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Formulation and evaluation of floating tablet of Valsartan

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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, carbopol 934, $NaHCO_3$ and citric acid 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. Among all the formulation (F1 to F8) prepared, batch F7 was the best formulation which showed buoyancy lag time 165 sec. and the tablet remained buoyant for >24 hr. The in-vitro drug release data is fitted in to different kinetic models and the best-fit was achieved with the zero order models. The optimized formulation F7 followed zero order release kinetics by non-fickian diffusion.

Key words: Valsartan, HPMC K100M, Carbopol 934, Direct compression method

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INTRODUCTION

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 [1, 2]. 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 [3].

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 [4]. 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 [5]. 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, bioadhesive or mucoadhesive systems, magnetic system and super porous hydro gel. All these, the floating dosage forms have been most commonly used [6]. 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 [7]. 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 [8].

Valsartan is an angiotensin receptor blocker widely prescribed for hypertension. It is absorbed from the upper part of gastrointestinal tract [9, 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]. It also has an advantage of minimizing the fluctuations in plasma drug concentration by delivering the drug in a controlled and reproducible manner [18, 19]. Therefore, in the current study, floating tablets of valsartan were prepared using HPMC K100M and carbopol 934 as the polymers, $NaHCO_3$ as gas generating agent and citric acid as floating enhancer. The aim of the study was to evaluate the effect of polymers on drug release and the effect of sodium bicarbonate on buoyancy.

EXPERIMENTAL SECTION

Materials:

Valsartan was used as the active ingredient and purchased from Calyx Pharma, Mumbai (India). HPMC K100M and Carbopol 934 were used as the polymers. Sodium bicarbonate was used a gas generating agent. The other ingredients used were citric acid, magnesium stearate and lactose. All the material used in experimental works except drug was obtained from CDH distributors. All reagents used were of analytical grade.

Methods:

Preparation of floating tablets of valsartan

The floating tablets containing valsartan (80 mg) were prepared by direct compression process using formula shown in table no. 1. HPMC K100M and carbopol 934 were used as swellable polymers. Sodium bicarbonate was used as gas generating agent and citric acid as floating enhancer. Lactose was added as diluent in different proportions to the floating tablets to achieve uniform weight. The tablets were prepared by mixing required quantities of drug, HPMC K100M, carbopol 934, sodium bicarbonate, citric acid and lactose. All excipients were passed through sieve no. 45, mixed using a mortar and pestle for 10 min. and lubricated with 0.5% of magnesium stearate and the blend was mixed again prior to compression. The drug mixtures were directly compressed by using rotary compression machine with a constant compression force. The excipients were taken according to drug weight.

Table No. 1: Composition of floating tablet of valsartan

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Valsartan	80mg	80mg	80mg	80mg	80mg	80mg	80mg	80mg
HPMC K100M	10%	20%	30%	40%	-	-	-	-
Carbopol 934	-	-	-	-	10%	20%	30%	40%
$NaHCO_3$	5%	5%	5%	5%	5%	5%	5%	5%
Citric acid	15%	15%	15%	15%	15%	15%	15%	15%
Mg. stearate	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Lactose	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

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 [20, 21]. For FTIR the sample was send into the laboratory and the results given below in fig. 1.

Differential scanning calorimetry (DSC):

DSC is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a reference and sample are measured as a function of temperature. The sample was send into the laboratory for the DSC study [22, 23].

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 no. 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 [24].

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/cm^2. Five tablets were randomly picked and hardness of tablets was determined [25, 26].

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:

$F= [(W_{initial}- W_{final}) \times 100]/ W_{initial}$

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.

$PD= [(W_H-W_L) \times 100]/ W_H$
Where, PD= percentage deviation
W_H= highest weight (mg)
W_L= lowest weight (mg)

Uniformity of drug content

10 tablets were weighed and powdered. Then powder equivalent to 10 mg of drug was taken and dissolved in 0.1N HCL, made up the volume up to 10 ml. after that 10 ppm solution was prepared and absorbance was measured at 248.8 nm by using SHIMADZU UV-1800 spectrophotometer.

***In-vitro* Buoyancy studies**

The *in-vitro* floating behaviour of the tablets was determined by floating lag time. The tablets were placed in 100 ml beaker containing 0.1N HCL. The floating lag time (time taken by the tablet to reach the surface) was determined [27]. 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 $37^oC \pm 0.5^oC$ 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. Absorbances of these solutions were determined at 248.8 nm using UV-visible spectrophotometer.

Drug release kinetics

To study the drug release kinetics, the data from *in-vitro* drug release studies were subjected to various kinetic models: zero order (eq. 1) as cumulative amount of drug release Vs time, first order (eq. 2) as log % drug remaining Vs time, higuchi model (eq. 3) as % CDR Vs square root of time and Korsmeyer – Peppas model (eq. 4) as log T Vs log % CDR [28, 29].

$C= K_ot$…… (1)

Where $K_{o=}$ zero order constant (concentration/time)
t= time (hrs)

Log C= Log Co-Kt/2.3….. (2)

Where Co= initial concentration of drug (first order constant)

t= time

$Q= kt^{1/2}$….. (3)
Where K= constant
t= time (hr)

$Mt/M\infty = Kt^n$
Where $Mt/M\infty$= fractional solute release
t= release time, K= kinetic constant

RESULTS AND DISSCUSSION

FTIR spectroscopy:

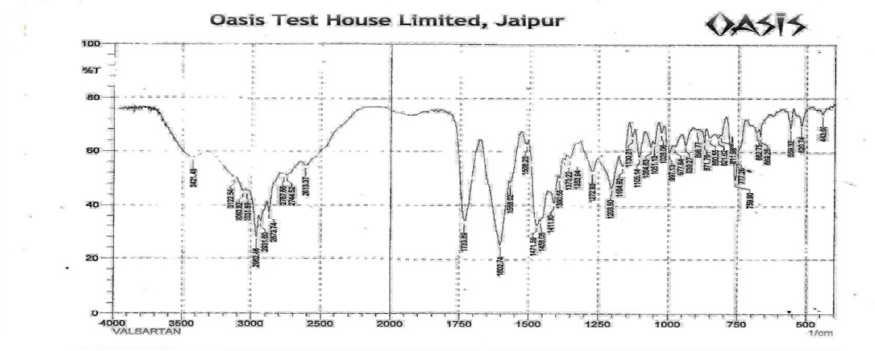

Fig. 1: IR spectra of valsartan

Table No. 2: Interpretation of drug (valsartan)

Functional group	Observed peak	Range
C- H (Stretching, Aliphatic)	2962.46	2960-2850
C=O (Stretching, Carboxyl)	1733.89	1775-1700
C=O (Amide)	1733.89	1760-1730
C=C (Aromatic)	1471.59	1450
C-N (Stretching)	1272.93	1375-1275

Interpretation of FTIR spectra is given in table no. 2. According to this interpretation the observed peak of drug was found to be in the range.

Differential Scanning Calorimetry studies:

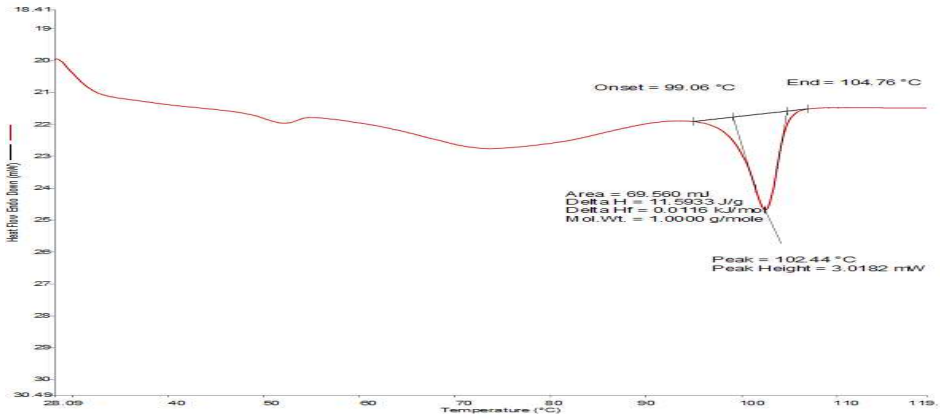

Fig. 2: DSC study of valsartan

The DSC analysis of valsartan is given in fig. 2. On the basis of DSC analysis the melting point of valsartan was found to be 104.76^0C.

Pre compression characterization: The bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose of floating tablet are given in table no. 3.

Table No. 3: Pre compression characterization

Batch	Bulk density (gm/ml)±SD	Tapped density (gm/ml)±SD	Carr's Index±SD	Hausner's ratio±SD	Angle of repose±SD
F1	0.65±0.015	0.74±0.020	12.16±1.45	1.13±0.035	24.22±1.67
F2	0.64±0.015	0.74±0.037	13.51±1.08	1.15±0.043	26.56±1.67
F3	0.64±0.020	0.78±0.055	17.94±1.36	1.21±0.030	30.54±1.86
F4	0.60±0.026	0.73±0.037	17.80±1.98	1.21±0.040	25.17±0.98
F5	0.62±0.025	0.73±0.026	15.06±2.15	1.17±0.015	25.64±1.43
F6	0.67±0.026	0.81±0.036	17.28±2.08	1.20±0.035	28.81±1.98
F7	0.67±0.026	0.80±0.035	16.25±1.01	1.19±0.026	27.02±1.68
F8	0.64±0.020	0.79±0.032	18.98±1.39	1.23±0.025	30.54±1.80

Mixture of all formulation has good to excellent flow property range. The angle of repose of all formulations shows excellent to passable flow.

Post compression characterization: All batches of formulation were evaluated for various physical parameters and results tabulated in table no. 4.

Table No. 4: Post compression characterization

Batch	Thickness±SD (mm)	Avg. weight±SD (mg)	Friability±SD (%)	Hardness (kg/cm^2)
F1	4.25±0.010	247.3±1.04	0.60±0.16	4.4
F2	4.27±0.011	245.1±1.28	0.81±0.077	4.4
F3	4.25±0.011	245.4±1.45	0.81±0.060	4.2
F4	4.26±0.010	246.1±0.70	0.89±0.161	4.4
F5	4.25±0.005	244.6±1.49	0.77±0.081	4
F6	4.27±0.010	247.6±1.75	0.76±0.045	5
F7	4.25±0.010	246.6±1.57	0.77±0.080	5
F8	4.27±0.010	245.4±1.45	0.89±0.043	5

The weight variation of each formulation was found in range. According to thickness of all formulation it was found in uniform size. The hardness of tablet was within range of standard and friability found in less than 1%. These all parameters were satisfactory as specified in the pharmacopoeia.

***In-vitro* Buoyancy studies:** Buoyancy studies were performed using 0.1N HCL solution at 37^oC; the tablets floated and remained buoyant are shown in table no. 5.

***In-vitro* drug release study:** The % CDR and drug content are given in table no. 5 and the *in-vitro* drug release profiles of F1-F8 are shown in fig. 3 and 4.

Table No. 5: Drug release, drug content and *in-vitro* buoyancy data

Formulation	%Cumulative drug release (12hr)±SD	Drug content±SD	FLT (Secs.)	Floating duration (Hrs.)
F1	71.43±1.78	96.0±1.66	115	15
F2	56.77±1.35	97.3±1.50	150	>24
F3	48.77±1.34	94.0±1.82	185	>24
F4	33.97±1.60	94.3±1.50	255	18
F5	74.86±1.10	95.6±0.85	145	16
F6	60.11±1.71	96.6±1.85	200	>24
F7	52.13±1.73	97.6±1.82	165	>24
F8	29.47±1.72	95.3±1.56	210	20

The concentration of HPMC K100M, carbopol 934, NaHCO3 and citric acid optimized on the basis of floating lag time and floating time. The optimized concentration of HPMC K100M, carbopol 934, NaHCO3 and citric acid was 20-30%, 20-30%, 5% and 15% respectively. To find *in-vitro* drug release, F1 to F8 formulations were prepared. The main components of F1 formulation was HPMC K100M (10%), NaHco3 (5%), citric acid (15%) and its drug release was 71.43%. This drug release is high because of low concentration of HPMC K100M. In F2 formulation, the concentration of HPMC K100M was increased up to 20%, thus the drug release was reduced to 56.77%. Further the concentration of HPMC K100M was increased to 30% in F3 and 40% in F4, and then the drug release was reduced to 48.77% in F3 and 33.97% in F4.

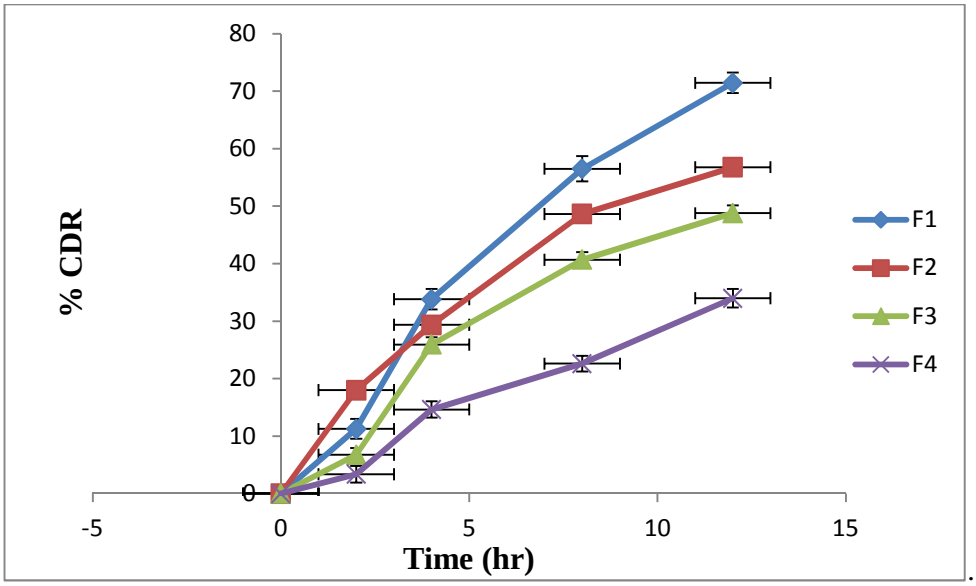

Fig. 3: Drug release curve (F1-F4)

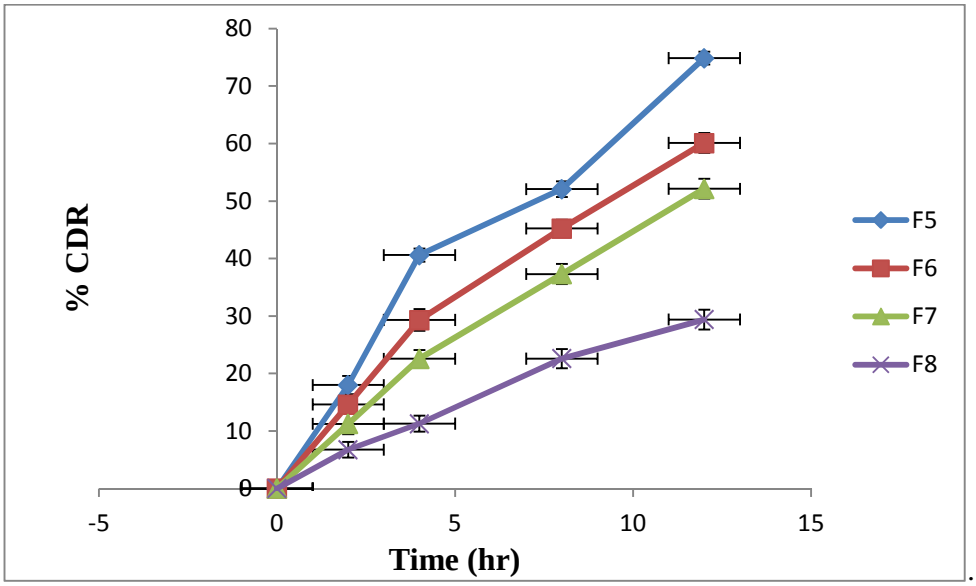

Fig. 4: Drug release curve (F5-F8)

In formulation F5 to F8, HPMC K100M was replaced by carbopol 934 with the concentration 10% in F5, 20% in F6, 30% in F7 and 40% in F8. Then the drug release was 74.86% in F5, 60.11% in F6, 52.13% in F7 and 29.47% in F8. This decrease in drug release from F5 to F8 is due to increase in the concentration of carbopol 934.

The drug content in each formulation was found in uniform range. This range is uniform and satisfies the specifications of pharmacopoeia. In whole process the formulation F7 was considered as best on the basis of drug release, drug content and floating lag time. The drug release, drug content and floating lag time of F7 was 52.13%, 97.6% and 165 secs respectively.

Drug release kinetics: Data of drug release kinetics is shown in table no.6.

The data were plotted according to zero-order, first-order, higuchi model and Korsmeyer-peppas pattern for kinetics of drug release. The regression equation of optimized formulation F7 was found out according to zero-order equation 0.989, first-order equation 0.254, and higuchi model 0.952 respectively. These values clearly indicate that formulation show to be best expressed by zero-order kinetics. It was follow the zero-order pattern.

Table No. 6: Data of release kinetics

Form.	Zero order		First order		Higuchi		Korsmeyer peppas	
	R^2	K_0(-) (1/S)	R^2	K_1(-) M/L.S	R^2	K_H	R^2	n
F1	0.969	6.113	0.163	0.149	0.937	20.64	0.888	0.66
F2	0.943	4.626	0.240	0.186	0.984	16.40	0.799	0.71
F3	0.940	4.233	0.256	0.198	0.927	14.09	0.912	0.79
F4	0.979	2.865	0.295	0.221	0.902	21.63	0.961	0.92
F5	0.952	5.909	0.159	0.147	0.962	9.81	0.813	0.63
F6	0.973	4.886	0.224	0.181	0.970	17.37	0.836	0.70
F7	0.989	4.267	0.254	0.195	0.952	15.06	0.869	0.74
F8	0.990	2.484	0.311	0.225	0.943	8.51	0.915	0.92

The dissolution data was also plotted to the well known exponential equation (Korsmeyer-peppas eq.), which is often used to describe the drug release behaviour from polymeric system. According to this model, a value of n<0.45 indicates fickian release, n>0.45 but n<0.89 for non-fickian (anomalous) release and n>0.89 indicates super case II type of release. Case II generally referred to the erosion of the polymeric chain and anomalous transport (non-fickian) refers to a combination of both diffusion and erosion control drug release. On the basis of n-value the optimized formulation (F7) exhibit non-fickian type drug release.

CONCLUSION

Valsartan floating tablets were successfully formulated using the mixture of carbopol 934 (30%), $NaHCO_3$, (5%) and citric acid (15%). The floating drug delivery was a promising approach to achieve a prolongation of gastric residence time of drug. The gas generating agent $NaHCO_3$ used to improve the floating capacity of tablet and citric acid used as a floating enhancer. Finally the optimized formulation shows desired drug release profile over 12 hrs.

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