using a direct compression technique. By using Fourier-transform infrared spectroscopy, we assessed parameters such as powder flow properties, compressibility, and drug-excipient compatibility before optimizing the formulation. Based on the results of in vitro dissolution studies, a controlled release profile of bilastine over a period of 12 hours has been observed, following a zero-order kinetics model. It can be concluded that the formulation of the bilastine floating tablet highlights the potential of gastroretentive drug delivery systems to optimize the pharmacokinetic profile of drugs with a narrow window of absorption in the upper gastrointestinal tract when using gastroretentive drug delivery systems.

Keywords: Oral, Bilastine, Formulation, Floating Tablets.

INTRODUCTION

Oral solid dosage (OSD) is a pharmaceutical term that refers to tablets (also called pills). Medications in tablet form contain excipients for their preparation [1]. Solid dosage forms are usually compressed or pressed from powdered active ingredients and excipients. Tablets have many advantages, including consistent doses and ease of administration [2].

In order to create tablets, either compression or moulding can be used. The excipients may include diluents, binders, gliders, and lubricants for efficient tabletting, disintegrants for preventing the tablet from disintegrating in the digestive tract, enhancing sweetness or flavor, and pigments to make the tablet easier to recognize. The polymer coating also improves tablet smoothness and shelf life, enhances appearance, and regulates active ingredient release [3].

Tablets must be handled and shipped properly by pharmacies and patients. There are various methods for testing tablet mechanical strength, such as simple failure tests, erosion tests, and engineering tests that require more advanced engineering skills [4]. Quality control tests are easier for research and development, but formulation and manufacturing processes are more complex. Tablet properties are described in a number of international pharmacopoeias (USP/NF, EP, JP, and so on). In order to determine the mechanical strength of a tablet, the hardness of the tablet is taken into account. With tablet hardness testers, tablets are tested for their hardness. Despite unit changes since the 1930s, hardness measurements have historically been expressed in kilograms per square centimeter. Several hardness testers were developed around 1950, including the Pfizer Hardness Tester and the Strong Cob Hardness Tester.

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Floating Drug Delivery System

A floating tablet delivers drugs to the stomach, and there are a wide variety of types available. Gastroretentive systems boost the bioavailability of medications with water solubility issues in alkaline pH environments of small intestines or whose stability occurs in the colon or intestines. In recent years, controlled release oral dosage forms have become more popular thanks to their ability to provide a longer duration of drug delivery and prolong the duration of drug presence in the stomach. Drugs passing quickly through the GI tract may not arrive at the absorption zone in time, thus reducing their efficacy. It is pharmacokinetically and pharmacodynamically more effective to keep the reservoir above the absorption zone. Zero-order kinetics can be used to extend and predict the duration of drug delivery profiles in the stomach and GIT. In addition to being appropriate for medications with low bioavailability, floating drug delivery is also highly effective in delivering medications to the upper gastrointestinal tract. In order to maximize bioavailability, it is imperative that the dosage form remains at the absorption site while it is being absorbed [5].

Limitations of floating drug delivery system

1. After meals, the FDDS must be administered, but how well it is absorbed and how long it stays in the body depends on your digestive system
2. Hydration status determines a dosage form's flotation ability. Floating in vivo requires intermittent administration of the tablets (one tumbler full every two hours).
3. Because drugs float differently in the stomach, their floating ability varies with their position.

Application of floating drug delivery system

1. Due to their ability to treat hypertension better than normal tablets, flotation tablets of Diltiazem are more beneficial to hypertensive patients.
2. As a result of FDDS administration over a period of 6-8 hours, significant plasma concentrations were maintained in Parkinson's disease patients.
3. As with riboflavin, furosemide is also delivered indirectly to the stomach or small intestine, depending on its site of delivery [6].

METHODOLOGY

Analytical method development:

Determination of absorption maxima:

In 0.1N HCL, a solution containing 10 µg/ mL of drug was prepared in which the UV spectrum was measured using a Double beam UV/VIS spectrophotometer to determine its concentration. During the scanning of the solution, the wavelength range was between 200 nm - 400 nm.

Preparation calibration curve:

A pure drug of 10mg of Bilastine was dissolved in 10ml of methanol (stock solution1), and from this solution one ml of solution was taken and made up with 10ml of 0.1N HCL (100 µg/ml). One milliliter was taken and dissolved in 0.1N HCL (10 µg/ml) for 10 milliliters. The above solution was diluted further with 0.1N HCL to obtain a series of dilutions containing 5, 10, 15, 20, 25 µg/ml of the above solution per ml, and this was then followed by a series of dilutions with 0.1N HCL. In order to determine the absorbance of the above dilutions at 210 nm, UV-Spectrophotometers were used in conjunction with 0.1N HCL to serve as a blank. Following that, a graph was plotted by taking concentration on the X-axis and absorbance on the Y-axis of the plot, resulting in a straight line. The linearity of the standard curve was evaluated by determining the square of the correlation coefficient (R2), which was determined by least-square linear regression.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

A FTIR spectrum which was obtained on a Bruker FTIR Germany Alpha T system was used to determine whether the pure drug and excipients were compatible. A sample of the solid powder was placed directly on a yellow crystal which was composed of ZnSe. It was observed that the spectra were recorded over a range of wavelengths between 4000 cm-1 and 550 cm-1.

Preformulation parameters

In general, the quality of the tablet, once it has been formulated by rule, is governed by the physicochemical properties of the blends that form the tablet. The formulation of a blend and the process variables involved in the mixing process can all be affected by the characteristics of the blend that is being produced by these processes. It is important to know the various characteristics of blends tested in accordance with Pharmacopoeia.

Angle of repose:

The angle of repose, which is a measure of frictional force, can be used to determine the frictional force within loose powder. As you can see, it is defined as the maximum angle that can be made between the surface of the pile of powder and the horizontal plane at any given time. As more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles, which produces a surface angle, is in equilibrium with the gravitational force created by the pile. The angle of repose was measured using the fixed funnel method using a fixed funnel. The tip of a funnel was placed at a particular height above a graph paper that was placed on a flat horizontal surface, with its tip at a

given height (h). Using the funnel, the blend was carefully pored until the apex of the conical pile just touched the tip of the funnel as it passed through the funnel. A radius (r) was measured at the base of the conical pile in order to determine its radius.

Bulk density:

The density of an object can be defined as the weight per unit volume. The bulk density is defined as the mass of the powder divided by the bulk volume. Particle size distribution, particle shape, and adhesion tendencies are the primary factors that determine bulk density. It is very important to consider bulk density when selecting containers that will be used to handle, ship, and store raw materials and blends. In size blending equipment, it is also important. The powder blend has been sieved and introduced into a cylinder without compacting, containing a volume of 20 ml. A leveling test was run without compacting the powder, and the volume of the unsettled powder, Vo, was calculated.

Tapped density:

Using the procedure as described in the procedure for measuring the bulk density, the cylinder containing the sample was tapped by a mechanical tapped density tester with 100 drops per minute capability. This procedure was repeated until the difference between successive measurements was less than 2 %, then the tapped volume, V, was measured to the nearest graduated unit by following it up.

Measures of powder compressibility:

A powder's compressibility index (or Carr's Index) is a measurement of how much of a powder can be compressed by a given force. Based on the bulk and tapped densities, it can be calculated. Material flowability increases with its compressibility. Interparticulate interactions are thus measured in terms of their relative importance. Free-flowing powders have fewer such interactions, and their bulk and tapped densities are closer.

Poorer flowing materials frequently have greater inter particle interactions, and tapped and bulk densities will differ more dramatically. In order to represent these differences, the Compressibility Index

Formulation development of floating Tablets:

Using direct compression, granules were prepared in order to optimize the sodium bicarbonate concentration in the final product.

The following is the procedure for the direct compression method:

- During the testing procedure, each of the ingredients, including the drug, was individually passed through sieve 60.
- It was triturated over a period of 15 minutes in order to thoroughly mix all the ingredients.
- Talc was used as a lubricant for the powder mixture.
- A 12 mm punch was used in order to prepare the tablets using the direct compression method by using a direct compression method.

Optimisation of Sodium bicarbonate:

Effervescent gas was generated using sodium bicarbonate as the effervescent gas generating agent. The ingredient aids in floatation of the formulation. There was a significant difference between floating duration and floating lag time between various concentrations of sodium bicarbonate. On the basis of the concentration of sodium bicarbonate, the formulation process was finalised and prepared for further implementation.

Evaluation of post compression parameters for prepared Tablets

There has been a study conducted on the designed compression tablets in terms of their physicochemical properties, such as weight variation, hardness, thickness, friability and extent of drug content.

Weight variation test:

A digital weighing balance was used to determine the weight of twenty tablets individually and collectively, in order to study how weight varies between tablets. Using the collective weight of the tablets, the average weight of one tablet was determined. It would be possible to deter mine the uniformity of drug content using the weight variation test. Two or fewer individual weights are found to have deviated from the average weight by more than the percentage shown in the following table, while none of them deviate by more than twice that percentage.

Hardness:

The hardness of a tablet is defined as the force required to break a tablet when applied across its diameter across a specific point on its surface. In storage transformations and handling before use, the hardness of the tablet affects its resistance to chipping, abrasion, or breakage. Three tablets for each formulation were tested using a Monsanto hardness tester, and the average and deviations were calculated.

Thickness:

The thickness of a tablet is one of the most important characteristics in reproducing appearances. The thickness of the tablet plays an important role in reproducing the appearance of the tablet. We calculate average thicknesses and present deviations for core and coated tablets.

Friability:

A tablet's mechanical strength is measured by this test. The following procedure was used to determine the friability of the Roche friabilator. The friabilator was filled with pre-weighed tablets. A total of 100 rotations were performed on the tablets for 4 minutes at 25 rpm. As a result of the test, the tablets were reweighed, and the loss in weight of the tablet was calculated.

Determination of drug content:

There was a test conducted on both compressed-coated tablets to determine their drug content. For full solubility of Bilastine, a volumetric flask was filled with 50 ml of water and 100 ml of powder weighing ten tablets of Bilastine. The medication was dissolved in water using a volumetric flask of 100 ml and left for 30 minutes to ensure complete solubility. Water was added to make up the volume of the mixture. A UV-visible spectrophotometer was used to measure the absorption of the diluted solution. Based on the calibration curve, the drug concentration was calculated.

***In vitro* Buoyancy studies:**

Floating lag time and total floating time were used to determine *in vitro* buoyancy. A 100ml beaker containing 0.1N HCL was used to dissolve the tablets. A floating lag time (FLT) was determined to determine how long the tablet floats on the dissolution medium once it rises to the surface, while the total floating time (TFT) was used to determine how long the tablet remains floating on the dissolution medium.

***In vitro* drug release studies**

Dissolution parameters:

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCL
RPM	--	50
Sampling intervals (hrs)	--	1, 2,4,6,8,10,11,12
Temperature	--	37°c + 0.5°c

For evaluation of dissolution profiles, different receptor fluids were used because the preparation was for floating drug administration.

Dissolution data analyzed using Release Rate Kinetics:

A variety of models were tested to explain the kinetics of drug release. The obtained data were fitted into zero-order, first-order, Higuchi, and Korsmeyer-Peppas release models to analyze the mechanism of drug release rate kinetics.

Zero order release rate kinetics:

The following equation is fitted to the release rate data to study zero-order release kinetics.

$$F = K_o t$$

Where, 'F' is the drug release at time 't', and 'K_o' is the zero order release rateconstant. The plot of % drug release versus time is linear.

First order release rate kinetics:

The release rate data are fitted to the following equation

$$Log (100-F) = kt$$

First order release is determined by plotting log cumulative percent of drug remaining to be released vs. time.

Higuchi release model:

Based on the release rate data, the following equation was fitted to study Higuchi release kinetics.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

Plotting the log percent of drug released against log time according to Korsmeyer-Peppas equation was used to evaluate the mechanism of drug release. Calculated by calculating the slope of a straight line, the exponent 'n' indicates the mechanism of drug release.

$$Mt/ M\infty = K\ tn$$

Where, Mt/ M∞ is fraction of drug released at time 't', k represents a constant, and 'n' isthe diffusional exponent, which characterizes the type of release mechanism during the dissolution process. Non-Fickian release has a n value between 0.5 and 1.0; Fickian diffusion has a n value of 0.5; zero-order release (case I I transport) has a n value of 1; and supercase II transport has a n value of >1. In this model, a plot of log (Mt/ M∞) versus log (time) is linear [7 - 12].

Table 1: Parameters that should be taken into account during pre-formulation of blends

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
F1	24.17	0.47	0.56	16.07	1.19
F2	23.65	0.43	0.51	15.68	1.18
F3	24.84	0.49	0.57	14.03	1.16
F4	25.79	0.52	0.59	11.86	1.13
F5	23.58	0.45	0.55	18.18	1.2

F6	23.95	0.51	0.60	15.0	1.17
F7	24.21	0.44	0.52	15.38	1.18
F8	25.63	0.50	0.57	12.28	1.14
F9	24.18	0.53	0.65	18.46	1.22

Table 2: In vitro quality control parameters

Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)	Total Floating Time(Hrs)
F1	120.3	4.2	0.41	3.2	98.52	5.9	6
F2	119.6	4.8	0.53	3.6	98.69	5.3	9
F3	119.3	5.1	0.42	3.1	99.83	4.5	12
F4	121	4.7	0.49	3.5	98.24	5	10
F5	120.2	5.4	0.51	3.3	99.98	4.1	12
F6	121.5	4.3	0.52	3.4	99.12	5.2	7
F7	119.9	5.0	0.47	3.8	99.56	4.8	12
F8	120	4.9	0.51	3.1	98.75	5.1	8
F9	121	5.3	0.61	3.7	98.62	5.5	6

Figure 1: In 0.1N HCL, the standard graph of bilastine

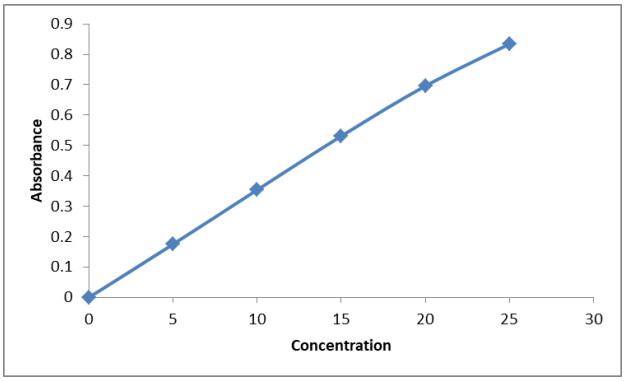


Figure 2: Formulation Vs Floating Lag Time

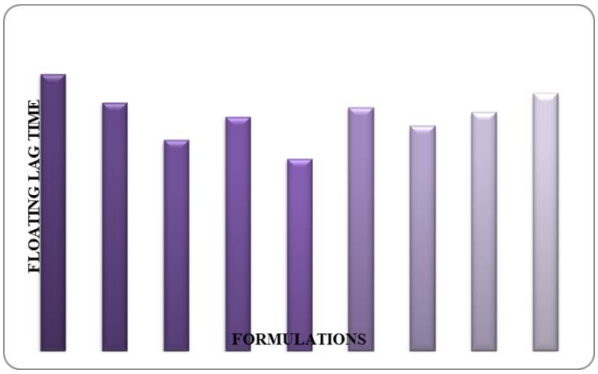


Figure 3: Formulations Vs Total Floating Time

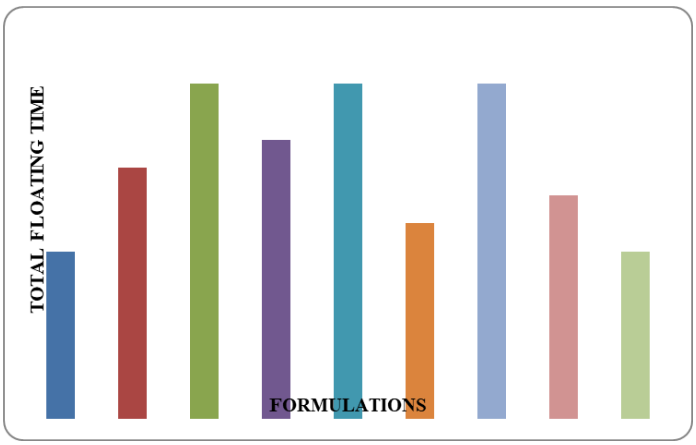


Figure 4: Dissolution data for Xanthan gum-containing Bilastine Floating Tablets

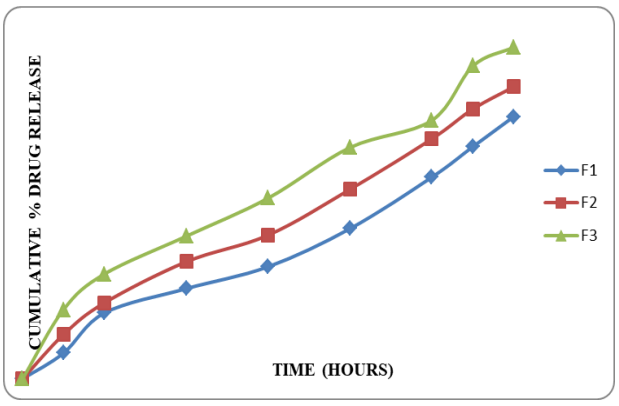


Figure 5: Dissolution data of Guar gum-containing Bilastine Floating Tablets

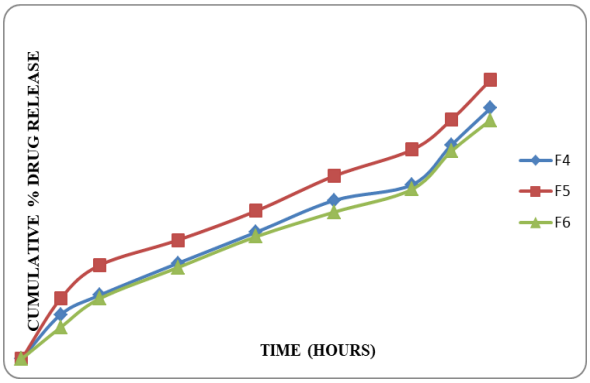


Figure 6: Dissolution data for Bilastine Floating Tablets containing Karaya Gum

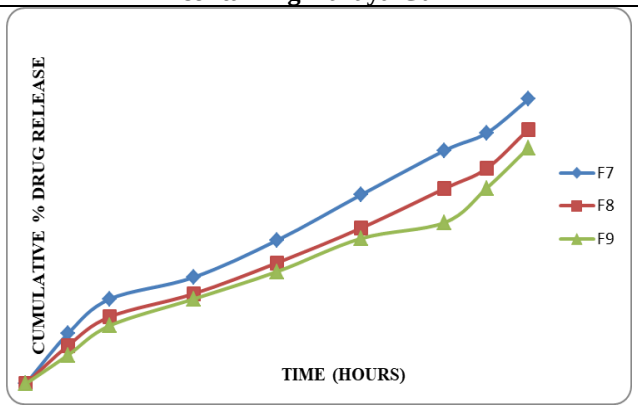


Figure 7: The dissolution data for Bilastine Floating tablets contain all formulations (Xanthan gum, Guar gum, Karaya gum).

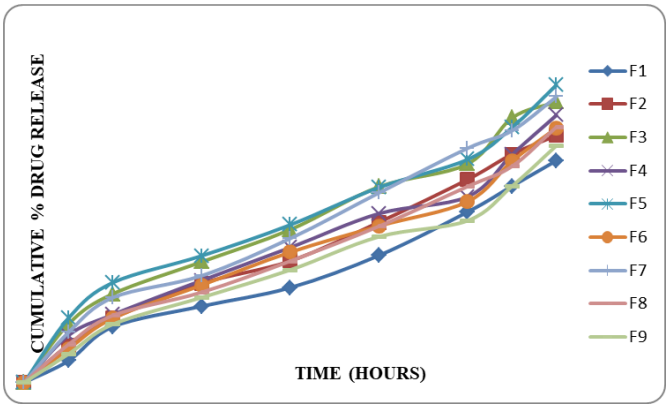


Figure 8: Zero order release kinetics

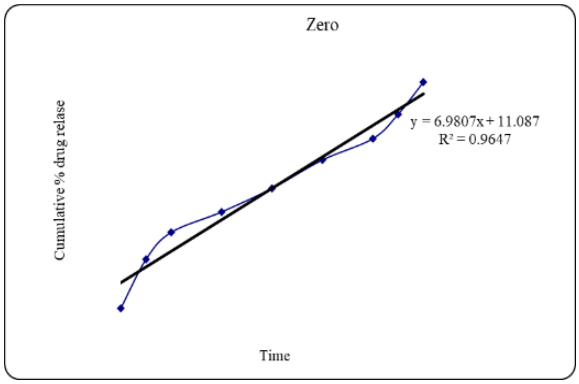


Figure 9: Higuchi release kinetics

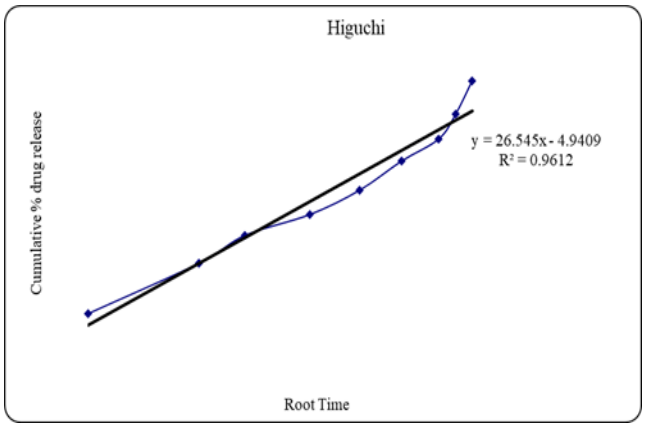


Figure 10: Kors mayer peppas release kinetics

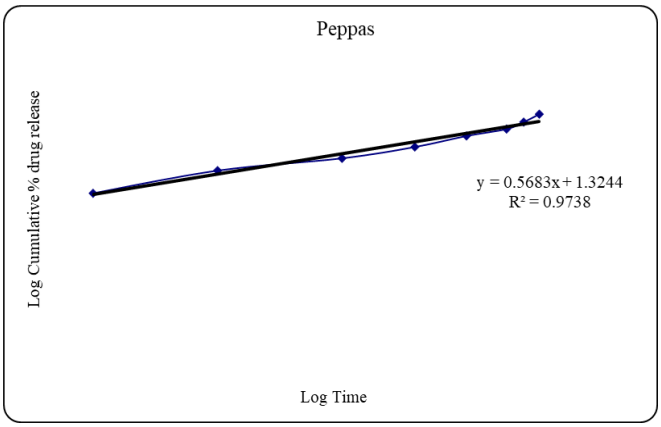
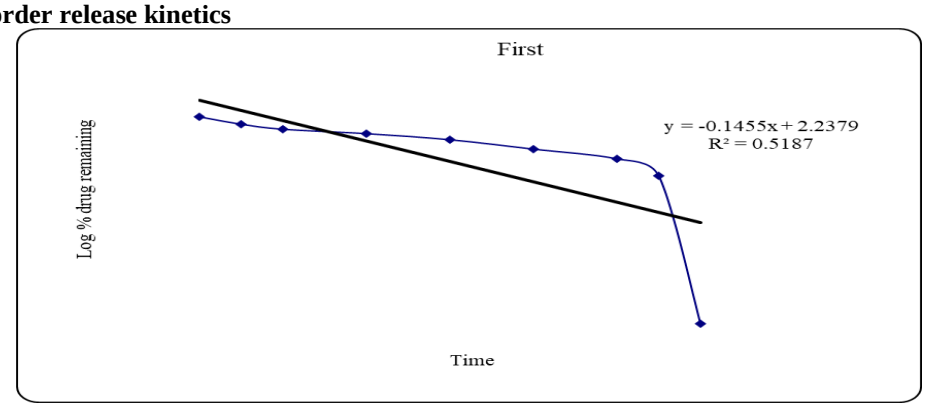


Figure 11: First order release kinetics



RESULTS AND DISCUSSION

Determination of absorption maxima

There is a standard curve which is calculated from the spectrophotometry measurements. A maximum amount of absorption was observed at a wavelength of 210 nm.

Calibration curve

In these graphs, Bilastine has been taken in the presence of 0.1N HCL (pH 1.2) as the buffer.

According to the experimental method, a standard graph was plotted for Bilastine, and its linearity can be seen in the tables and figures. Based on the standard graph of Bilastine, R2 is 0.999, which indicates that it complies with the Beer- Lamberts law.

Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy:

The FTIR spectrum of the drug and polymers did not show any disappearance of characteristic peaks. According to this, the polymers used to make the drug do not interact chemically with the drug. It is clear, therefore, that the materials used in the study are genuine and that there have been no possible interactions between them, as the peaks coincide with the expected range.

A physical mixture of the drug and the polymer was also found to contain bilastine, which indicates that there is no interaction between the chemical and the polymer, confirming its stability.

The preformulation parameters of a powder blend are as follows:

There are a number of pre-formulation parameters which were applied to the tablet powder blend. The angle of repose values indicate that the powder blend has good flow properties due to its good angle of repose values. There was a finding that the bulk density of all the formulations was between 0.43 and 0.53 grams per milliliter (gm/ml), indicating that the powder has good flow properties and has a good bulk density. All the formulations were found to have tapped densities which ranged between 0.51 and 0.65, demonstrating that the powder has good flow properties as indicated by its tapped density. It was found that all the formulations had a compressibility index below 19, which is a good indicator that the powder has good properties for flow, as the flow index is lower than 19.This indicates that all of the formulations have shown a Hausners ratio ranging between 1.13 and 1.22, which indicates that the powder has good flow properties despite the formulation.

Optimization of sodium bicarbonate concentration:

The direct compression method was used for the preparation of three formulations, with various concentrations of sodium bicarbonate, and the wet granulation method was used to prepare three additional formulations, in order to compare the floating buoyancy between the direct compression method and the wet granulation method. In wet granulation method, the formulation containing sodium bicarbonate in a concentration of 15mg showed a lower floating lag time, indicating that the tablet would remain floating for more than 12 hours despite the inclusion of sodium bicarbonate.

Tablet Quality Control Parameters:

Testing for floating tablets included weight variation, hardness, friability, thickness, drug content, and drug release.

It was found that all parameters, including weight variation, friability, hardness, thickness, and drug content, were within acceptable limits.

In Vitro Drug Release Studies

A study of the dissolution data indicated that the formulations (F1,F2,F3) containing xanthan gum polymer showed increasing levels of drug release in the order of preparation.

Guar gum is used in the preparation of the formulation F5 that shows good drug release over 11 hours at the concentration of 5 mg. F4 and F6 formulations delay the release of the drug.

In F7, the drug is released over a period of 11 hours with the help of Karaya Gum polymer. However, F8 and F9 formulations retard drug release.

Hence, with the above dissolution data, the F5 formulation was considered as the optimal formulation because of the high level of drug release in 12 hours (99.89%).

The application of release rate kinetics to dissolution data in order to optimize formulations:

A modified formulation, F5, was kept for kinetic studies of the release of the drug. As can be seen from the above graphs, the formulation F5 followed Kors Mayer Peppas release kinetics.

CONCLUSION

The floating drug delivery of Bilastine tablets is designed to extend the duration of the drug's action to 12 hours. Different polymers, such as Xanthan gum, Guar gum, and Karaya gum, were used to prepare floating tablets. A number of parameters were evaluated for the formulated floating tablets, including drug excipient compatibility studies, weight variation, thickness, hardness, and uniformity of content. In vitro drug release studies were conducted in 0.1N HCL for 12 hours, and the data were analyzed using zero order, first order, Higuchi release kinetics, and Karsmayer Peppas graphs.

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