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Formulation and Evaluation of Valsartan Floating Tablets

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Abstract

The present research work was an attempt to formulate and evaluate floating tablet containing valsartan in the form of tablets using polymers like HPMC K100M, Ethyl cellulose, $NaHCO_3$ as gas generating agent. Valsartan, an antihypertensive drug, with an oral bioavailability 23%, short half-life (6 hr) and largely present in unionized form in acidic pH, have been designed to increase gastric residence time and therapeutic efficacy. This can be achieved by fabricating floating tablets which retain in stomach for prolonged time to release the drug. The tablets were formulated by direct compression method. The effect of sodium bicarbonate and citric acid on drug release profile and floating properties were investigated. The tablets were characterized for the pre and post compression parameters such as friability, hardness, thickness, drug content, weight variation, *in-vitro* buoyancy studies and *in-vitro* drug release studies and the results were within the limits. The *in-vitro* drug release studies were carried out in a USP type-II apparatus in 0.1N HCl. Optimized formulation (F1) revealed that tablet was constantly floating in the stomach region of the rabbit, thereby indicating improved gastric retention time for more than 8 h. Consequently, all the findings and outcomes have showed that developed valsartan matrix tablets could be effectively used for floating drug delivery system.

Keywords

Valsartan, polymers, sodium bi carbonate and citric acid, FTIR studies, direct compression technique.

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INTRODUCTION:

Valsartan is an angiotensin receptor blocker widely prescribed for hypertension. It's absorbed from the upper part of gastrointestinal tract [1, 2]. The oral route is considered as the most convenient and extensive route of drug delivery among all the routes

that have been explored for the systemic delivery of drugs [3, 4]. In the development of oral sustained/ controlled drug delivery system other main challenge is to modify the GI transit time. Prolong gastric retention increases the duration of drug release, improves bioavailability and also beneficial for local action [5]. Gastro retentive drug delivery systems are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the GIT [6]. A modified release drug delivery system with prolonged residence time in the stomach is of particular interest for drugs- acting locally in the stomach; having an absorption window in the stomach or in the upper part of small intestine; those unstable in the intestinal or colonic environments; or those having low solubility at high pH values [7]. To formulate a successful gastro retentive drug delivery system, several approaches are currently used such as FDDS, low density systems, raft systems incorporating alginate gel, high density systems, bio adhesive or mucoadhesive systems, magnetic system and super porous hydro gel. All these, the floating dosage forms have been most commonly used [8]. Floating drug delivery systems have a bulk density less than gastric fluid and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [9]. While the system is floating on the gastric contents, the drug is released slowly at the desired rate. After drug release, the remaining system is emptied from the stomach. This result is an increased gastric retention time and control of the fluctuation in plasma drug concentration [10].

The oral bioavailability of Valsartan was reported to be 23% and largely present in unionized form in acidic pH. The recommended adult oral dosage of Valsartan is 80 mg for the effective treatment of hypertension [11, 12]. The short biological half-life of drug (6 hrs) also favors development of sustained release formulations [13, 14, 15]. 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 desired. To reduce this problem, gastro retentive drug delivery systems which provide effective plasma drug concentration for longer periods thereby reducing the dosing frequency are being formulated [16, 17]. The present research work was an attempt to formulate and evaluate floating tablet containing valsartan in the form of tablets using polymers like HPMC K100M, Ethyl cellulose, $NaHCO_3$ as gas generating agent. Optimized formulation (F1) revealed that tablet was constantly floating in the stomach region of the rabbit, thereby indicating improved gastric retention time for more than 8 h. Consequently, all the findings and outcomes have showed that developed valsartan matrix tablets could be effectively used for floating drug delivery system.

MATERIALS AND METHODS:

Materials:

Valsartan was procured from Hetro labs, Hyderabad, India. HPMC, Ethyl cellulose, Lactose, Microcrystalline cellulose, Sodium bi carbonate, Magnesium stearate and Talc were procured from A. R. Chemicals, Hyderabad, India.

Methods:

Preparation of Formulation:

Different tablet formulations were prepared by direct compression method (table 1). The formulations were composed of synthetic polymers. All powders were passed through 100-mesh sieve. The other excipients and the polymers were mixed uniformly. Drug was added to the polymers and other excipients for 20 min. The resulting mixtures were mixed with magnesium stearate and talc in polyethylene bag for 10 min. The lubricated granules were compressed using 8 mm punch (single punch tablet machine) into tablets. Compression pressure was adjusted during tableting of each formula to get the tablet hardness in the range of 2.5 to 5 $Kg/cm^{3.}$ The total weight of tablet was kept at 200 mg.

EVALUATION PARAMETERS OF DRUG AND EXCIPIENTS:

Fourier transforms infra-red spectroscopy (FTIR):

The primary objective of this investigation was to identify the drug using FTIR spectrophotometer [18, 19]. For FTIR the sample was send into the laboratory and the results given below in figs 1 & 2.

Preliminary study:

On the basis of buoyancy study the preliminary study of formulation was done. After that few formulations were selected and given in (table 1) for further evaluation.

Pre Compression Parameters:

Prior to the compression, the formulation powder blends were evaluated for their bulk and tapped density and from these values compressibility index and Hauser ratio were calculated. While the flow properties of the powder blend were accessed from the angle of repose [20].

Post Compression Parameters:

Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The Monsanto hardness tester was used to determine the tablet

hardness. It is expressed in kg/cm2. Five tablets were randomly picked and hardness of tablets was determined [21, 22].

Friability:

Tablet strength was tested by using Roche friabilator. 20 tablets were weighed and placed in the friabilator and operated for 100 revolutions, taken out and were dedusted. The percentage weight loss was calculated by reweighing the tablets. The % friability was calculated by:

F= [(W initial- W final) ×100]/ W initial

Thickness:

Control of physical dimension of the tablet such as thickness is essential for tablet uniformity and consumer acceptance. The diameter and thickness of the tablet was measured using Vernier calipers and expressed in mm.

Weight variation:

20 tablets were selected randomly from each batch were weighed individually and together in a single electronic balance. The average weight was noted.

PD= [(WH-WL) × 100]/ WH

Where, PD= percentage deviation

WH= highest weight (mg)

WL= lowest weight (mg)

Uniformity of drug content:

20 tablets were weighed and powdered accurately equivalent to 100 mg Valsartan. Then powder equivalent was taken and dissolved in 0.1N HCl solution and the volume was made up to 100 ml by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask and make up the volume with 0.1N HCl and the absorbance was measured by using UV spectrophotometer.

***In-vitro* Buoyancy studies:**

The *in-vitro* floating behavior of the tablets was determined by floating lag time. These tests are usually performed in simulated gastr ic fluid or 0.1NHCl maintained at 37 ^{0}C, by using USP dissolution apparatus containing 900 ml of 0.1N HCl as the dissolution medium. The time between introduction of dosage form and its buoyancy in 0.1N HCl and the time during which the dosage form remain buoyant were measured. The total duration of time by which the dosage form remains buoyant is called total floating time (TFT).

***In-vitro* drug release study:**

Drug release from the floating tablets was assessed by dissolution test USP type II dissolution apparatus equipped with paddles at 37oC ±0.5oC at 50 rpm. The test was performed using 900 ml of 0.1N HCl as dissolution media. A 5 ml sample was withdrawn from the dissolution apparatus at specified time points and the samples were replaced with fresh dissolution media. The samples were filtered and diluted if essential. Absorbance's of these solutions were determined using UV-visible spectrophotometer.

Stability studies:

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared Valsartan floating tablets were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2 ^{o}C and refrigerator 2-8 ^{o}C for a period of 30 days.

RESULTS AND DISSCUSSION:

FT-IR Spectrum of Valsartan:

FT-IR Spectra of Valsartan and F1 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Valsartan and polymer. It also confirmed that the stability of drug during microencapsulation process.

Pre compression characterization:

The properties like bulk density, tapped density, compressibility index, angle of repose and Hausner's ratio were calculated and given in (table 4).

Based on the above pre-formulation results it was observed that the flow was good.

Post compression characterization:

All formulations were tested for physical parameters like hardness, thickness, weight variation and friability and the results of the tests were tabulated in table no. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Floating lag time:

The floating tablets of Valsartan were prepared by using direct compression technique. Four different formulations were prepared using different ratios of polymers. The prepared formulations were evaluated for floating lag time and buoyancy time. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N HCl). It was observed that the gas generated is trapped and protected within the matrix, formed by polymers, thus density of the tablet decreased and it becomes buoyant. The floating lag time of the optimized formulation F1 was 32 sec.

***In-vitro* drug release study:**

The *in-vitro* drug release profiles of F1-F4 are shown in fig 4.

Stability Study:

There was no significant change in physical and chemical properties of the tablets of formulation F-1after 30 days. Parameters quantified at various time intervals were shown in (table 7).

Table 1: Composition of Valsartan floating tablets

Ingredient	Formulations			
	F1	F2	F3	F4
Valsartan (mg)	80	80	80	80
HPMC K15M (mg)	40	60	-	-
Ethyl cellulose(mg)	-	-	40	60
MCC(mg)	10	10	10	10
Sodium bi carbonate (mg)	20	20	20	20
Lactose(mg)	45	25	45	25
Magnesium stearate (mg)	3	3	3	3
Talc (mg)	2	2	2	2
Total wt (mg)	200	200	200	200

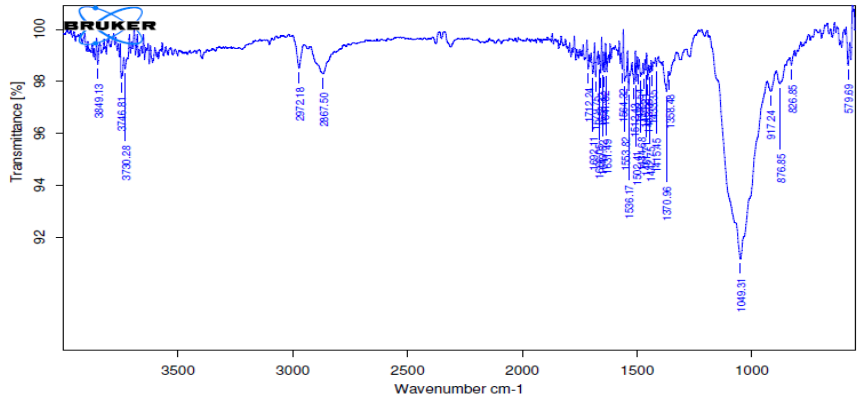

Fig 1: FTIR Studies of Valsartan

Table 2: Characteristic Peaks for Valsartan

S. No.	Characteristic Peaks	Frequency range (cm-1)	Frequency(cm-1)
1	OH Stretching	3500-3000	2972.18
2	OH Bending	1000-1500	1049.31
3	C-H Stretching	3000-2500	2867.50
4	C=O Stretching	2000-1500	1692.11

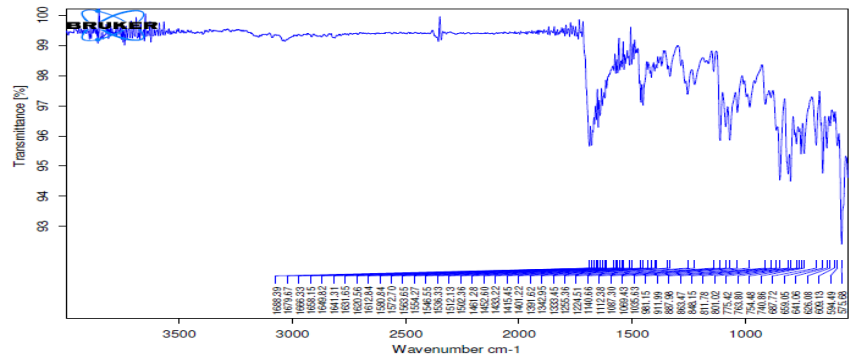

Fig 2: FTIR Spectra of optimized formulation

Table 3: Characteristic Peaks and frequency of optimized formulation

S. No.	Characteristic Peaks	Frequency range (cm^{-1})	Frequency (cm^{-1})
1	OH stretching	3500-3000	3500.90
2	OH Bending	1100-1070	1084.03
3	C-H stretching	3200-3100	3095.95
4	C=O stretching	2000-1500	1745.61

Table 4: Evaluation parameters of Valsartan

S. No	Bulk density	Tapped density	Compressibility index	Hausner's ratio	Angle of repose(0)
F1	0.512 ±0.03	0.623 ±0.34	17.81±0.71	1.21 ±0.04	29^0 ±0.32
F2	0.509 ±0.08	0.619 ±0.37	17.77±0.74	1.21 ±0.05	28^0 ±0.32
F3	0.518 ±0.02	0.635 ±0.33	18.42±0.78	1.22 ±0.03	31^0 ±0.56
F4	0.521 ±0.08	0.640 ±0.38	18.59±0.75	1.22±0.05	30^0 ±0.14

Table 5: Evaluation parameters of Valsartan floating tablets

Parameter	F1	F2	F3	F4
Weight variation(mg)	200±0.87	199±0.82	201±1.12	200±0.87
Thickness (mm)	2.9±0.02	2.8±0.02	2.5±0.01	3.0±0.03
Hardness (kg/cm^2)	3.9±0.75	3.7±0.72	4.0±0.75	3.8±0.73
Friability (%)	0.45	0.42	0.40	0.39
Content uniformity (%)	95.38±0.5	89.65±0.34	90.53±0.38	92.40±0.42
Floating lag time (Sec)	32	45	38	42

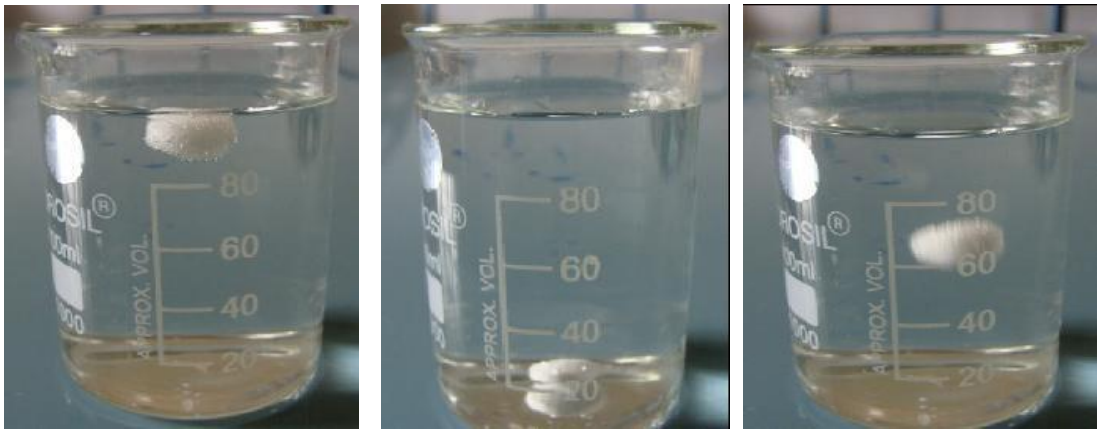

Fig 3: Buoyancy of Valsartan floating tablets

Table 6: *In vitro* drug release of Valsartan floating tablets

	%Drug Release			
Time	**F1**	**F2**	**F3**	**F4**
0	0	0	0	0
1	13.60±0.31	11.34±0.62	9.70±0.51	10.65±0.15
2	28.58±0.25	24.12±0.24	19.65±0.15	20.68±0.35
3	35.20±0.5	30.45±0.45	28.25±0.21	33.88±0.25
4	42.25±0.41	39.28±0.25	44.58±0.34	41.36±0.15
5	55.23±0.12	50.12±0.35	58.74±0.51	53.23±0.24
6	69.38±0.55	62.15±0.41	68.45±0.16	63.56±0.56
7	82.18±0.55	78.98±0.25	79.50±0.55	77.20±0.38
8	91.62±0.39	85.70±0.25	86.69±0.38	90.91±0.25

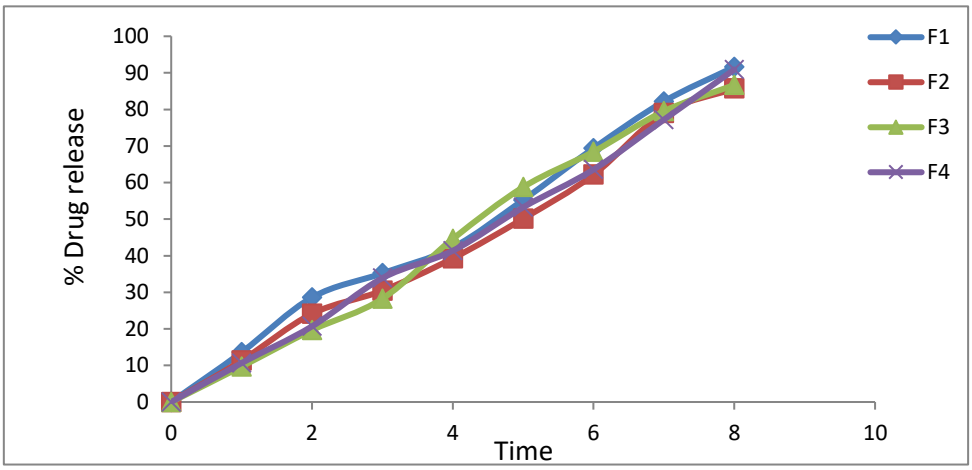

Fig 4: *In vitro* drug release for all the formulations

Table 7: Stability study for optimized formulation

Formulation Code	Parameters	Initial	1st Month	Limits as per Specifications
F-1	25^0C/60%RH % Release	91.62	91.26	Not less than85 %
F-1	30^0C/75% RH% Release	91.62	91.18	Not less than85 %
F-1	40^0C/75% RH %Release	91.62	91.10	Not less than85 %

CONCLUSION:

The objective of the present study was to develop floating bio adhesive tablets of Valsartan. In this present study an attempt was made to increase the GI residence time of Valsartan, as the drug is having less gastric residence time, by formulating into Floating tablets. The gastro retentive floating tablets were obtained by direct compression technique and evaluated for the pre-compression parameters, post-compression parameters like hardness, thickness, drug content, and weight variation, friability, floating lag time, and stability studies; and the results were found to be within limits. Based on the performances finally it was concluded that: Among all the formulations (F1-F4), it was observed that formulation-1 has shown better buoyancy and dissolution profile, hence Formulation-1 was found to be the best formulation among others.

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