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FORMULATION & EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF AZELASTINE

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ABSTRACT

This study examines the formulation and evaluation of floating tablets containing azelastine hydrochloride intended to treat gastroretention. Gastroretentive drug delivery systems increase absorption and bioavailability while reducing the frequency of administration. Considering its short biological half-life and the need for sustained release formulations, azelastine, a potent antihistamine with potential anti-inflammatory properties, was chosen as the model drug. As a means of achieving buoyancy and controlling drug release, polymers were used in the preparation of the tablets. A central composite design (CCD) was used to study the effects of polymer concentration and gas-forming agent (sodium bicarbonate) on tablet properties such as floating lag time, total floating time, and drug release. A number of parameters, including weight variation, hardness, friability, and in vitro drug release, were measured on the tablets. The developed azelastine floating tablets showed promising gastroretentive properties and sustained drug release.

Keywords: Gastro Retention, Azelastine, Prolong, Floating Tablets.

INTRODUCTION

Oral delivery of drugs is by far the most preferred route of drug delivery due to ease of administration, patient compliance, and flexibility in formulation [1, 2]. From immediate release to site- specific delivery, oral dosage form has really progressed. It is evident from the recent scientific and patented literature that an increased interest in novel dosage forms that are retained in the stomach for prolong and predictable period of time exist today in academic and industrial research groups. Various attempts have been made to develop Gastro retentive delivery systems [3, 4].

Floating Drug Delivery Systems

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period [5, 6]. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the Surface of the meal [7]. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positives ideas shown in fig. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations [8].

Classification of Floating Drug Delivery Systems (FDDS)

- Effervescent FDDS
- Gas generating system (II) volatile liquid containing system
- Non- Effervescent FDDS
- Colloidal gel barrier system

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- Microporous compartment system
- Floating microsphere
- Alginate floating beads
- Raft forming system

Advantages of FDDS

FDDS is highly advantageous in the treatment of the disorders related to the stomach. As the prime objective of such systems is to produce a gastro retentive product or a product which has an enhanced retention time in the stomach [9, 10].

Biological aspects of gastric retention dosage forms:

To comprehend the considerations taken in the design of gastric retention dosage forms and to evaluate their performance the relevant anatomy and physiology of the G.I tract must be fully understood. The extent of drug absorption in a segment of the G.I. tract depends generally on the rate of absorption as well as on the exposed surface area and time available for drug absorption. The G.I. Transit times of dosage forms in the various segments of the G.I. tract are listed in Table 1. The other factors influencing drug absorption are surface area, absorption mechanisms, pH values, enzymes and number of microorganisms [11].

MATERIALS AND METHODS

Materials:

Azelastine, Guar gum, Tartaric Acid, NaHCO3, PVP K30, Talc, Magnesium Stearate, Dicalcium Phosphate.

Methods

Analysis of the drug:

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ mL drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve:

10mg Azelastine pure drug was dissolved in 10ml of methanol (stock solution1) from stock solution 1ml of solution was taken and made up with10ml of 0.1N HCL (100µg/ml). From this 1ml was taken and made up with 10 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 5, 10, 15, 20, 25 µg /ml of per ml of solution. The absorbance of the above dilutions was measured at 259 nm by using UV- Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R2) which determined by least-square linear regression analysis.

Drug – Excipient compatibility studies Fourier Transform Infrared (FTIR) spectroscopy:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm-1 to 550 cm-1.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The angle of repose was calculated using the following formula:

$$\tan \theta = h / r \quad \tan \theta = \text{Angle of repose}$$

h = Height of the cone , r = Radius of the cone base

Bulk density:

The bulk density was calculated using the formula:

Bulk Density = M / Vo

Where, M = weight of sample

Vo = apparent volume of powder

Tapped density:

The tapped density was calculated, in gm per L, using the formula:

Tap = M / V Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density Tap = Tapped Density

Formulation development of floating Tablets:

For optimization of sodium bicarbonate concentration, granules were prepared by direct compression method.

Procedure for direct compression method:

- Drug and all other ingredients were individually passed through sieveno 60.
- All the ingredients were mixed thoroughly by triturating up to 15 min.
- The powder mixture was lubricated with talc.
- The tablets were prepared by using direct compression method by using 12 mm punch.

Optimisation of Sodium bicarbonate:

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were

employed; floating lag time and floating duration were observed. Based on the concentration of sodium bicarbonate was finalised and preceded for further formulations.

Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re-weighed, and loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W1] × 100

Where, W1 = Initial weight of tablets

W2 = Weight of the tablets after testing

Determination of drug content:

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Azelastine were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro Buoyancy studies:

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) The tablets were placed in a 100ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

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

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure:

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c +0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCL was taken and process was continued from 0 to 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 259 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

RESULTS AND DISCUSSION

Analytical Method

a. Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 259 nm.

b. calibration curve

Graphs of Azelastine was taken in 0.1N HCL (pH 1.2)

Standard graph of Azelastine was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Azelastine showed good linearity with R2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Drug – Excipient compatibility studies Fourier Transform-Infrared Spectroscopy:

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions. Azelastine is also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43 to 0.53 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.51 to 0.65 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 19which shows that the powder has good flow properties. All the formulations has shown the Hausners ratio ranging between 1.13 to 1.22 indicating the powder has good flow properties.

Optimization of sodium bicarbonate concentration:

Three formulations were prepared with varying concentrations of sodium bicarbonate by direct compression method and three more formulations were prepared by wet granulation method to compare the floating buoyancy in between direct and wet granulation methods. The formulation containing sodium bicarbonate in 15mg. concentration showed less floating lag time in wet granulation method and the tablet was in floating condition for more than 12 hours.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.

All the parameters such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

Table 1: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Table 2: Pre-formulation parameters of blend

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 3: In vitro quality control parameters

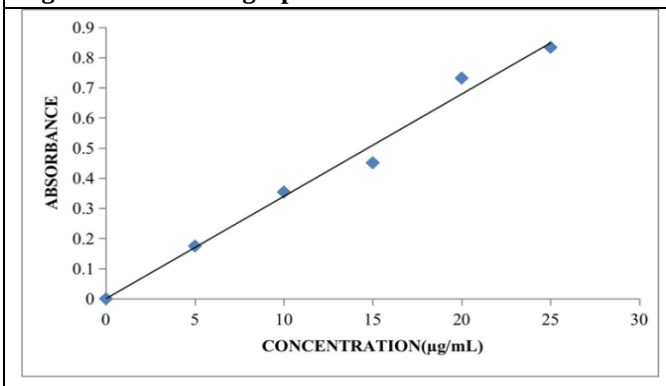
Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)
F1	121.4	4.24	0.42	3.23
F2	118.7	4.83	0.52	3.62
F3	118.2	5.12	0.43	3.15
F4	122.3	4.75	0.48	3.54
F5	121.4	5.42	0.52	3.38
F6	122.4	4.34	0.53	3.47

F7	118.6	5.05	0.48	3.86
F8	121.1	4.91	0.52	3.15
F9	122.3	5.32	0.62	3.78

Table 4: In vitro physical parameters of the tablets

Formulationcodes	Drug content(%)	Floating lagtime (min)	Total FloatingTime(Hrs)
F1	98.51	5.94	6.3
F2	98.68	5.33	9.4
F3	99.85	4.52	12.2
F4	98.21	5.2	10.3
F5	99.96	4.13	12.5
F6	99.14	5.22	7.3
F7	99.53	4.84	12.6
F8	98.77	5.15	8.1
F9	98.65	5.52	6.3

Figure 1: Standard graph of Azelastine in 0.1N HCL



Y=0.034x+0.015; R2=0.998

Figure 2: FTIR Spectrum of pure drug

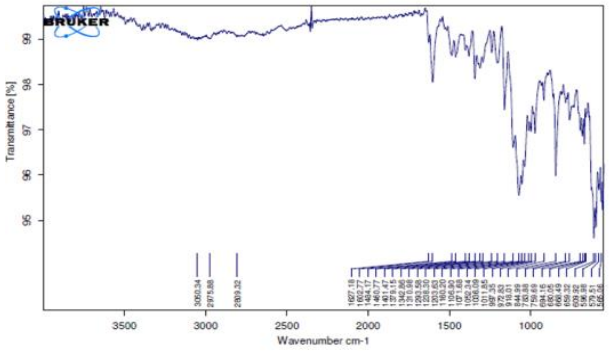


Figure 3: FTIR Spectrum of optimised formulation

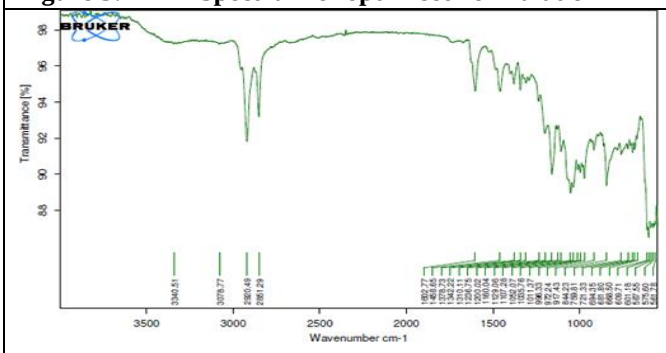


Figure 4: Formulation vs Floating Lag Time

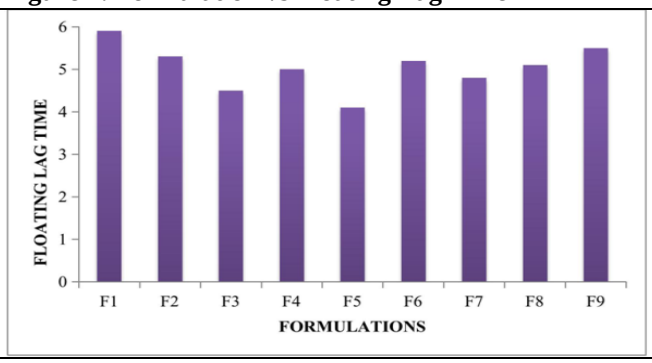


Figure 5: Formulations vs Total Floating Time

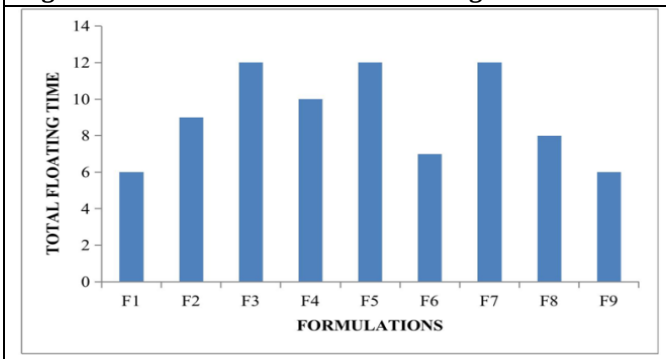


Figure 6: Zero order release kinetics

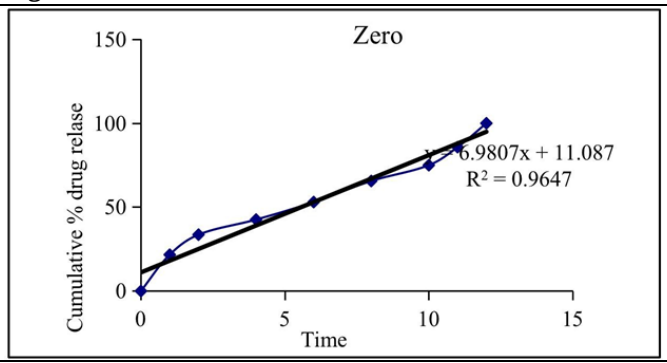


Figure 7: Higuchi release kinetics

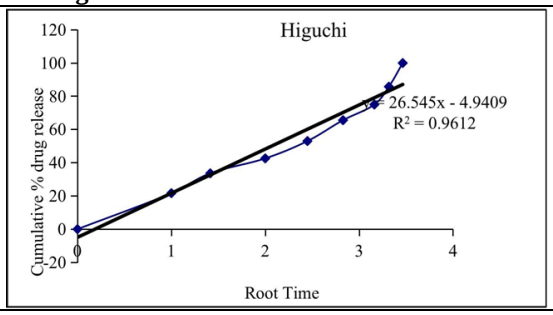


Figure 8: Kors mayer peppas release kinetics

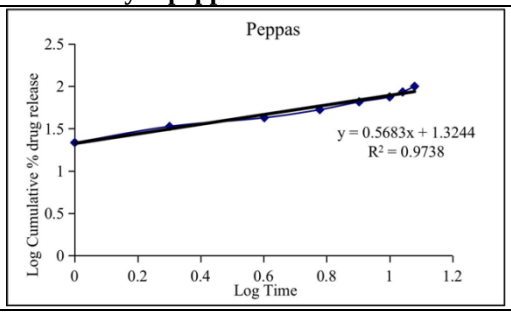
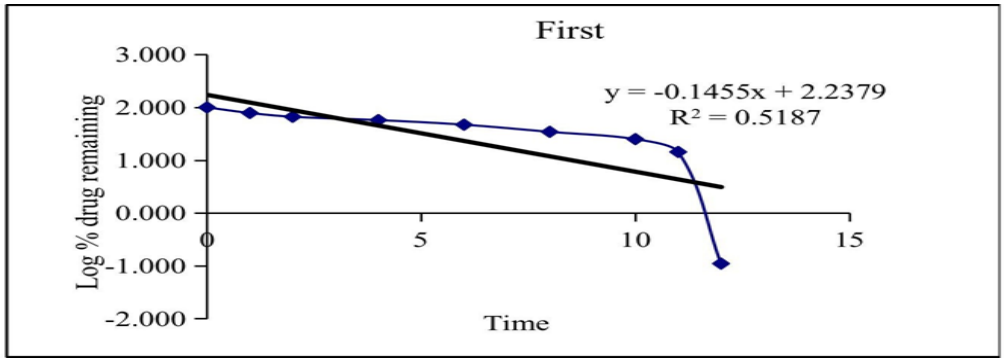


Figure 9: First order release kinetics.



In Vitro Drug Release Studies

From the dissolution data it was evident that the formulations (F1, F2, F3) prepared with xanthan gum polymer showed drug release in increasing order. The formulation F5 prepared with Guar gum shows good drug release more than 11 hours in the concentration 5 mg. Whereas F4 and F6 formulations retards the drug release. The formulation F7 prepared with Karaya Gum polymer releases the drug up to 11 hrs. But F8 and F9 formulations retards the drug release. Hence from the above dissolution data it was concluded that F5 formulation was considered as optimised formulation because good drug release (99.89%) in 12 hours.

Application of Release Rate Kinetics to Dissolution Data for optimised formulation:

Optimised formulation F5 was kept for release kinetic studies. From the above graphs it was evident that the formulation F5 was followed Kors mayer peppas release kinetics.

CONCLUSION

Development of floating drug delivery of Azelastine tablets is to provide the drug action up to 12 hours. Floating tablets were prepared by direct compression method using various polymers like Xanthan gum, Guar gum, Karaya Gum. The formulated Floating tablets were evaluated for different parameters such as drug excipient compatibility studies, weight variation, thickness, hardness, content uniformity, In vitro Buoyancy studies, In vitro drug release studies performed in 0.1N HCL for 12 hrs and the data was subjected to zero order, first order, Higuchi release kinetics and karsmayer peppas graph

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