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Design and optimization of oral osmotic pump based controlled drug delivery system for betahistine dihydrochloride

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ABSTRACT

The aim of the present study was to develop and optimize elementary osmotic drug delivery system of betahistinedihydrochloride to give control release of drug by utilizing the osmosis principle with better patient compliance. Suitable analytical method based on uv-visible spectrophotometer developed for betahistinedihydrochloride. By performing preformulation studies by ft-ir, drug-excipient compatability studies, no interaction was confirmed. Prior to compression, drug and granules were evaluated for flow properties such as angle of repose, loose bulk density, tapped bulk density, % compressibility, and hausner's ratio. The present study shows that the release of bht could be extended over a period of 12 hours through the design of an osmotic drug delivery system by using peo (mw:1,00,000 gm) as swellable polymer , mannitol as osmogen and ethyl cellulose as semi permeable coating membrane. Hence twice a day administration of this ndds can ensure therapeutic concentration throughout the day and can enhance patient compliance.

Keywords: Betahistinedihydrochloride, osmotic drug delivery system, Ethyl cellulose

INTRODUCTION

Osmotic devices are most promising strategy based systems for controlled drug delivery systems. They are among the most reliable controlled drug delivery system and could be employed as oral drug delivery systems or implantable device[1]. Osmosis is aristocratic bio phenomenon, which is exploited for development of systems with every desirable property of an ideal controlled drug delivery system. Osmotic system utilizes the principles of osmotic pressure for delivery of drug.Osmotic drug delivery systems for oral and parenteral use offer distinct and practical advantages over other means of delivery[2].

Elementary osmotic pump (EOP) works on the same mechanism as the impalatable pumps it is simplest possible form of osmotic pump as it does not require special equipment and technology. This device was further simplification of Higuchi – Theeuwes pump. It was developed in the year 1975 by Theeuwes. The EOP consist of single layered tablet core containing a water soluble drug with or without other osmotic agent. A semi permeable membrane surrounds the tablet core. When such a system is swallowed water from the GIT enter through the membrane in the core, the drug dissolved and the drug solution is pumped out through the exit orifice. This process continues at a constant rate until the entire solid drug inside the tablet has been dissolved drug continues to be delivered but at a declining rate until the osmotic pressure between outside environment and saturated drug solution. Normally the EOP delivers 60 - 80% of its content at a constant rate and there is a short lag time of 30- 60 min as the system hydrates before zero order drug release from the EOP is obtained[3].

Betahistine has a very strong affinity as an antagonist for histamine H_3 receptors and a weak affinity as an agonist for histamine H_1 receptors. Betahistine seems to dilate the blood vessels within the middle ear which can relieve pressure from excess fluid and act on the smooth muscle. In addition, Betahistine has a powerful antagonistic effects at H3 receptors, and increases the levels of neurotransmitters

released from the nerve endings. This is thought to have two consequences; The increased amounts of histamine released from histaminergic nerve endings can stimulate H_1 receptors, thus augmenting the direct agonistic effects of Betahistine on these receptors[4]. This explains the potent vasodilatory effects of Betahistine in the inner ear, which are well documented.

MATERIALS AND METHODS

MATERIALS

Betahisitine dihydrochloride was obtained as a gift sample from Orchid Pharma; Chennai, Colloidal Silicon dioxide, Povidone k-30, Microcrystalline Cellulose, Polyethylene Glycol and Ethylcellulose (EC) from SD Fine- Chemicals Ltd; Mumbai.

Calibration curve of Betahisitine dihydrochloride

48.15 mg of BHT was weighed and transferred into 100 ml volumetric flask , 60 ml of methanol was added and sonicated for 2 min to dissolve then dilute with diluents to make up to 100ml. Pipette out 5ml in 50 ml volumetric flask and and make up to 50 ml with water. Take 1 ml sample into 10 ml flask and make up to 10 ml with water. The standard stock solution was prepared as per the method described in methodology and scanned by UV-Visible spectrophotometer. The UV absorption spectrum of Betahisitine dihydrochloride showed peak at 260.0 nm.

Pre Compression Parameters for pure drug[5,6]

Organoleptic evaluation

These are preliminary characteristics of any substance which is useful in identification of specific material. Physical properties of API were studied for Color, Odour and Taste.

Bulk Density (BD)

Bulk density = Weight of powder / Bulk volume

Tapped density (TD)

Tapped Density = Weight of powder / Tapped volume

Carr's Index

It is a simple test to evaluate the BD and TD of a powder and the rate at which it is packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x100]/TD

Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flowability of a powderor granular material and their standard values are given in table 1.

Hausner's Ratio = TD / BD

Angle of repose

The angle of repose of API powder was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The diameter of the powder cone was measured and angle of repose was calculated using the following equation**.**

Tanθ=h/r Where,h=Heightofthepowdercone,
R=Radiusofthepowdercone.

Table 1: Effect of Carr's Index and Hausner's Ratio and Angle of repose on flow property

Flow Character	Carr's Index (%)	Hausner's Ratio	Angle of repose
Excellent	≤10	1.00-1.11	<20
Good	11-15	1.12-1.18	20-30
Fair	16-20	1.19-1.25	-----
Passable	21-25	1.26-1.34	30-34
Poor	26-31	1.35-1.45	-------
Very poor	32-27	1.46-1.59	>35
Very very poor	>38	>1.6	-------

Particle Size analysis (sieve method)

The procedure involves the Electromagnetic Sieve shaking of the sample through the series of successively arranged sieves (sieve no. - 20, 30, 40, 60, 80, and receiver), and weighing of the portion of the sample retained on each sieve and calculate percentage retained on each sieve[7].

Drug Excipient Compatibility Study

Compatibility was performed by preparing compatibility blends at different ratio of different excipients with API, based on the tentative average weight. These mixtures were kept in a 5ml glass white colored vials and packed properly. These vials are exposed to 1) room temperature 2) 2 – 8° C and 3) 40˚c / 75%RH. 15gm of blend is prepared which is filled in 3 vials. The samples were compared with initial samples data after the 2nd and 4th week of the study[8,9].

Formulation of Betahisitine dihydrochloride oral osmotic delivery

Mix Betahistinedihydrochloride with Aerosil until the wetting is not observed. Co-sift above material along with Mannitol, Mcc PH 102 and PEO through sieve # 30. Citric acid monohydrate was crushed in mortar and passed through sieve no #60. Co-Sift above material along with material and PVP k-30, talc through sieve no # 30.Load the above materials into blender and mix for 30 mins. 6. Sift Magnesium stearate through sieve # 40 along with a portion of pre lubricated blend[9]. Load the material to the blender and mix for 5 mins. Compress the lubricated blend into tablets by maintaining 20% RH and slow rpm with the help of 16 station tablet compression machine. Disperse ethyl cellulose in Isopropyl alcohol under stirring to prepare clear solution and add Water soluble plasticizer (PEG) and stir well. Coat the tablets of step no.8 in a coating machine with dispersion to achieve a target weight gain of 2.5 ± 0.5% w/w,5.0 ±.5%w/w ,7.5 ±5%w/w and 10.0 ± 0.5% w/w each. 13. Warm the coated tablets in coating pan at 50°C ± 5°C for 20 -30 mins. Make a whole at the centre of the coated tablets with the help of different sizes of needles.

Table 2: Compilation of Betahisitine dihydrochloride oral osmotic delivery

S.NO.	INGREDIENTS	mg/Tab		
		F1	F2	F3
1	Betahistinedihydrochloride	24	24	24
2	Mannitol (SD 200)	140	140	140
3	MCC102	78.2	78.2	78.2
4	PVPk30	19.8	19.8	19.8
5	Polyethyleneoxide	60	60	60
6	Colloidalsilicon dioxide	47	47	47
7	Citricacidmonohydrate	24	24	24
8	Talc	3.5	3.5	3.5
9	MagnesiumStearate	3.5	3.5	3.5
	Totalweight	400	400	400
Coatingcomposition(%w/w)		5%	5%	10%
10	Ethylcellulose	2.5	2.5	4

Post-compressional Studies

Uniformity of thickness

Both core and coated tablets' thickness and thickness were restrained expending a calibrated dial calipers. Three tablets of each formulation were chosen arbitrarily and dimensions resolute. It is articulated in mm, and the standard deviation was also premeditated[7,8].

Weight variation test

To study weight variation 20 tablets of each pulse dose formulation were weighed discretely using a Sartorius electronic balance. The test was executed bestowing to the official method.The average weight was prominent and standard deviation designed. The tablet passes the test if not more than two tablets fall outside the percentage limit, and none of the tablets diverges by more than double the percentage limit[9].

Hardness test

Hardness designates the ability of a tablet to withstand mechanical shocks while handling. The hardness of core tablets was resolute using a validated dial type hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated[10].

Friability test

For each pulse dose tablet formulation, the friability of 6 tablets was indomitably using the Roche friabilator. The following equation can dog friability:

$F = [wt_{initial} - wt_{final} / wt_{initial}] \times 100$

Disintegration time

Disintegration time of the tablet was observed with the help of disintegration test apparatus[11].

In vitro dissolution studies

Dissolution was carried out in 0.1N HClfor 60 min. in 900ml volume of type 2 paddle apparatus with rotation Speed 75 rpm and at temperature[12]: 37^0C $\pm$ 0.5^0C. The percentage drug release can be calculated by following equation;

$$\% \text{ drug content} = \frac{\text{Absorbance X 900 X Dilution}}{\text{Slope X 1000 X label claim}} \text{ X } 100$$

Release kinetics

In edict to apprehend the mechanism and kinetics of drug release, the results of the in vitro drug release study were fitted with various kinetic equations, namely zero-order (% release vs time), first-order (log% unreleased vs time), and Higuchi matrix (% release vs square root of time). To delineate a model which will epitomise a better fit for the formulation, drug release data advance considered by Peppas equation, $Mt/M\infty=ktn$, where Mt is the amount of drug released at time t and $M\infty$ is the amount released at time ∞, the $Mt/M\infty$ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent, a degree of the primary mechanism of drug release. Regression coefficient (r^2) values were intended for the linear curves acquired by regression analysis of the above plots[13].

RESULTS AND DISCUSSION

Calibration curve of Betahistine dihydrochloride

This showed an absorption maximum at 260 nm. The calibration curve was prepared in Purified waterand its R^2-value is 0.999 as displayed in Figure 1.

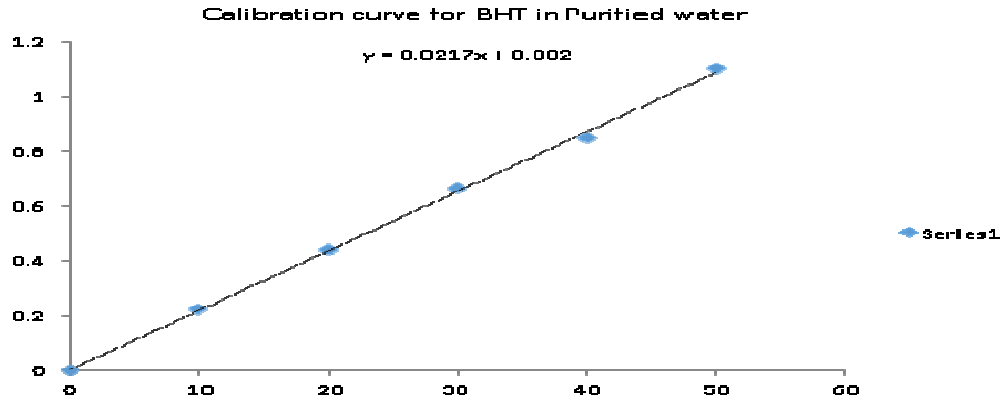

Figure 1: Calibration Curve of Betahisitine dihydrochloride

Pre-Compression Parameters

Organoleptic evaluation

Physical properties of API were White to almost yellow crystalline powder.

Table 3:Physical Properties of Pre-Compression Blend

Batch. No	Angle of Repose(^{0})	Bulk Density(g/ml)	Tapped bulk density(g/ml)	Carr's index(%)	Huasner Ratio
F1	23.39±0.02	0.453±0.01	0.59±0.016	16.53±1.38	1.227±0.04
F2	25.06±1.06	0.48±0.015	0.556±0.015	19.78±2.6	1.229±0.05
F3	24.93±0.19	0.456±0.005	0.543±0.015	18.41±3.82	1.19±0.022

* Each value is the mean ± SD (n=3)

The angle of repose for the formulated blend F1-F3 was found to be in the range 23.39 to 25.06 shows good flow property. The compressibility index for the formulations F1-F3 found between 16.53 % to 19.78%, indicating the powder blend has the required flow property for compression.

Drug Excipient Compatibility Study

From the above Drug-Excipient compatibility studies data, it was clear that Betahistinedi hydrochloride was compatible with all the excipients listed below Table 4.

Table 4: Results of Compatibility study

Sl.no	Name of Excipient	Ratio API:Expt	Initial observation	Final observation		conclusion
				40^{o}C/75%RH		
				2ndweek	4thweek	

1	API(BHT)	-----	White to yellowish white	White to yellowish white	White to yellowish white	compatible
2	API+MCC (PH102)	1:1	White fine powder	White fine powder	White fine powder	compatible
3	API+PEO(N12)	1:1	Off-white	Off-white	Off-white	compatible
4	API+ Mannitol(SD200)	1:2	Off-white	Off-white	Off-white	compatible
5	API+ Sodiumstearylfumerate	1:0.05	white	white	white	compatible
6	API+Mg.stearate	1:0.05	white	white	white	compatible
7	API+Ethylcellulose	1:2	white	white	white	compatible
8	API+Talc	1:0.05	white	white	white	compatible
9	API+PVP(k-30)	1:0.5	white	white	white	compatible

Post-compressional Studies

Uniformity of thickness

The thickness of the formulations from F1- F3 was found to be in the range of 4.31 to 4.41.

Weight variation test

The weight variation of the tablet in the range of ± 1.65% to ± 1.57% (below 7.5%) complying with pharmacopoeial specification.

Hardness test

The hardness of the formulated tablets was found to be 3.5±1.25 to 4.0±1.15, indicating a satisfactory mechanical strength.

Friability test

The friability of the tablet in the range of 0.24±0.02 % to 0.39±0.03% **(**below 1%) complying with pharmacopoeial specifications

Table 5: Post-compressional studies of Betahisitine dihydrochloride

Formulation	Weight Variation (%)	Friability (%)	Thickness (mm)	Hardness (Kg/cm^2)	Disintegration time (Min)
F1	±1.57	0.27±0.01	4.31±0.005	3.5±1.52	5.36± 0.3
F2	±1.62	0.39±0.03	4.32±0.03	4.0±1.15	5.08± 0.42
F3	±1.65	0.24±0.02	4.41±0.01	3.5±1.25	4.18± 0.34

***** Each value is the mean ± SD (n=3)

In-vitro Dissolution Study

In-vitro release studies using the USP type II (paddle) dissolution test apparatus. 900ml of purified water was filled in the dissolution vessel, and the temperature of the medium was set at 37^0c±0.5^0c. Sink condition was maintained for the whole experiment. The speed was set at 50 rpm. 5ml of the sample was withdrawn at predetermined time intervals for 12 hours and the same volume of fresh medium was replaced. The samples were analyzed for drug content against purified water as a blank at max 260nm using U.V. spectrophotometer.

Table 6: Dissolution Profiles of Betahisitine dihydrochloride Formulations

Time (hrs)	F1	F2	F3
0.5	32	48	34
1	38	67	49
2	40	78	64
4	42	101	96
6	44	-	99
8	49	-	-
12	55	-	-

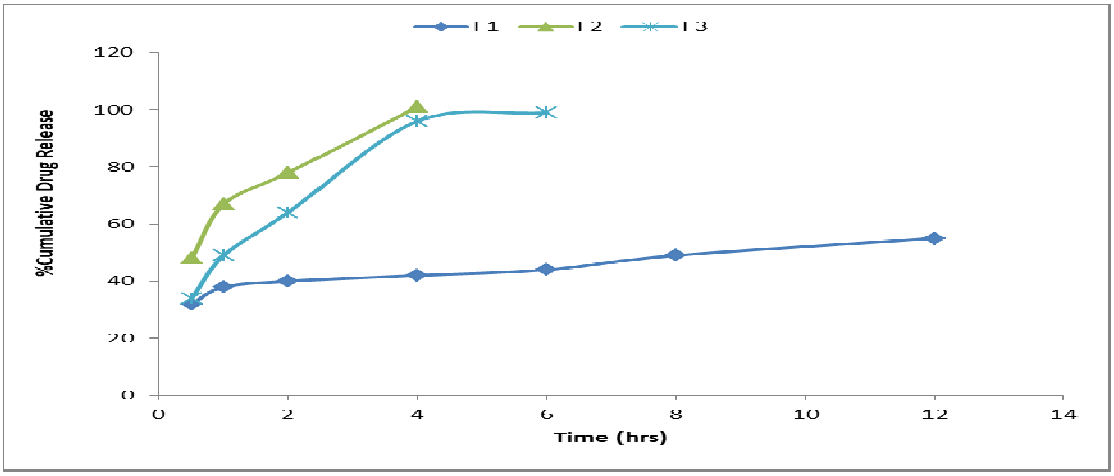

Figure 2: % Cumulative drug release from F1 – F3 formulations

Release kinetics

From table 7 the drug release data were best fitted with zero-order kinetics. The Higuchi equation explains the diffusion-controlled release mechanism. The diffusion exponent 'n' values of Korsmeyer-Peppas model was found to be in the range of 0.5 to 0.1, indicating Non-fickin diffusion of drug through Betahisitine dihydrochloride oral osmotic delivery .

Table 7: kinetic models for Betahisitine dihydrochloride oral osmotic delivery

Formulation	Zero order	First order	Higuchis matrix	Peppas model	
				R^2 value	n valuve
F1	0.9714	0.5161	0.9573	0.0223	0.2396
F2	0.9731	0.5337	0.9479	0.0262	0.2578
F3	0.9989	0.567	0.9329	0.5939	0.9926

CONCLUSION

Osmotic drug deliver y system utilizes the principle of osmosis for release of drug. Release of drug from osmotically controlled system is found to be independent of pH of the body fluid, presence of food in GIT, hydrodynamic conditions, and other body's physiological factors. Osmotic system has a high degree IVIVC, because release is found to be independent of the above mentioned factors, which are responsible for causing differences in release profile in vivo and in vitro. The aim of the present study was to develop and optimize elementary osmotic drug delivery system of Betahistinedihydrochloride to give control release of drug by utilizing the osmosis principle with better patient compliance. Suitable analytical method based on UV-Visible spectrophotometer was developed for Betahistine dihydrochloride. λ max of 260 nm was identified for Betahisitine dihydrochloride. By performing preformulation studies by FT-IR, Drug-excipient compatability studies, no interaction was confirmed. Prior to compression, drug and granules were evaluated for flow properties such as angle of repose, loose bulk density, tapped bulk density, % compressibility, and hausner's ratio. Core tablets of Betahistinedihydrochloride were successfully prepared using mannitol as osmogen, Polyethylene oxide as water swellable polymer and PVP K-30 as dry binder. Dissolution kinetics follows Zero order and it was also found that release was independent of pH of the medium and agitational intensity.

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