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FORMULATION AND *IN VITRO* EVALUATION OF GASTRORETENTIVE FLOATING DRUG DELIVERY OF VALSARTAN

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ABSTRACT

The purpose of this research was to develop a novel gastro retentive floating tablets of Valsartan. Valsartan is an angiotensin receptor blocker(ARB) effective in the treatment of hypertension. Valsartan has short half-life (3-6hrs) and it has a gastric absorption. The preparation of floating tablets of Valsartan was done by incorporating natural polymers such as guar gum and sesbaniagum and gas generating agent like sodium bicarbonate and other excipients are also blended and compressed on a rotary compressed machine. The floating tablet formulations were evaluated for physical characterizations namely hardness, friability, weight variation, drug content uniformity and buoyancy studies, in vitro drug release study. The drug-excipient compatible studies were performed by FTIR, and the study revealed that there is no drug excipient interaction. The in-vitro drug release pattern of Valsartan floating tablets was fitted to different kinetic models which showed highest regression for zero order kinetics with Higuchi mechanism. Invitro drug release study was performed by using united states pharmacopeia 23 type dissolution test apparatus employing paddle stirrer at 50 rpm. Dissolution medium used was 900ml of 0.1NHCL 37±0.5^{0}c. The Formulation F2 was shown a satisfactory result regarding buoyancy studies and in vitro drug release studies as compared to other formulations.

KEY WORDS

Valsartan, gastro retentive, gastric floating tablet, floating drug delivery, controlled release.

INTRODUCTION

Valsartan was an angiotensin receptor blocker widely prescribed for hypertension. It absorbed from the upper part of gastrointestinal tract[1,2]. The oral bioavailability of Valsartan was reported to be 25%. The recommended adult oral dosage of Valsartan is 80mg for the effective treatment of hypertension[3,4]. The short biological half-life of drug (3-6 hrs) also favors development of controlled release formulations. Drugs which are easily absorbed from the gastrointestinal tract and those with short half-lives are quickly eliminated from the systemic circulation due to which frequent dosing is required. To overcome this problem, gastro retentive drug delivery systems which provide effective plasma drug concentration for longer periods thereby reducing the dosing frequency are being formulated. It also has an advantage of minimizing the fluctuations in plasma drug concentration by delivering the drug in a controlled and reproducible manner. The present study aims in designing floating tablets of Valsartan using Guar gum and sesbania gum and evaluating the prepared tablets for physicochemical properties, buoyancy lag time, total floating time, swelling index and *invitro* drug release

MATERIALS AND METHODS

Materials: Valsartan was obtained as a gift sample from Aizant laboratory. Guar gum, Sesbania gum India were received from Finar labs, Hyderabad, India. Citric acid, sodium bicarbonate, talc, magnesium stearate and lactose were purchased from S.D. chemicals

Methods

Formulation of Floating tablets of Valsartan were prepared by direct compression method according to

the formula given in Table 1. Valsartan (80 mg) was mixed with the required quantity of polymer using Guar gum and sesbania gum, sodium bicarbonate (40 mg), citric acid (10 mg), lactose is taken in a mortar and pestle for 15 min. The powder blend was then lubricated with talc (10 mg) and magnesium stearate (10 mg) for additional 3min prior to the compression. The powder was then compressed into tablets.

Preparation of standard curve of Valsartan: The samples of different concentration were analyzed at 271nm using UV-Spectrophotometer against 0.1N Hcl buffer as blank.

Compatibility Studies: The compatibility of drug and polymers under experimental condition is important prerequisite before formulation. Incompatibility between drugs and excipients can alter stability and bioavailability of drugs, thereby, affecting its safety and/or efficacy.

Formulation design: Floating tablets containing Valsartan were prepared by direct compression technique using varying concentrations of different grades of polymers with sodium bicarbonate and lactose. The compositions of all formulations are given in Table No. 1.

EVALUATION PARAMETERS:

Pre-compression parameters:

Bulk density and tapped density: Both bulk density (BD) and tapped density (TD) were determined. BD and TD was calculated using following formula:

Bulk density (ρb) = Bulk volume of the powder/Weight of the powder

Tapped density (ρt) = Tapped volume of the powder/ Weight of the powder

Compressibility index: Percentage compressibility of powder mix was determined by Carr's compressibility index. Grading of the powders for their flow properties according to Carr's Index is calculated by following formula.

Carr's index (%) = [(TD -BD) × 100]/TD

Angle of repose (Θ): The frictional forces in a loose powder or granules can be measured by the angle of repose[5].

$\tan \theta = h / r$

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

Where,

θ= the angle of repose

h=is height of pile

r= is radius of the base of pile

Post compression parameters:

Weight variation test: Twenty tablets from each formulation were selected randomly and weighed individually average weight was determined. Individual tablets weighed were then was compared with average weight[6].

Hardness test: The resistance of tablets to shipping or breakage under the conditions of storage, transportations and handling before usage depends on its hardness. The hardness of tablet was measured by Pfizer hardness tester. The hardness was measured in terms of Kg/cm2[7].

Friability: Roche friabilator was used for testing the friability. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

Content uniformity test: Twenty tablets were finely powdered; quantities of the powder equivalent to 5mg of Valsartan were accurately weighed and transferred to a 100 ml of volumetric flask. The flask was filled with 0.1N HCl (pH 1.2 buffer) solution and mixed thoroughly. The solution was made up to volume 100ml and filtered. Dilute 1 ml of the resulting solution to 10 ml with 0.1N HCl. The absorbance of the resulting solution was measured at 271 nm using a Shimadzu UV-visible spectrophotometer.

In vitro Dissolution Studies: The In vitro dissolution study was performed by using a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 50 rpm. Exactly 900 ml of 0.1 N HCl was used as the dissolution medium and the temperature was maintained at 37ºC ± 0.5ºC[8,9,10].

Release kinetics:

In order to understand the mechanism and kinetics of drug release, the results of the in vitro drug release study for optimized formulation were fitted with various kinetic equations namely zero order (% drug release vs. time), first order (log% unreleased drug vs. time), and Higuchi matrix (% drug release vs. square root of time). In order to define a model which will represent a better fit for the formulation, drug release data further analysed by Peppas equation

$$Mt/M\infty = kt^n$$

Where Mt is the amount of drug released at time t and M∞ is the amount released at time ∞, the Mt/M∞ is the fraction of drug released at time t, k is the kinetic

constant and n is the diffusion exponent, a measure of the primary mechanism of drug release. Regression coefficient (r2) values were calculated for the linear curves obtained by regression analysis of the above plots[11].

RESULTS AND DISCUSSION

Standard calibration curves of Valsartan: This shows the standard calibration curves for Valsartan with slope, regression co-efficient and intercept. The results are shown in Table 2.

Compatibility Studies: Compatibility studies of pure drug Valsartan with all excipients were carried out prior to the preparation of floating tablets. I.R spectra of pure drug Valsartan and combination of Valsartan and excipients were obtained.

Formulation development of floating tablets: The floating tablets of Valsartan were prepared using direct compression method.

Precompression Parameters:

Angle of repose: The values were found to be in the range of 25.3^0 to 34.4^0. All the formulation showed angle of repose below 35^0 which indicates a good flow property of the granules

Compressibility index: Carr's index lies between the range of 12.4 to 19.5%. All formulations show good compressibility. The results are shown in Table 3.

Hausner ratio: Hausner ratio was found to be in the range of 1.04 to 1.20as shown in Table 3.

Post compression Parameters:

Weight variation test: The values of tablets were ranged from 298±0.87 to 303±2.13 mg. All the tablets passed weight variation test as the % weight variation was within the Pharmacopeial limits of ±10 % of the weight and is shown in Table 4.

Hardness test: The hardness of all formulations was in the range of 5.5±0.02 to 6.4±0.08 kg/cm2.

Friability test: The friability values of prepared tablets are given in Table 6. The values ranged from 0.23 to 0.70%

Content uniformity test: The percent drug content of tablets was found to be in between 96.85to 99.21 of Valsartan and all results are shown in Table 4.

In vitro Dissolution Studies: The tablets containing guar gum F1, F2 and F3 showed the release of 90.5±0.25%, 97.1±0.61% and 87.1±0.61% at the end of 24 hours respectively.

The tablets containing sesbania gum (F4, F5, F6) showed release of 92.5±0.15%, 90.8±0.55% and 91.7±0.39% respectively at the end of 24 hrs.

***In vitro* Buoyancy Studies:** On immersion in 0.1N HCl solution pH (1.2) at 37±0.5 ^{0}c, the tablets floated, and remained buoyant without disintegration. Formulation F1 to F3 containing guar gum showed floating lag time of 30 to 55 sec, and total floating time of upto24 hrs. The formulation F4 to F6 containing sesbaniagum showed floating lag time of 50 to 80. This may be due to the amount of polymer. As the polymer concentration got increased the floating lag time got increased thereby total floating time and is shown in Table 6.

Release kinetics:

As shown in Figure, the corresponding plot (square root of time vs % CDR) for the Higuchi equation indicated a good linearity (R^2= 0.969). The diffusion exponent n was 0.698, which appears to indicate a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and may indicate that the drug release was controlled by more than one process. The optimized formulation was found to be guar gum (F2). Formulations subjected to curve fitting analysis showed that the formulations best fit for zero-order release with diffusion mechanism. The formulation F2 follows zero order and Higuchi order release kinetics governed by Non-Fickian diffusion mechanism and is shown in Table7.

Table 1: Composition of Gastroretentive Floating Tablets of Valsartan (F1 to F6)

Ingredients In mg	F_1	F_2	F_3	F_4	F_5	F_6
valsartan	80	80	80	80	80	80
Guar gum	40	80	120	–	–	–
Sesbania gum	–	–	–	40	80	120
Sodium bicarbonate	40	40	40	40	40	40
Citric acid	10	10	10	10	10	10
MCC	110	70	30	110	70	30
Mg stearate	10	10	10	10	10	10
Talc	10	10	10	10	10	10

Table 2: Standard Calibration curve of Valsartan at 271 nm in 0.1N Hcl.

Concentration (µg/mL)	Absorbance (nm)
0	**0**
2	**0.053**
4	**0.078**
6	**0.139**
8	**0.199**
10	**0.253**
12	**0.285**

Table 3: Pre-compression parameters from formulation F1 to F6

Formulation Code	Carr's Index (%)	Bulk density(gm/cc)	Tapped density(gm/cc)	Angle of repose (^{0})	Hausner's Ratio
F1	14.84±0.01	0.234±0.05	0.241±0.03	26.49±1.03	1.15±0.14
F2	15.68±0.01	0.275±0.02	0.355±0.04	24.21±1.12	1.04±0.03
F3	16.56±0.02	0.315± 0.01	0.374± 0.20	30.5 ±1.32	1.18 ±0.07
F4	12.11± 0.11	0.341± 0.02	0.388± 0.01	29.97± 1.11	1.10± 0.05
F5	17.82± 0.16	0.324± 0.03	0.378± 0.06	34.25± 1.29	1.21± 0.04
F6	19.45± 0.09	0.320± 0.01	0.397± 0.30	31.27 ±1.14	1.24± 0.14

Table 4: Physical Characterization of Gastroretentive Floating Tablets of Valsartan (F1 to F6)

Formulation Code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	301.56±2.12	5.46±0.08	3.13±0.17	0.23±0.04	97.25±0.39
F2	299.18±1.10	5.6±0.23	3.34±0.15	0.25±0.02	99.45±0.50
F3	302.52±1.76	6.3± 0.05	3.60± 0.14	0.43 ±0.07	97.12 ±0.13
F4	298.16±0.87	6.16± 0.13	3.76± 0.17	0.63± 0.02	98.23± 0.86
F5	303.25±1.40	5.75± 0.05	3.07± 0.15	0.70± 0.06	98.44± 0.25
F6	302.18±1.13	6.4± 0.09	3.81± 0.05	0.58 ±0.04	99.43± 0.7

Table 5*: In vitro* Dissolution Data for Formulation F1 to F6

Time(hrs)	Cumulative % drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	11.5±0.31	15.6±0.62	13.1±0.51	19.1±0.15	18.5±0.21	12.9±0.31
2	24.7±0.25	26.8±0.24	22.4±0.15	23.5±0.35	26.1±0.45	22.6±0.15
3	37.8±0.5	35.7±0.45	31.5±0.21	35.7±0.25	32.7±0.35	35.7±0.25
4	43.2±0.41	48.6±0.25	45.6±0.34	41.8±0.15	46.8±0.15	44.6±0.55
5	56.1±0.12	57.1±0.35	56.1±0.51	55.9±0.24	54.1±0.34	57.9±0.69
6	62.2±0.55	63.5±0.41	62.5±0.16	69.1±0.56	61.7±0.45	63.6±0.56
8	71.5±0.12	75.8±0.50	70.1±0.25	75.6±0.45	75.2±0.15	74.7±0.42
12	82.7±0.55	86.7±0.25	80.5±0.55	86.1±0.38	83.6±0.34	82.9±0.35
24	90.5±0.25	97.1±0.61	91.5±0.62	92.5±0.15	90.8±0.55	91.7±0.39

Table 6: Floating properties of prepared tablets.

Formulation code	Floating lag Time(sec)	Floating time(hr)
F1	55	Upto 24
F2	30	Upto 24
F3	43	Upto 24
F4	50	Upto 24
F5	65	Upto 24
F6	80	Upto 24

Table 7: Release kinetics of optimized formulation

Formulation	% Drug release	Time (hr)	R^2 Value				n value
			Zero order	First order	Higuchi	Korsemeyer-peppas	
F2	97.1	24hr	0.967	0.942	0.969	0.680	0.698

CONCLUSION

By incorporating natural gums in given formulations, it is possible to effectively control the pH within the matrix surrounding the Valsartan molecules and thereby enhance the drug's solubility in the body. The tablets of formulation(F2) showed satisfactory results with short buoyancy lag time, long total floating time and controlled drug released up to24 hrs. Thus, the formulated floating tablets of Valsartan using natural polymers offer a superior alternative to improve the patient compliance over other dosage forms.

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