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FORMULATION AND EVALUATION OF FLOATING TABLETS OF BEPOTASTINE BESILATE

Nageswararao G*[1], Vaishnavi P [1], Avinash Kumar G[2], Pravallika P

[1]Department of Pharmaceutics, Rao's College of Pharmacy, Venkatachalam, Nellore-524320, Andhra Pradesh, India
[2]Department of Pharmacognosy and Phytochemistry, Sun Institute of Pharmaceutical Education and Research, Nellore Rural, Nellore-524346, Andhra Pradesh, India
[3]Department of Pharmacology, Sun Institute of Pharmaceutical Education and Research, Nellore Rural, Nellore-524346, Andhra Pradesh, India

ABSTRACT

Bepotastine besilate is an effective second-generation antihistamine for treating allergic rhinitis and chronic urticaria. However, its short half-life necessitates frequent dosing, decreasing patient compliance. A floating tablet formulation of bepotastine besilate was developed and evaluated with the goal of prolonging gastric retention and improving therapeutic efficacy. A variety of polymers, including hydroxypropyl methylcellulose (HPMC), xanthan gum, and carbopol, as well as effervescent agents like sodium bicarbonate and citric acid, were used to prepare floating tablets using the direct compression method. In preformulation studies, bepotastine besilate was found to be compatible with the selected polymers and excipients. A variety of physical properties were evaluated for the floating tablets, including hardness, friability, weight variation, and uniformity of drug content. FTIR analyses have confirmed the stability of bepotastine besilate within the polymer matrix and the absence of significant drug-polymer interactions. Floating tablets of bepotastine besilate developed in this study may improve patient compliance by reducing dosing frequency and ensuring sustained therapeutic effects.

Keywords: Bepotastine Besilate, Floating Tablets, Polymers, Sustained Release, In Vitro Evaluation, Gastric Retention.

INTRODUCTION

Bepotastine besilate belongs to the second generation of antihistamines used in the treatment of allergic rhinitis and chronic urticaria, and is known for its effectiveness and minimal sedative effects. Although its short half-life necessitates frequent dosing, this can result in poor patient compliance, due to the short half-life. There is possibility of developing floating tablets of bepotastine besilate in order to address this issue by providing prolonged drug release and prolonged gastric retention, thereby improving therapeutic efficacy and adherence of patients [1 -3].

It is designed to remain buoyant in the stomach for an extended period of time without having an adverse effect on the gastric emptying rate [5]. This is known as a floating drug delivery system (FDDS). It has been found that drugs that spend a prolonged period of time in the stomach are more likely to be absorbed in the upper gastrointestinal tract, where many drugs, including bepotastine besilate, are absorbed most effectively. As a result of FDDS, the dosage form is maintained at the surface of the stomach, facilitating controlled drug release and improving bioavailability [5].

For the purpose of achieving desired buoyancy and controlled release characteristics, floating tablets are typically formulated using polymers and effervescent agents. There are effervescent agents such as sodium bicarbonate and citric acid that generate gas when they are in contact with gastric fluids, which helps aid the buoyancy of the tablet [6 - 8].

MATERIALS AND METHODS

Materials Used

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

Analytical method development:

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.

Corresponding Author :- **G.Nageswararao** Email:- nagesh.gollapalli@gmail.com

b) Preparation calibration curve:

10mg Bepotastine Besilate 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 (R^2) 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 frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force.

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together.

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit.

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. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

Formulation development of floating Tablets:

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

Procedure for direct compression method:

1) Drug and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method by using 12 mm punch.

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, *In vitro* Buoyancy studies, *In vitro* drug release studies.

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.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$F = K_o t$

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

First order release rate kinetics: The release rate data are fitted to the following equation

$Log (100-F) = kt$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following

equation.

$$F = k\ t1/2$$

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:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K\ t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear [9 -13].

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 Bepotastine Besilate was taken in 0.1N HCL (pH 1.2)

Standard graph of Bepotastine Besilate was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Bepotastine Besilate showed good linearity with R^2 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.

Bepotastine Besilate 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.

Preformulation parameters of powder blend:

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.

***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.

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Table 1: 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 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

Table 3: Dissolution data of Floating Tablets

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	7.32	12.59	19.67	15.87	21.64	11.31	16.85	12.79	9.59
2	18.74	21.61	29.79	22.83	33.57	21.59	28.54	22.54	19.57
4	25.64	33.28	40.54	34.27	42.55	32.72	35.87	30.33	28.57
6	31.87	40.83	51.35	45.34	52.97	43.78	48.39	40.78	37.82
8	42.69	53.85	65.73	56.75	65.52	52.58	63.71	52.49	48.99
10	57.32	68.21	73.44	62.42	74.93	60.77	78.69	65.87	54.37
11	65.97	76.67	88.89	76.57	85.67	74.35	84.57	72.63	65.94
12	74.52	82.98	94.23	89.76	99.89	85.54	95.97	85. 83	79.56

Figure 1: Standard graph of Bepotastine Besilate in 0.1N HCL

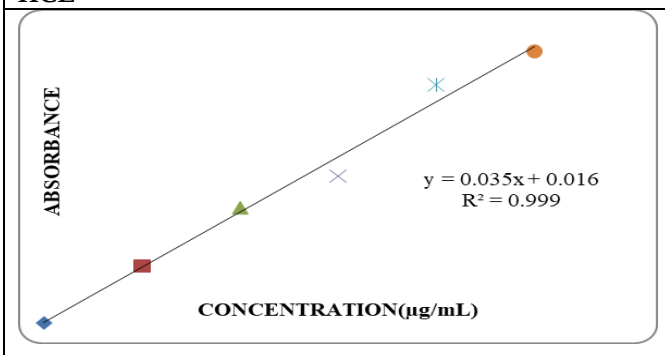


Figure 2: FTIR Spectrum of pure drug

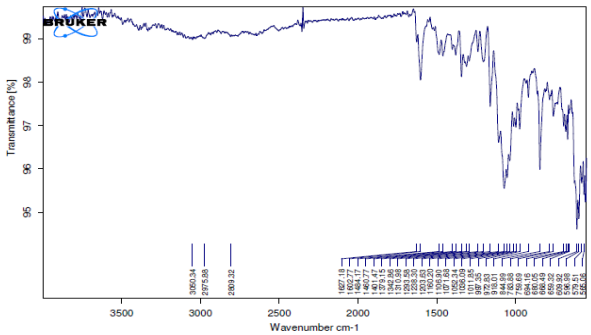


Figure 3: FTIR Spectrum of optimised formulation

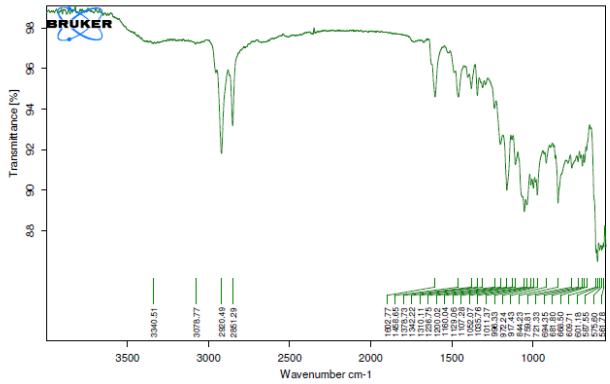


Figure 4: Zero order release kinetics

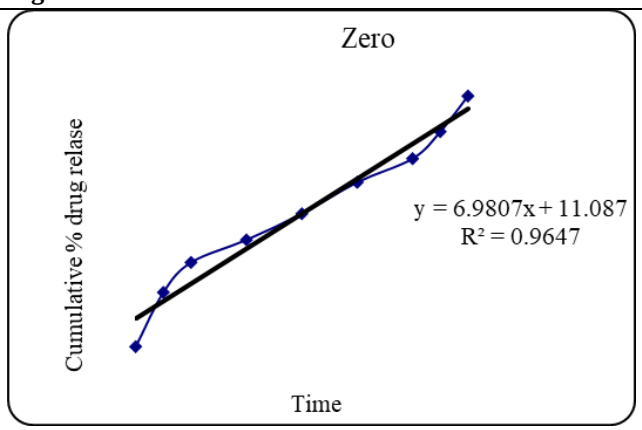


Figure 5: Higuchi release kinetics

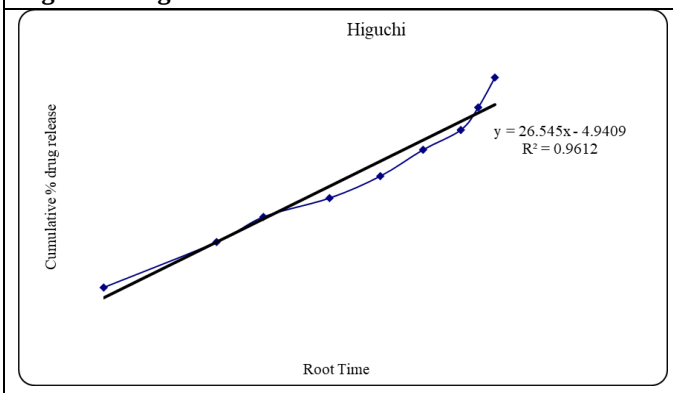


Figure 6: Kors mayer peppas release kinetics

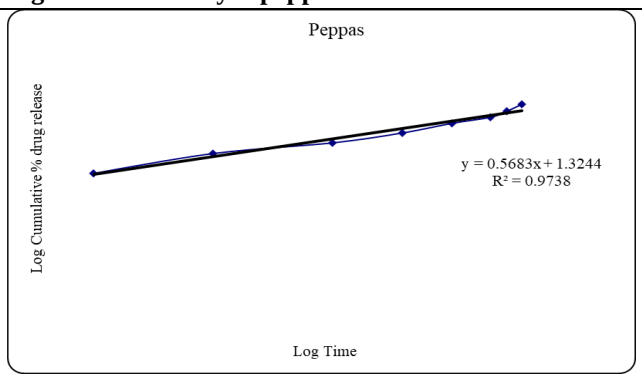
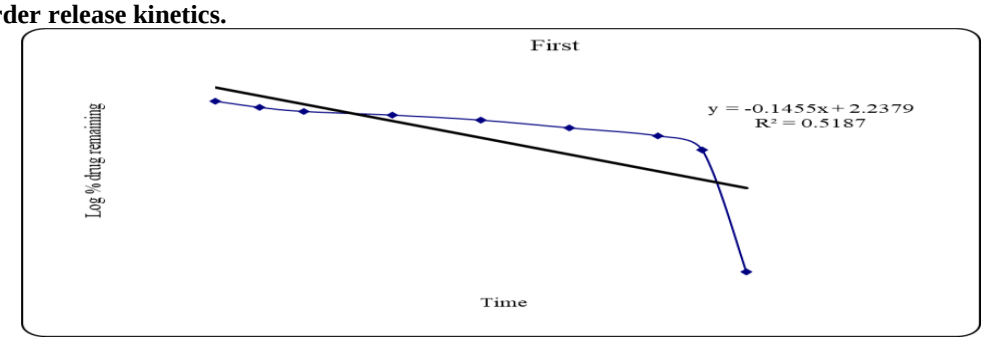


Figure 7: First order release kinetics.



CONCLUSION

Development of floating drug delivery of Bepotastine Besilate 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.

The following conclusions could be drawn from the results of various experiments. FTIR studies concluded that there was no interaction between drug and excipients. The physico-chemical properties of all the formulations prepared with different polymers Xanthan gum, Guar gum, Karaya Gum were shown to be within limits. Quality control parameters for tablets such as weight variation, Hardness, Friability, thickness, drug content and floating lag time were found to be within limits. In-vitro drug release studies were carried out for all prepared formulation and from that concluded F5 formulation has shown good results. Finally concluded release kinetics to optimised formulation (F5) has followed kors mayer peppas kinetics. Present study

concludes that Floating system may be a suitable method for Bepotastine Besilate administration.

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