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FORMULATION AND EVALUATION OF SUSTAINED RELEASE FLOATING TABLETS OF VALSARTAN

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ABSTRACT

Objective: The objective of the study was to develop and evaluate the gastro retentive floating drug delivery system (GFDDS) of Valsartan to achieve prolonged release in the treatment of hypertension and myocardial infections. **Methods:** The sustained release floating formulations were prepared by direct compression method using HPMCE15, HPMCK15 and Carbopol polymers in various ratios and gas generating agents (Sodium bicarbonate and Citric acid) MCC. FT-IR and DSC studies indicates absence of any interaction between Valsartan, polymers and excipients. **Results**: The tablets were also evaluated for its hardness, friability and other *in vitro* evaluation tests. All parameter complied with IP limits. The *invitro* drug release profiles obtained for F_8 prepared by combination of HPMCE15, HPMCK15, Carbopol showed lesser floating time(FLT) 3minutes and prolong floating duration and was a controlled release characteristic(98.87%) for 20 hours. The drug release data were analyzed as per zero order (0.951) and first order (0.997) models. Drug release was diffusion controlled and followed first order kinetics. Non-Fickian diffusion was the drug release mechanism from all the tablets formulated. **Conclusion**: It can be concluded that the gastro retentive floating tablets of valsartan were prepared and evaluated for once daily administration.

KEYWORDS: Floating drug delivery system, Valsartan, HPMC, Carbopol, Floating time, Floating lag time.

INTRODUCTION

Oral drug delivery is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost–effective manufacturing process.[1] The oral conventional drug delivery system are designed for immediate release of drug for rapid absorption even though this system has limitations[2,3] as requirement of frequent administration of drugs which has short half-life may leads to poor patient compliance due to chance of missing dose, difficulty to attain steady state concentration, chance of overmedication and under medication as the as the fluctuation of steady state concentration, precipitation of adverse drug reaction of drugs which have narrow therapeutic index whenever overmedication occurs. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[4]

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS). GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.[7,8]

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include: floating systems, bio adhesive systems, swellable and expandable systems, high density systems.[9,10]

Floating dosage systems[11] form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include: improved drug absorption because of increased GRT and more time spent by the dosage form at its absorption site, controlled delivery of drugs, delivery of drugs for local action in the stomach, minimizing the mucosal irritation duo to drugs, by drug releasing slowly at controlled rate, treatment of gastrointestinal disorders such as gastro-esophageal reflux, simple and conventional equipment for manufacture, ease of administration and better patient compliance, site specific drug delivery.[12,13]

Valsartan is an angiotensin-receptor blocker that is used for variety of cardiac conditions including hypertension, diabetic nephropathy, heart failure, myocardial infraction and coronary artery disease. It acts by angiotensin II receptor. Valsartan has specific absorption window at upper gastro intestinal tract so that drug in dissolved form must be available before this region therefore there is a need for developing delivery system that release the drug at the right time, at the specific site. Therefore a gastro retentive extended release drug delivery system was developed in order to retain the drug product in stomach for extended period of time. Development of such dosage form involves a combination of high viscosity polymer and a rate controlling polymers to design floating drug delivery system.[14,15,16]

METHODOLOGY

Materials: Valsartan was obtained as a gift sample from Dr. Reddy's laboratories, Hyderabad, HPMC (K15 & E15), Carbopol, MCC citric acid sodiumbicarbonate talc Hydrochloric acid and Aerosil were procured from were procured from microlabs Bangalore.

Used were of analytical reagent grade.

Methods

I) Preformulation studies

The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms.

Characterization of Drug: The drug is characterized for Physical appearance, Melting point, water content by KF, hygroscopicity, density and the results were shown in table.1.

Drug excipients interaction studies: By FTIR and DSC Studies the Spectras and thermograms were shown in fig 1-5. and fig 6 respectively.

Formulation of floating tablets

Tablets were fabricated by direct compression technique. Valsartan and all other ingredients were individually passed through sieve #60 and mixed thoroughly by triturating up to 15minute. The powder mixture was lubricated with talc and tablet were prepared by direct compression.

Pre compression characteristics

Pre compression characteristics studies including Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose were performed for the crude drug, Valsartan resulted as table no 2.

Carr's index

Carr's index was calculated by using following formula and result was shown in table no.2

Carr's Index= (Tapped density-Bulk density) × 100/ Tapped density.

Hausner's Ratio

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 –1.5. It was calculated by using following formula and result was shown in table no 2.

Hausner's Ratio=Tapped density/Bulk density

Angle of repose (θ)

Angle that can be obtained between the free surface of a powder heap and horizontal plane. The angle of repose was measured by funnel method and result was shown in table no.2.

The angle of repose is given as,

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

Where

θ= angle of repose

h= height of the heap

r=radius of the base of the heap

Post compression characteristics

Determination of physicochemical parameters

Hardness test

Hardness test was performed by using the procedure given in USP Monsanto hardness tester was used for the determination of hardness of 6 tablets and result was given in table no.3.

Friability

Twenty tablets were accurately weighed and placed in the friabilator (Roche's Friabilator) and operated for 100 revolutions and result was shown in table no.3.

Weight variation

20 tablets were selected randomly from the lot and weighed individually to check for weight variation as per USP and result was given in table no.3.

Disintegration test

Tablets were taken and one tablet was introduced in each tube disintegration apparatus and placed in 1litre beaker containing water at $37^0 \pm 2^0$C and the time of disintegration was recorded according USP and result was shown in table no.3.

Drug content

20 tablets were randomly selected from the batch, weighed and powdered. Powder equivalent to100 mg of valsartan was weighed and transferred in to a 10ml volumetric flask and volume made up with 0.1N HCl. Further 1 ml of the above solution was diluted to 10ml with 0.1NHCl and absorbance of resultant solution was observed at 270nm as per USP and result was shown in table no.3.

Thickness

10 tablets were measured for their thickness and diameter with vernier calipers and result was given in table no.3.

***In-vitro* dissolution study**

Dissolution was done for each of sustained release floating tablets of valsartan in 0.1N HCl for 24 hours. *Invitro release studies were* carried out by using United States Pharmacopoeia (USP) Dissolution Testing Apparatus II (Paddle method). The dissolution test was performed using 900 ml of 0.1N HCl (pH 1.2) at 37±0.5^{o}C. 50 rpm was maintained, 5 ml of sample was withdrawn at predetermined time intervals for 24 hours and the same volume of the fresh medium was replaced. The absorbance of the withdrawn sample was measured spectrophotometrically at a wavelength at 270nm and cumulative percentage drug release was calculated using an equation obtained from a standard curve and graph were shown in figure 6 to 9.

Determination of floating parameters

a) *In-vitro* buoyancy test

The *in-vitro* buoyancy was determined by observing floating lag time, as per the method described by Rosa. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The

time required for the tablet to rise to the surface and float was considered as the floating lag time.

b) Swelling index

Swelling of hydrophilic polymer such as Hydroxy Propyl Methyl Cellulose greatly depends upon the contents of the stomach and the osmolarity of the medium. These eventually influence the release, slowing action and the residence time. For each formulation, one tablet was weighed and placed in a beaker containing 200 ml of distilled water. After each hour the tablet was removed from beaker and weighed again up to 8 hours. The percentage weight gain by the tablet was calculated by using the formula and result was given in table no.4.

Swelling index (S.I) = $\{(W_t-W_o)/W_o\}$ x 100.

Where, S.I. = swelling index

W_t = Weight of tablet at time t

W_o = Weight of tablet before immersion.

RESULTS AND DISCUSSION

In the Preformulation studies, Characteristic of drug compatibility studies were performed using FTIR spectrophotometer. The FTIR spectrum of pure drug and physical mixture of drug and polymer were studied. The peaks obtained in the spectra's of each formulation correlated with the peaks of pure drug spectrum. So it was concluded that no significant difference in peak pattern in IR spectrum of drug, polymer and the excipients exists. The values obtained for the preformulation parameters for the formulations F1,F2,F3,F4,F5,F6,F7,F8,F9 and F10 are tabulated in Table 5. The values for the angle of repose were found to be in the range of 24.25 to 29.36. This indicates good flow property of the powder blend as the concentration of HPMC E15, HPMC K15 decreases. Compressibility index ranges between 10.1891% and 12.6161% indicating that the powder blend has the required flow property for direct compression. Microscopic examinations of tablets from each formulation batches have showed round shape (oval) with no cracks.

Hydrodynamically balanced tablets of Valsartan (intra-gastric buoyant tablets) were prepared and evaluated to increase its local action and bioavailability. In the present study ten formulations with variable concentration of polymer (HPMC) were prepared by direct compression and evaluated for physicochemical properties, buoyancy lag time, total floating time, swelling index and *in-vitro* drug release. The results indicated that on immersion in

0.1N HCl solution at pH 1.2 at 37±0.5^{o}C tablets float immediately and remain buoyant up to8-12 hours without disintegration. Floating property of the tablet is governed by both the swelling (hydration) of the polymer when it contacts with the gastric fluid, which in turn results in increase in the bulk volume and the presence of internal voids in the dry centre of the tablet (porosity). These two factors are essential for the tablet to acquire bulk density < 1, so that it remains buoyant on the gastric fluid. Hardness of the tablets was in the range of 6.5 to 6.8 ±0.28 kg/cm2. This ensures good handling characteristics of all the batches. % weight loss in the friability test was less than 1% in all the cases, ensuring that the tablets were mechanically stable.

All the floating tablets prepared contained the drug within 102±5% of the label claim. All the formulated tablets (F1 to F10) passed the weight variation test as the % weight variation was within the Pharmacopoeial limits of ±5% of the average weight. Table 4 shows the results of physicochemical characters of Valsartan tablets. In the present study, the higher degree of swelling and slow drug release was found for tablets of F8 containing 20% HPMC K15 and HPMC E15. Thus, the concentration of polymer and ratio of lactose had major influence on swelling process, matrix integrity, as well as on floating capability. Hence from the above results it can be proved that linear relationship exists between swelling process and concentration ratio as shown in Table 5 and Fig. 1. From the *in-vitro* drug profiles, it was found that drug release rate decreased as the concentration of polymers HPMC K15 and HPMC E15 increases as shown in and Fig 7-9.

Stability studies were performed for the all formulation as per ICH guidelines for 2 months. Dissolution testing was performed during and after study. Results showed no significant difference after testing indicating that these formulations were stable. The percentage of drug release and total floating time was comparatively good in Formulation F8 compared with that of other formulations.

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order, diffusion and Hixson Crowell and Korsmeyer Peppas equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug

release from matrix systems was studied by using Higuchi equation, erosion equation and Peppa's-Korsemeyer equation. The results are given in Table no.7.

Table 1: Physical characterization of valsartan

Physical Properties	Valsartan
Physical appearance	White to partially white in color
Melting Point	116-117ºC
Water content by KF	NMT 2%W/W
Hygroscopicity	Hygroscopic powder
Partition Coefficient	5.8
Density (gm/cm²)	1.212

Table 2: Physical properties of blend

	Angle Of repose ±SD*	Bulk Density (gm/ml) ± SD*	Tapped Density(gm/ml) ±SD*	Carr's Index(%)±SD*	Hausner's Ratio±SD*
F1	24.25±0.23	0.487±0.0202	0.5424±0.0252	10.1891±1.9083	1.1137±0.0234
F2	26.96±0.15	0.5103±0.0055	0.5704±0.0012	10.5366±0.7895	1.1211±0.0123
F3	25.58±0.34	0.4958±0.0069	0.5459±0.0051	10.2693±1.0665	1.1011±0.011
F4	28.65±0.12	0.4784±0.0068	0.544±0.0093	12.1114±0.3176	1.2041±0.1119
F5	29.36±0.15	0.5018±0.0056	0.5706±0.0009	12.0564±0.9247	1.1195±0.0418
F6	25.93±0.64	0.4983±0.0019	0.5702±0.0011	12.6161±0.3054	1.1443±0.004
F7	26.15±0.15	0.5107±0.005	0.5807±0.0014	12.0596±0.6848	1.1371±0.0088
F8	25.45±0.43	0.5203±0.0007	0.5918±0.0008	12.0914±0.2266	1.1375±0.0029
F9	26.69±0.21	0.5379±0.0031	0.6002±0.0017	10.3683±0.3794	1.1158±0.0049
F10	28.63±0.11	0.5393±0.0005	0.6011±0.0016	10.2697±0.1994	1.1144±0.0025

*n=3.

Table 3: Physicochemical evaluation data parameters of Valsartan tablets formulations

Formulation code	Weight variation(mg) ±SD**	Thickness (mm) ±SD*	Hardness ($Kg/cm^{2)}$ ±SD*	Friability (%W/W) ±SD*	Content uniformity (%)	Floating lag time (min)	Total floating time (hrs)
F1	400.2±2.8205	4.62±0.03	6±0.5	0.36±0.02	98.67±2.5166	<1	<8
F2	399.2±2.4855	4.61±0.02	6.5±0	0.42±0.02	99±1	<1	<11
F3	400.3±3.4334	4.71±0.01	6.6±0.28	0.38±0.04	100±1	<1	<13
F4	399±3.0184	4.68±0.02	6.6±0.28	0.44±0.01	99.33±1.5275	<1	<12
F5	399.9±4.1525	4.79±0.02	6.6±0.28	0.48±0.03	98.67±1.5275	<2	<20
F6	399±4.0842	4.67±0.03	6.6±0.28	0.41±0.01	99±1	<2	<20
F7	399.3±2.9832	4.81±0.01	6±0.5	0.38±0.04	99.33±1.5275	<2	<24
F8	399.8±2.0439	4.72±0.02	6.66±0.28	0.28±0.01	99.67±1.1547	<3	<24
F9	400.7±3.4009	4.69±0.02	6.8±0.28	0.48±0.02	99±1	<3	<24
F10	399.7±1.9465	4.87±0.01	6.8±0.28	0.36±0.03	98.33±1.5275	<3	<24

*n= 10 **n=20.

Table 4: Swelling index % of formulation F1 to F10 of Valsartan

Time (hrs.)	Swelling index (%)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	24.55	30.45	36.56	45.83	50.83	56.32	60.49	66.56	72.5	81.21
2	31.65	37.47	48.74	56.44	62.44	66.89	69.84	75.43	80.75	94.5
4	39.33	46.12	61.85	69.12	71.84	75.12	79.45	88.24	92.82	111.4
6	44.29	57.9	75.2	77.03	84.12	89.12	91.73	101.3	121.5	128.5
8	-	-	-	89.12	99.03	104	107.4	119.6	130.4	155.9
12	-	-	-	-	109.11	-	-	127.9	144.4	169.4

Table 5: Formulation trials for sustained release floating tablet of valsartan

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Valsartan	80	80	80	80	80	80	80	80	80	80
HPMC E15	80	160	240	-	-	-	80	80	-	80
HPMC K15	-	-	-	80	160	240	80	80	80	-
Carbopol	-	-	-	-	-	-	-	40	40	40
MCC	198	118	38	198	118	38	118	78	158	158
SBC	30	30	30	30	30	30	30	30	30	30
Citric acid	5	5	5	5	5	5	5	5	5	5
Talc	7	7	7	7	7	7	7	7	7	7
Total weight	400	400	400	400	400	400	400	400	400	400

Table 6: Results analyzed after 2 months of accelerated stability studies

S.No	Test	Initial	After 1 month	After 2 months
1	Description	Complies	Complies	Complies
2	Post compression parameters a. Weight variation b.Hardness c.Floating lag time d.Total floating time	Complies	Complies	Complies
3	Dissolution (In 0.1N HCl)	98.87%	98.13%	97.6%
4	Assay	99.67%	98.77%	98.69%

Table 7: Release Kinetics Studies for all formulations

Formulation	R^2 Values					n-values
	Zero order	First order	Rate constant (k)in hr^{-1}	Hixson Crowell	Higuchi	Peppas
F1	0.802	0.917	0.177	0.883	0.973	0.455
F2	0.877	0.955	0.156	0.941	0.982	0.446
F3	0.917	0.988	0.145	0.934	0.992	0.448
F4	0.903	0.988	0.177	0.977	0.996	0.453
F5	0.922	0.954	0.165	0.981	0.996	0.463
F6	0.914	0.993	0.135	0.989	0.997	0.52
F7	0.856	0.992	0.142	0.970	0.984	0.474
F8	0.951	0.997	0.116	0.981	0.993	0.655

F9	0.894	0.99	0.135	0.988	0.99	0.543
F10	0.900	0.994	0.119	0.986	0.992	0.507

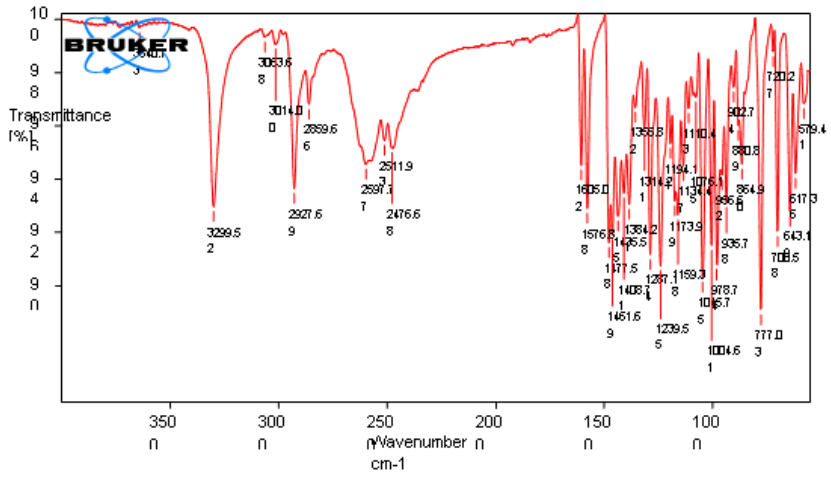


Fig 1: FTIR of Valsartan

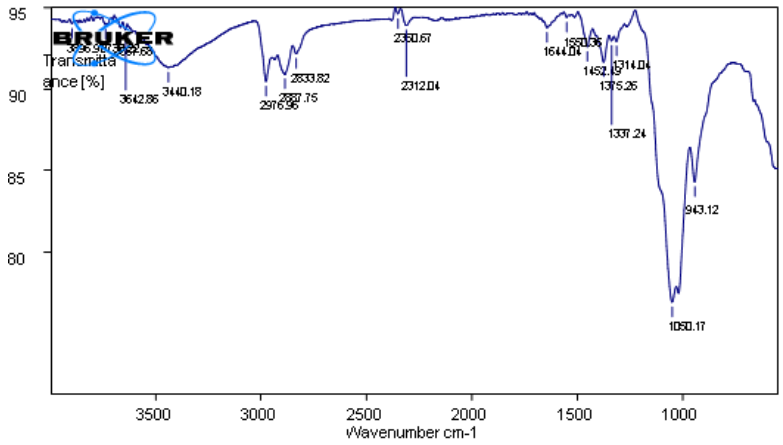


Fig 2: FTIR of HPMC K15

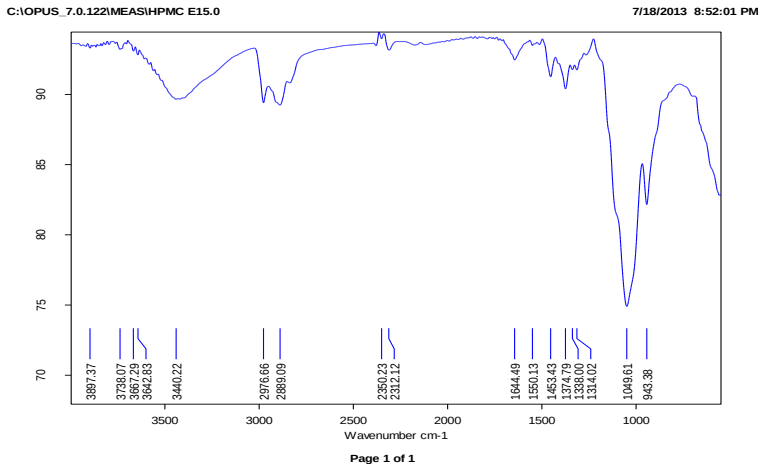


Fig 3: FTIR of HPMC E1

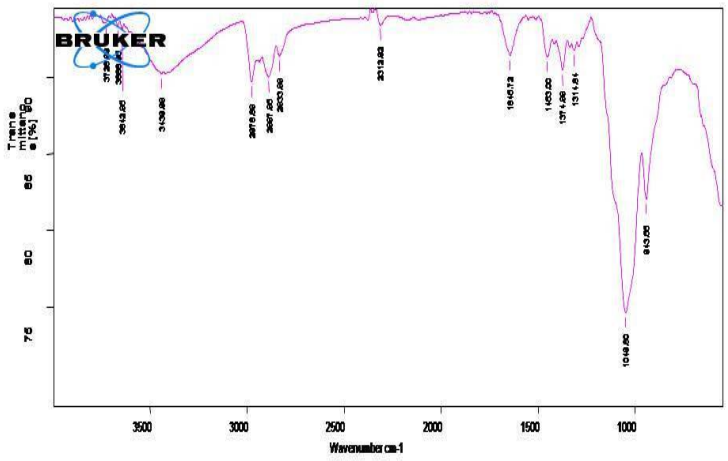


Fig 4: FTIR of Carbopol

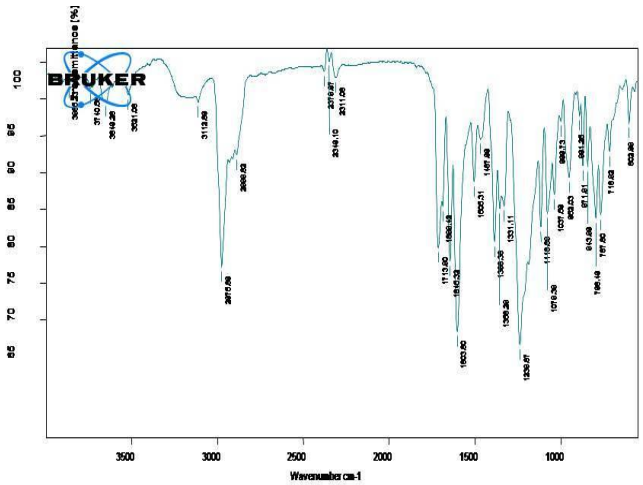
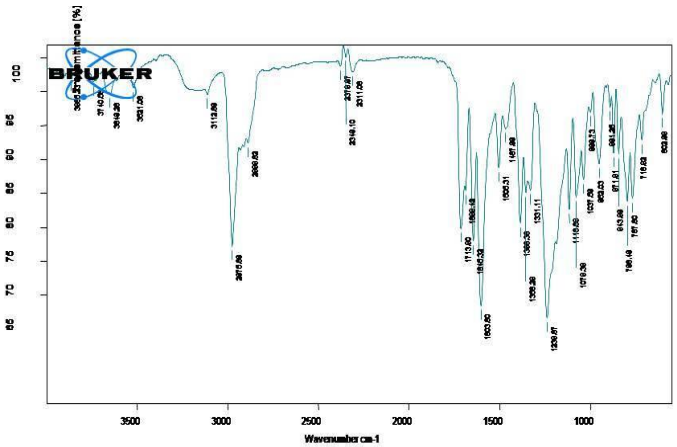


Fig 5: FTIR of Best Formulation



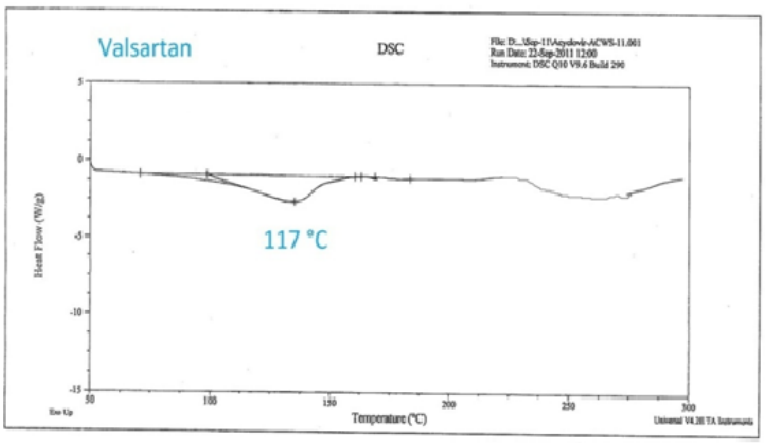


Fig 6: DSC of best formulation

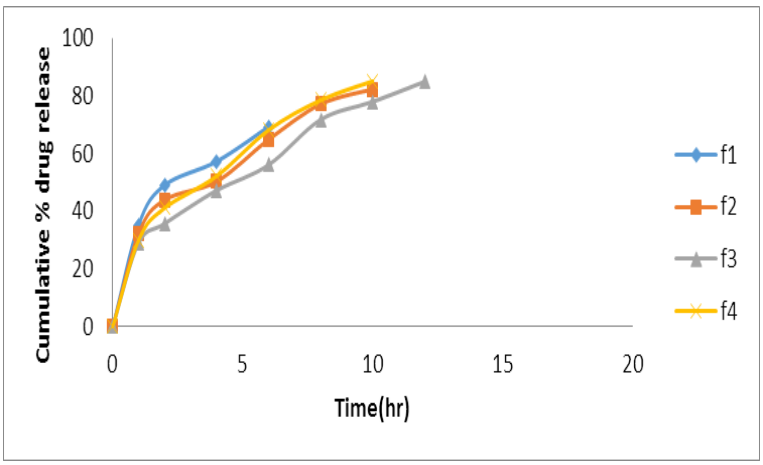


Fig 7: *In vitro* Drug Release Profile of formulations F1 –F4

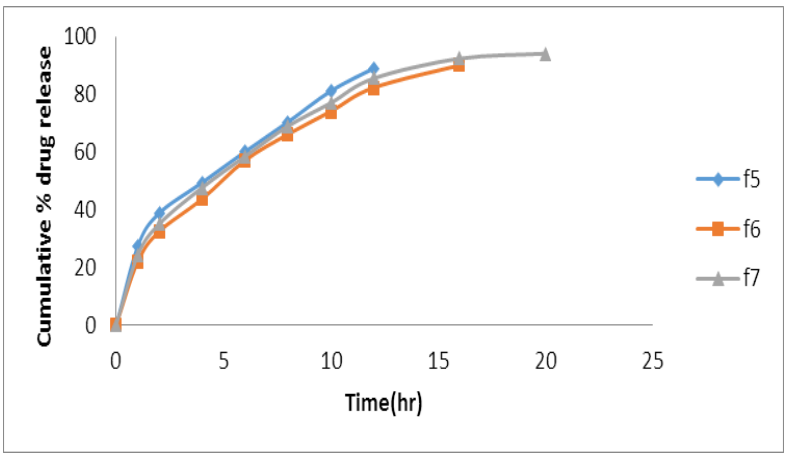


Fig8: *In vitro* Drug Release Profile of formulations F5 - F7

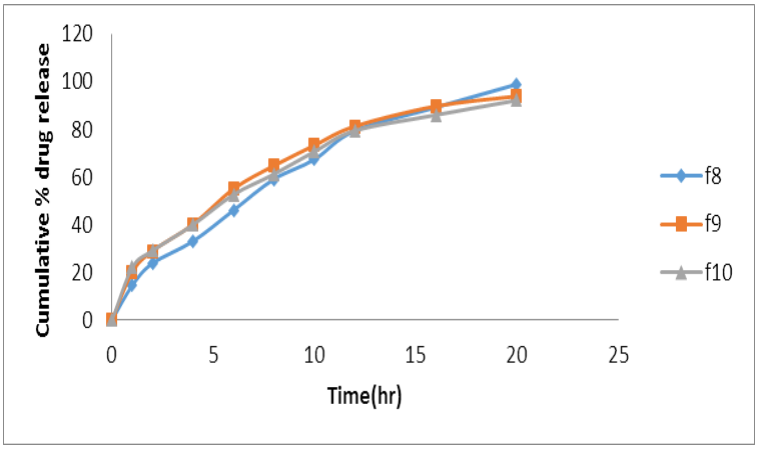


Fig 9: *In vitro* Drug Release Profile of formulations F8 – F10

CONCLUSION

The gastro retentive floating drug delivery system (GFDDS) of Valsartan to achieve prolonged release could be prepared and the drug showed compatibility with all the excipients. Physical parameters and in-vitro drug release studies were found to be within the limits. Drugs release kinetics like zero-order, first order, diffusion and Hixson Crowell plots of optimized formulation was plotted and the drug release found to be following the first order kinetics and the area to volume of the dosage form changes with time. Stability studies of the final formulations were performed according to ICH guidelines for 2 months and no major changes were observed indicated that the optimized formulation was stable. It can be concluded that the gastro retentive floating tablets of valsartan were prepared and evaluated for once daily administration.

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