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FORMULATION AND EVALUATION OF BILAYER FLOATING TABLETS OF BETAHISTINE HYDROCHLORIDE

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ABSTRACT

The objective of the present study was to develop bi-layer tablets of betahistine hydrochloride is an orally administered antihistaminic drug with short half-life, which is characterized by initial burst drug release in the stomach and complies with the release requirements of sustained-release products. But they take lag time to start the action. Hence a new approach is tried that gives one immediate release dose and a sustained release dose in single dosage form call bilayer tablets. Immediate release layer delivers the initial dose, it contains superdisintegrants which increase drug release rate whereas sustained release layer float due to gas generating agent and releases drug at sustained manner for prolonged period. A direct compression method was used to formulate 9 batches. Superdisintegrants like sodium croscarmellose, crospovidone was used for immediate release layer and HPMC K4 M, HPMC K 15 M, PVP K30 like polymers were used in floating layer.A simple visible spectrophotometric method was employed for the estimation of betahistine at 264 nm and Beer's law is obeyed in the concentration range of 5-25 µg/ml. Preformulation studies were carried out to optimize the ratios required for various grades of polymers. The prepared floating tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, buoyancy lag time, total floating time, water uptake (swelling index), and *in vitro* dissolution studies. Successful formulation was developed having floating lag time as low as 36 sec and drug release was sustained up to 12 hrs. A biphasic drug release can be obtained by using bilayer tabletting technology which involved compression of immediate and sustained release layer together. Bilayered floating tablets with release characteristics offer critical advantages such as, site specificity with improved absorption and efficacy. This technology can be inculcated to various medicaments which have stomach as the major site of absorption.

Keywords: Bilayer floating tablets, Betahistine, Biphasic drug release, HPMC K 15 M.

INTRODUCTION:

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 [1-3]. One of the novel approaches in the area of oral sustained release drug delivery is gastro retentive drug delivery

system [4]. GRDDS can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability [5]. Extended-release dosage forms with prolonged residence time in the stomach are highly desirable for drugs with i) narrow absorption windows, ii) stability problems in the intestinal or colonic environment, iii) local action in the stomach and iv) low solubility at high pH values [6]. The layered tablet concept has been utilized to develop controlled-release formulations [7-12]. Such a tablet is considered as a biphasic delivery system that is designed to release the drug at two different rates and is usually composed of a fastrelease layer combined with single [7-10] or double sustained-release layers [11, 12]. Generally, conventional controlled-release dosage forms delay the release of drugs and do not provide a rapid onset of action after oral administration [13, 14]. Hence, the layered tablets offer a pharmacokinetic advantage over conventional controlled- release dosage forms as the drug is quickly released from the fast-release layer leading to rapid rise of drug plasma concentration followed by continuation of drug release from the sustained release layer [14]. This release pattern is required for successful treatment in many therapies, primarily when maximum relief needs to be achieved as soon as possible, and is followed by a sustained-release phase to avoid repeated drug administration. The present work concern with the formulation and evaluation of bilayer floating tablets of Betahistine hydrochloride having immediate and floating sustain release layer. These tablets showed the biphasic drug release means an immediate release layer releases the drug immediately as loading dose. Floating sustained release layer releases the drug for prolonged period of time as maintenance dose.

MATERIALS AND METHODS

Betahistine Hydrochloride-IP was received as a gift sample from Meridian Medicore Ltd., Baddi India. HPMC K4M, K15M, PVP K30 was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Sodium bicarbonate, citric acid, magnesium stearate and talc were obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Procedure for the determination of λ_{max}

Accurately weighed 10 mg of betahistine HCl separately and dissolved in 10 ml of 0.1N HCL in 10 ml of volumetric flask and prepared suitable dilution to make it to a concentration of 10 µg/ml make adequate of sample with concentration range of 10-50 µg/ml betahistine HCl calculate the spectrum of this solution

was run in 200-400 nm range in U.V spectrophotometer. (Labindia UV 3000 +). The higher absorption peak was obtained at 264nm which was the λ_{max} of drug.

FORMULATION DEVELOPMENT

Formulation of immediate release (IR) layer

The immediate release granules were prepared by blending the drug with different concentration of superdisintegrants like sodium starch glycolate, crospovidone, croscarmellose sodium and other excipients like microcrystalline cellulose by direct compression method. The powder blend was lubricated with magnesium stearate and talc. A weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 8 mm flat faced punch of 16 station Rimek mini press rotary compression machine to get IR layer. Nine formulation batches with different super superdisintegrants were made in order to achieve desired disintegration time and drug release. The composition of betahistine immediate release tablets were shown in Table 1.

Formulation of floating sustained release (SR) layer

The floating sustained release granules were prepared by direct compression technique. Required quantity of betahistine and polymers like HPMC K4M, HPMC K15M, PVP K30, alkalizing agent sodium bicarbonate and acidifying agent citric acid were weighed and passed through sieve with mesh #40 and were mixed homogeneously in a poly-bag for about 5-10 min and was taken in a mort. The powder mass was passed through mesh #14. Finally the powder was lubricated with lactose and talc Table 2.

Formulation of bilayer tablet

Optimized formulation IF-7 of immediate release layer and optimized formulation of F-6 for sustained release used for formulation of Bi-layer tablet.

Table 1 Composition of betahistinefast dissolving tablets

Ingredients(mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Betahistine	8	8	8	8	8	8	8	8	8
Na starch glycolate	10	15	20	_	_	_	_	_	_
CroscarmelloseNa	_	_	_	10	15	20	_	_	_
Crospovidone	_	_	_	_	_	_	10	15	20
MCC	71	66	61	71	66	61	71	66	61
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	100	100	100	100	100	100	100	100	100

Table 2 Formulation of sustained release floating layer

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Betahistine	8	8	8	8	8	8	8	8	8
HPMC K 15	_	_	_	160	170	180	80	85	90
HPMC K 4	160	170	180	_	_	_	80	85	90
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	82	72	62	82	72	62	82	72	62
Total Weight	300	300	300	300	300	300	300	300	300

Evaluation of Precompression Parameter

Angle of Repose (θ)

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

$$\text{Carr's index (\%)} = [(TBD - LBD)/TBD] \times 100.$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculatedby the following formula [15-17].

Hausner's ratio = Tapped density/Bulk density.

Evaluation of post compression Parameter

General appearance

Morphological characters like shape and texture was determined visually.

Thickness

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) and measured in terms of kg/cm^2.

Weight variation

The weight variation test was performed as per the U.S guidelines. Twenty randomly taken tablets were weighedtogether and the average weight was determined. Each tablet was then weighed individually and deviation fromaverage weight was calculated.

Friability

A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche friabilator. The friabilator was operated for 4 min at a speed of 25 rpm. The tablets were removed from the friabilator, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,

%Friability= (Loss in weight/ Initial weight) x 100

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 reacts with dye and analyzed for drug content by UV spectrophotometer at a λmax of 264.0nm using of 0.1 N HCL as blank.

Buoyancy lag time determination & total floating time

*Invitro*buoyancywasdeterminedbyfloating lag timeasperthemethod describedbelow.Thetabletswere placedseparately ina100 mlglassbeakercontaining simulated gastricfluid(SGF),pH1.2asperUSP.The time required for the tablet to rise to the surface for floating was determined as the buoyancy lag timeand further total floating time of all tablets was determined by visual observation.

In vitro disintegration time of immediate release tablets

The disintegration time for all immediate release formulations was carried out using tablet disintegration testapparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed.The medium, water was maintained at a temperature of 37° ± 2°C and time taken for the entire tablet to disintegratecompletely was noted.

In vitro dissolution studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.5^{0}C and rpm of 75.One Betahistine tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^{0}C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCL and take the absorbance at 264nm using spectroscopy.

Stability studies

The stability of betahistine HCl bilayer floating tablets to assess their stability with respect to their physicalappearance, drug content and release characteristics after storing at 25°C/60% RH and 40°C/75% RH in properlyclosed HDPE bottles along with 1 g desiccant for 3 months.

RESULTS AND DISCUSSIONS

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 5-25µg/ml Fig.1.

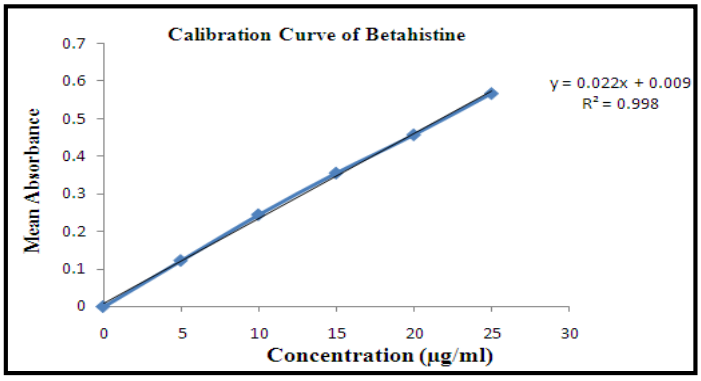

Fig. 1Calibration curve of betahistine in 0.1 HCL at 264nm

The powdered blends of different formulations of immediate release tablets and sustained release floating tablets were evaluated for angle of repose, bulk density (BD), tapped density (TBD) and compressibility index. The results of immediate release tablets and SR floating tablets are summarized in Table 3& 4.

The results of SR floating tablets of BD and TBD ranged from 0.545to 0.598and 0.756to 0.795 respectively. The range of angle of repose and compressibility index was found to be 29 to 36 and 21.83to 30.57respectively. The results of angle of repose (<35) indicate good flow properties of the powdered blend. The formulation of immediate release tablet prepared by using the superdisintegrants exhibited the LBD, TBD, angle of repose, compressibility index and Hausner's ratio of within the range, which shows good flow properties of the powdered blend.

Table 3 Results of pre-compression parameters of powder blend of immediate release

F.Code	Parameters				
	Bulk density (gm/ml)	**Tapped density (gm/ml)**	**Carr's Index (%)**	**Hausner's Ratio**	**Angle of Repose (θ)**
IF1	0.38	0.48	20.833	1.263	42^0
IF2	0.36	0.46	21.739	1.278	41^0
IF3	0.37	0.48	22.917	1.297	43^0
IF4	0.38	0.49	22.449	1.289	42^0
IF5	0.39	0.48	18.750	1.231	43^0
IF6	0.38	0.49	22.449	1.289	41^0
IF7	0.37	0.48	22.917	1.297	40^0
IF8	0.38	0.47	19.149	1.237	42^0
IF9	0.39	0.49	20.408	1.256	40^0

Table 4 Result of pre-compression properties of sustained release floating tablets

Material	Angle of repose (θ)	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's Index (%)	Hausner's ratio
			Betahistine		
F1	30^0	0.595±0.025	0.795±0.021	25.157	1.336
F2	32^0	0.587±0.020	0.765±0.032	23.268	1.303
F3	35^0	0.565±0.014	0.756±0.012	25.265	1.338
F4	30^0	0.598±0.045	0.765±0.014	21.830	1.279
F5	29^0	0.545±0.036	0.785±0.023	30.573	1.440
F6	36^0	0.558±0.045	0.761±0.032	26.675	1.364
F7	35^0	0.558±0.014	0.772±0.014	27.720	1.173
F8	34^0	0.589±0.027	0.762±0.015	22.703	1.106
F9	32^0	0.584±0.041	0.795±0.021	26.541	1.361

The prepared tablets were evaluated for different physico-chemical properties and the results are summarized inTable 5 & 6. The tablets were white, circular in shape and were found to be uniform with respect to weight variation, hardness; thickness, friabilityand content uniformity ofdifferent batch of tablets were found within acceptable range and the distribution of drug in all the formulations was uniform.

Table 5 Results of post-compression parameters of immediate release

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drugcontent (%)	*In vitro* Disintegration Time (sec.) (n=3) *Mean ± SD
IF1	4.15±0.15	0.658±0.045	Passes	2.12±0.456	98.98±0.45	38±5
IF2	4.26±0.25	0.621±0.025	Passes	2.45±0.23	97.45±0.65	36±2
IF3	4.56±0.25	0.698±0.032	Passes	2.32±0.48	98.21±0.45	32±1
IF4	4.21±0.32	0.698±0.041	Passes	2.21±0.47	97.65±0.36	45±3
IF5	4.50±0.45	0.458±0.036	Passes	2.32±0.65	99.20±0.46	40±4
IF6	4.32±0.32	0.658±0.045	Passes	2.45±0.45	97.89±0.36	32±5
IF7	4.65±0.36	0.758±0.065	Passes	2.32±0.41	98.98±0.78	28±4
IF8	4.58±0.47	0.721±0.048	Passes	2.15±0.47	97.98±0.69	30±1
IF9	4.65±0.48	0.854±0.025	Passes	2.30±0.43	98.89±0.41	32±2

***(n=3)**

Table 6Results of post compression properties of sustained release floating tablets

F. Code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating lag times (sec)	Total Floating Time (hrs)
F1	3.53±0.05	4.8	300.19± 2.94	0.58 ± 0.10	98.33± 0.92	65s	>12
F2	3.94± 0.10	4.4	300.18 ± 3.77	0.51 ± 0.08	97.20 ± 0.34	60s	>12
F3	3.96± 0.05	4.5	300.33 ± 1.50	0.38 ± 0.12	99.60 ± 1.39	58s	>12
F4	3.95± 0.05	4.7	300.30 ± 3.30	0.16 ± 0.04	98.14 ± 1.69	70s	>12
F5	3.93± 0.10	5.2	300.13 ± 2.83	0.31 ± 0.07	97.21 ± 1.07	58s	>12
F6	4.03± 0.06	5.3	300.16 ± 2.33	0.27 ± 0.05	97.50± 1.81	52s	>12
F7	4.05± 0.05	4.8	300.18 ± 3.11	0.29 ± 0.08	98.34 ± 0.37	36s	>12
F8	3.98± 0.05	4.5	300.04 ± 2.56	0.34 ± 0.12	98.31± 0.91	70s	>12
F9	3.69±0.06	4.9	300.02±2.11	0.32±0.09	97.83±0.59	51s	>12

The prepared bilayer tablets were evaluated for different physico-chemical properties and the results are summarized in Table 7. The tablets were found to be uniform with respect to weight variation and hardness (6.45kg/cm^2). The thickness (5.65mm) and friability (0.765%) of optimized batch of tablets were found within acceptable range. Content uniformity of formulations was found to be 99.78 %, where the distribution of drug in all the formulations was uniform.

Table 7 Post-compressional parameters of bilayer tablets

F. code	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Drug content	Thickness (mm)
FIS	6.45± 0.36	0.765± 0.01	Passes	99.78	5.65±0.03

The Instant layer of betahistine HCl release Approx98.32 percent drug within 15 minutes and control floating layer betahistine HCl shows release up to 12 Hours Approx99.12 percent. The release of bilayer tablet is shown in Fig.2.

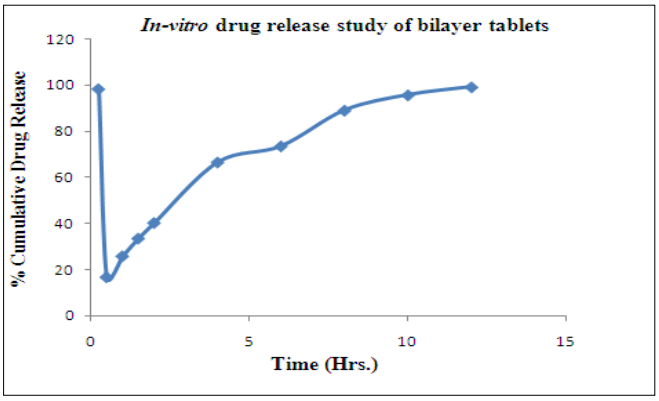

Fig. 2 Graph of release of bilayer tablets

CONCLUSION

The Experiment relates to formulation and development of oral pharmaceutical bilayer tablet of betahistine HCl for administration of therapeutically and prophylactically effective amount of antihistaminic drug substance to obtain both a relatively fast or quick onset of therapeutic effect and maintenance of a therapeutically active plasma concentration for relatively long period of time. Experiment conclude that Bi-layer tablet is suitable for delivering same drugs with different release pattern like one layer of drug as immediate release to get quick relief from of symptoms associated with Meniere's disease and second drug as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose.

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