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FORMULATION DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF BETAHISTINE HYDROCHLORIDE

Deepika Suryavanshi[*1], Sandesh Asati[1], Shailendra Lariya[1], Geeta Parkhe[2]

[1] Radhraman College of Pharmacy, Bhopal (M.P.)
[2]Scan Research Laboratories Bhopal (M.P.)

***Correspondence Info:**
Deepika Suryavanshi,
Department of Pharmaceutics,
Radhraman College of
Pharmacy, Bhopal (M.P.)
*Email:*deepikabarpete@gmail.com

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ABSTRACT

The purpose of this research was to develop a novel gastro retentive drug delivery system based on direct compression method for sustained delivery of active agent to improve the bioavailability, reduce the number of doses and to increase patient compliance. Gastro retentive floating tablets of betahistine hydrochloride were prepared by direct compression method using altered concentrations of HPMC K4, HPMC K15 and PVP K30 as polymers. The prepared tablets of betahistine hydrochloride were evaluated for hardness, thickness, friability, weight variation, drug content uniformity, buoyancy lag time, total floating time, *in-vitro* dissolution study, etc. All the compositions were resulted in adequate Pharmacopoeial limits. Compatibility studies was execution during FTIR shown that there was absence of probable chemical interaction between pure drug and excipients. The varying concentration of gas generating agent and polymers was found to effect on *in-vitro* drug release and floating lag time. *In vitro* drug release of floating gastro retentive tablet of betahistine shown that the formulation F6 was found to be the best formulation as it releases 99.89% betahistine in a controlled manner for an extended period of time (up to 12 hrs). The release data was fitted to various mathematical models such as Higuchi, Korsmeyer-Peppas, first order and Zero order to evaluate the kinetics and mechanism of the drug release. The Optimized formulation (F6) showed no significant change in physical appearance, drug content, floating lag time, *in vitro* dissolution studies after 75%±5% RH at 40±20C relative humidity for 6 months. Prepared floating tablets of betahistine may prove to be a potential candidate for safe and effective controlled drug delivery over an extended period of time for gastro retentive drug delivery system.

Key words: Betahistine hydrochloride, Gastro retentive, Floating tablet, Total floating time.

Introduction:

Oral sustained drug delivery system is complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose, since the majority of drugs are absorbed in stomach or the upper part of small intestine (Choi et al., 2008; Mahant and Nasa, 2011). Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part

of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability (Kaza et al., 2009). Betahistine hydrochloride is an orally administered antihistaminic drug. The chemical name of betahistine is N-methyl2-(pyridin-2-yl)-ethanamine. Betahistine has a very strong affinity for histamine H3 receptors and a weak affinity for histamine H1 receptors. It has been used to control vertigo in patients of Meniere's disease; it possibly acts by causing vasodilation in the internal ear. However short biological half-life of betahistine 2-3 h necessitates frequent 4 times a day administration of the drug (Moffat and David, 2004; Khedr and Sheha, 2008; Kumar et al., 2010). The objective of the present research work was to provide gastroretentive formulation that will provide once daily, sustained release dosage form of betahistine.

MATERIALS AND METHODS

Materials

Hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M) was procured from Meditab Specialities Pvt. Ltd., Satara. PVP K30 was purchased from S.D fine chemicals, Mumbai. Sodium bicarbonate, magnesium stearate, talc were purchased from Mapromax, Life sciences Pvt. Ltd., Dehradun. Other solvents and chemicals used in the research were of LR grade. All the studies were carried in distilled water.

Methods

Procedure for the determination of λ_{max}

10mg of drug was accurately weighed and dissolved in 10ml 0.1N HCl in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 5, 10, 15, 20, and 25 µg/ml with 0.1N HCl. This solution was scan at wavelength 400-200 nm on UV spectrophotometer (Labindia UV 3000 +). The higher absorption peak was obtained at 264nm which was the λmax of drug.

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical assortment were comparing with those of lafutidine pure drug. Samples was assorted comprehensively through 100mg potassium bromide IR powder as well as compacted under vacuum at a pressure of concerning 12 psi for 3 minutes. The ensuing disc was mounted in an appropriate holder in Brukers Alpha IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Pre compression evaluation

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, tapped density, carr's index, and hausner ratio.

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation**.**

$$\theta = \tan^{-1}(h/r)$$

Where, h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index**.**

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula (Sinko, 2006; Chein, 1992; Liberman et al., 1990).

Hausner's ratio = Tapped density/Bulk density.

Formulation development of Tablets

Direct compression method

Different tablets formulations (F1-F9) were prepared by direct compression technique. All powders were passed through 40 meshes. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as glidant. Lactose was used as diluents. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests (Ambati et al., 2011). The composition of betahistine floating tablets was shown in Table 1.

Table 1 Formulation composition of betahistine hydrochloride gastro retentive tablets

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Betahistine	16	16	16	16	16	16	16	16	16
HPMC K 15	100	120	140	-	-	-	50	60	70
HPMC K 4	-	-	-	100	120	140	50	60	70
PVP K30	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	84	64	44	84	64	44	84	64	44
Total Weight	250	250	250	250	250	250	250	250	250

Evaluation of tablets

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape were evaluated. Appearance was judged visually.

Thickness and diameter Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab).Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed

after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at a λmax of 264 nm using of 0.1 N HCl as blank.

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al* (Rosa et al., 1994). The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time necessary for the tablet to increase to the outside and float was determined as floating lag time. The experiments were conducted in triplicate. Total floating times were measured during *in vitro* dissolution studies.

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask maintaining the temperature of 37 ± 0.5^0c and rpm of 75. One Betahistine hydrochloride tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 10 hours using 10ml pipette. The new disintegration medium (37^0C) was supplanted each time with a similar amount of the sample and takes the absorbance at 264 nm using spectroscopy (Rajesh et al., 2009; Patil et al., 2006; Ritger- and Peppas, 1987; Brahamankar and Jaiswal, 2009; Higuchi, 1963; Korsmeyer et al., 1983).

Stability studies

The optimized formulation of betahistine were packed in strips of 0.04 mm thick aluminum foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40 0C and 75% RH for 6 months. The samples were withdrawn periodically and evaluated for their floating lag time, content uniformity and for in vitro drug release.

RESULTS AND DISCUSSION

Solubility of betahistine HCl was very soluble in water, soluble in ethanol (95%), practically insoluble in 2-Propanol. The melting point of betahistine HCl was 150-154°C and λ_{max} of betahistine HCl was found to be 264 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25 µg/ml fig.1. Identification of betahistine was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification fig.2. IR spectra of BH show peak at 3060.16 cm−1 which is due to N–H stretching. IR of drug also shows peak at 1340.61 cm−1 due to C=N stretching. The peak at 1601.82 cm−1 is due to C=C stretching. Tablet powder blend was subjected to various pre-formulation parameters Table 2. 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 0.423±0.3to 0.432±0.65 (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 0.481±0.47 to 0.489±0.14 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 10.83±0.25 to 12.78±0.45 which shows that the powder has good flow properties. All the formulations have shown the Hauser's ratio ranging between 1.12±0.36 to 1.14±0.56 indicating the powder has good flow properties. Betahistine HCl tablet quality control tests such as weight variation, hardness and friability, thickness, drug content and drug release studies in different media were performed on the compression tablet. All the parameters such as weight variation, hardness, friability, thickness and drug content were found to be within limits Table 3.

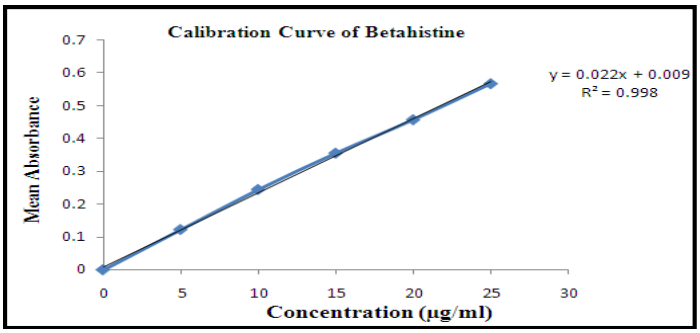

Fig. 1Calibration curve of betahistine in 0.1 HCL at 264nm

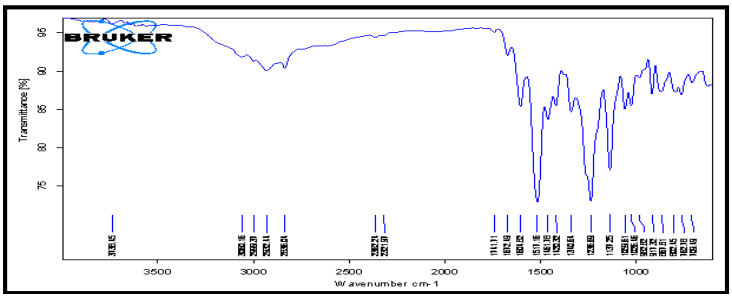

Fig. 2 FT-IR Spectrum of Betahistine (Pure Drug)

Table 2 Result of pre-compression properties of Betahistine GRF tablets

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's index	Hauser's ratio
F1	0.425±0.25	0.487±0.25	12.73±0.32	1.14±0.32
F2	0.432±0.32	0.485±0.32	10.92±0.21	1.12±0.31
F3	0.436±0.21	0.489±0.14	10.83±0.25	1.12±0.36
F4	0.425±0.25	0.482±0.56	11.82±0.65	1.13±0.35
F5	0.423±0.34	0.485±0.54	12.78±0.45	1.14±0.56
F6	0.425±0.15	0.481±0.47	11.64±0.45	1.13±0.47
F7	0.426±0.25	0.485±0.87	12.16±0.78	1.13±0.54
F8	0.432±0.65	0.486±0.98	11.11±0.78	1.12±0.65
F9	0.431±0.32	0.485±0.45	11.13±0.32	1.12±0.32

Average of three determinations (±SD)

Table 3 Results of post compression properties of Betahistine GRF tablets

F.Code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.65±0.21	4.6±0.2	Pass	0.856±0.25	98.89±0.25
F2	3.85±0.25	5.1±0.5	Pass	0.658±0.21	99.65±0.65
F3	3.45±0.21	4.9±0.6	Pass	0.789±0.32	98.65±0.45
F4	3.65±0.14	4.6±0.4	Pass	0.458±0.12	99.45±0.25
F5	3.45±0.25	5.1±0.6	Pass	0.658±0.32	98.78±0.32
F6	3.46±0.27	4.9±0.4	Pass	0.852±0.14	99.78±0.14
F7	3.65±0.21	4.8±0.5	Pass	0.896±0.56	99.65±0.56
F8	3.56±0.41	4.7±0.2	Pass	0.874±0.65	99.21±0.74
F9	3.65±0.21	4.7±0.6	Pass	0.965±0.45	99.45±0.32

Average of three determinations (±SD

In the present study 9 formulations with vari able concentration of polymer (HPMC-K15, HPMC-K4) were prepared by direct compression method and evaluated for physicochemical properties, buoyancy lag ti me, total floating time and invitro drug release table 4, 5 & fig. 3. The results indicated that optimized formulation F6 on immersion in 0.1N HCl at 37±0.5^{0}C tablets immediately and remain buoyant upto 12hr without disintegration. These two factors are essential for the tablet to acquire bulk de nsity < 1, so that it remains buoyant on the gastric fluid. The *in vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Korsmeyer-Peppas was maximum i.e. 0.976 hence indicating drug release from formulations was found to follow Korsmeyer-Peppas release kinetics. Table 6, 7 & fig. 4-7.

Table 4 Results of *in-vitro* buoyancy study of betahistine hydrochloride

F. Code	Floating lag times (sec)	Total floating time (hrs)
F1	30±5	>12
F2	25±4	>12
F3	33±6	>12
F4	32±8	>12
F5	35±7	>12
F6	25±4	>12
F7	32±5	>12
F8	25±6	>12
F9	36±7	>12

Table 5 *In-vitro* drug release study of GRF tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	36.56	35.45	32.12	30.25	28.98	26.54	24.65	22.45	20.14
1	50.98	45.56	42.25	38.98	35.45	32.25	30.12	28.78	25.65
1.5	65.45	62.65	58.98	45.65	43.23	40.25	38.98	35.65	31.45
2	89.12	85.45	78.98	55.65	52.45	48.78	45.65	40.12	38.98
3	99.78	98.98	88.98	75.65	65.45	62.23	55.45	51.45	48.98
4	-	-	99.65	89.98	78.98	75.45	68.89	65.45	61.45
6	-	-	-	99.89	85.65	83.12	73.12	70.32	68.65
8	-	-	-	-	98.89	93.12	85.65	80.12	75.65
12	-	-	-	-	-	99.89	90.12	85.45	79.89

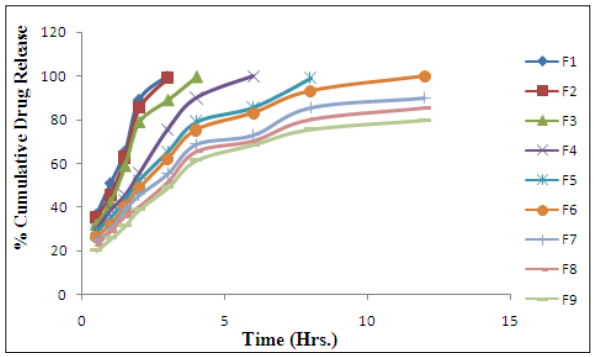

Fig.3 *In-vitro* drug release study of GRF tablets

Table 6 *In-vitro* drug release data for optimized formulation F6

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	26.54	1.424	73.46	1.866
1	1	0	32.25	1.509	67.75	1.831
1.5	1.225	0.176	40.25	1.605	59.75	1.776
2	1.414	0.301	48.78	1.688	51.22	1.709
3	1.732	0.477	62.23	1.794	37.77	1.577
4	2	0.602	75.45	1.878	24.55	1.390
6	2.449	0.778	83.12	1.920	16.88	1.227
8	2.828	0.903	93.12	1.969	6.88	0.838
12	3.464	1.079	99.89	2.000	0.11	-0.959

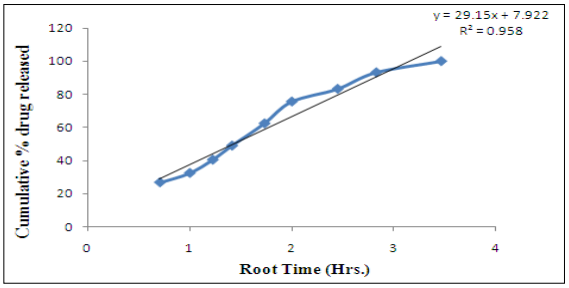

Fig. 4 Zero order release Kinetics

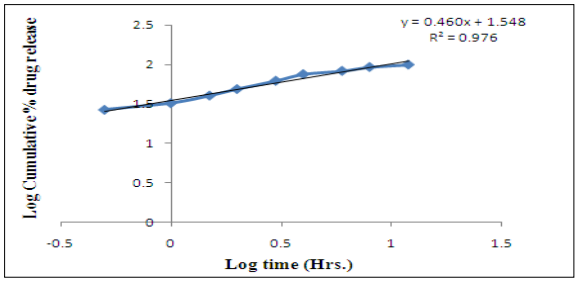

Fig. 5 First order release kinetics

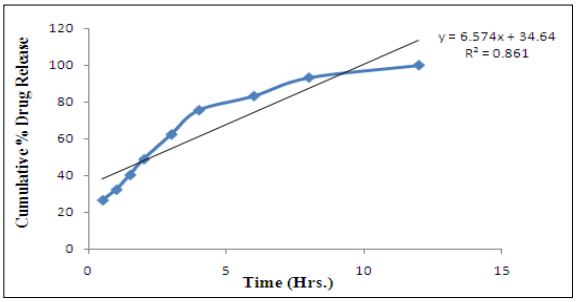

Fig. 6 Higuchi release Kinetics

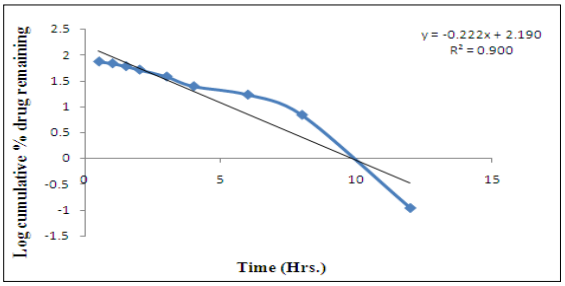

Fig. 7 Korsmeyer-Peppas release Kinetics

Table 7 Regression analysis data of betahistine floating tablets

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	R^2
F6	0.861	0.900	0.958	0.976

CONCLUSION

In the present work, it can be concluded that the betahistine floating tablets can be an innovative and promising approach for the delivery of betahistine. The optimized formulation F6 contains HPMC K15, K4 and a gas generating agent. The optimized formulation F6 showed drug release of 99.89% within 12h. The In vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, higuchi's, and korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Korsmeyer-Peppas was maximum i.e. 0.976 hence indicating drug release from formulations was found to follow Korsmeyer-Peppas release kinetics.

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