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Formulation and characterization of floating matrix tablets for an antihypertensive drug: Valsartan

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Abstract
Valsartan is an angiotensin receptor blocker (ARB) drug that may be used to treat a variety of cardiac conditions, including hypertension, diabetic nephropathy and heart failure. The aim of the present study was to develop floating matrix tablets of Valsartan. The floating matrix tablets of Valsartan were prepared based on hydrophilic matrix and low density copolymer that retains the dosage form in the stomach. The prepared tablets were evaluated for various pre-compression & post-compression parameters, *in vitro* drug release and *in vivo* X-ray imaging in rabbits. All tablets showed excellent swelling and floating capabilities, short floating lag times and maintained controlled release for more than 17 h. The release of Valsartan from optimized formulation F13 was found to be non-Fickian type. Gastric X-ray imaging of formulation F13 (Containing drug, Chitosan, Carbopol-940, Poly (Styrene Divinyl Benzene), Lactose, Magnesium Stearate and Talc) showed that the floating matrix tablet was continuously floating in the stomach region of the rabbit; hence, it could prolong the gastric retention time to more than 12 h. These results indicated that developed matrix tablets of Valsartan could be successfully used for floating drug delivery system.

Keywords: Angiotensin receptor blocker, floating matrix tablets, valsartan and low density polymer

Introduction
Despite tremendous advancements in drug delivery the oral route remains the preferred route of administration of therapeutic agents because of low cost of therapy and ease of administration lead to high levels of patient compliance. But the issue of poor bioavailability (BA) of orally administered drugs is still a challenging one, though extensive advancements in drug discovery process are made [1]**.** A major constraint in oral controlled release drug delivery systems is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract. Some drugs are absorbed in a particular portion of gastrointestinal tract only or are absorbed to a different extent in various segments of gastrointestinal tract. Such drugs are said to have an "absorption window". Thus, only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. After crossing the absorption window, the released drug goes to waste with negligible or no absorption. This phenomenon drastically decreases the time available for drug absorption after it and limits the success of delivery system. These considerations have led to the development of oral CRDFs possessing gastric retention capabilities [2].
One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in gastrointestinal tract is to control the gastric residence time (GRT) using gastro retentive dosage forms (GRDFs) that offer a new and better option for drug therapy. Dosage forms that can be retained in stomach are called gastro retentive drug delivery systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability [3].
The floating drug delivery system (FDDS) is one of the gastro retentive dosage forms designed to prolong the gastric residence time (GRT) of the dosage form within the GIT to enhance bioavailability [4]. The FDDS has lower density than the gastric fluids and thus remains buoyant in the stomach [5]. Drug dissolution/release from the FDDS takes place at the desired rate in the stomach under fairly controlled conditions [6, 7]. Valsartan belongs to a class of antihypertensive agents called angiotensin II receptor blockers (ARBs). Valsartan selectively inhibits the binding of angiotensin II to AT1, which is found in many tissues such as vascular smooth muscle and the adrenal glands. This effectively inhibits the AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in a decrease in

vascular resistance and blood pressure. Valsartan have short half-life, short GRT, low bioavailability and narrow absorption window [8].

Therefore, it was selected as a model drug for FDDS. The floating matrix tablets of Valsartan were prepared based on low density copolymer that retains the dosage form in the stomach. The developed tablet formulations were evaluated for pre and post-compression parameters such as hardness, friability, tensile strength, weight uniformity, drug content, water uptake, *in vitro* floating time, *in vitro* drug release, release kinetics and its mechanisms and *in vivo* X-ray imaging in rabbit.

The aim and objective of proposed research work is to formulate a floating drug delivery system for an antihypertensive drug Valsartan using hydrophilic matrix and low density polymer, evaluate the designed system as per the various parameters and to study the physical stability of the system. The effect of various formulation variables on the size and drug release was also investigated in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability.

Materials and methods

Materials

Valsartan pure drug was obtained as gift sample from Mann Pharmaceuticals Pvt. Ltd., Mehsana, India, Low Density Powder - Poly (Styrene Divinyl Benzene) Copolymer was obtained from Polygenetics Inc. (CA, USA), Chitosan from Central Institute of Fisheries Technology, Cochin, Carbopol 940 and other chemicals were purchased from S. D. Fine Chemicals Ltd., Mumbai, India. All other ingredients, reagents and solvents used were of analytical grade.

Determination of Valsartan by UV Visible Spectrophotometric method

0.1 N HCl solution was used for preparation of Valsartan solution and absorption were measure by Shimadzu UV-1601 UV/Vis double beam spectrophotometer. The λ max of Valsartan was found to be 250 nm[9]. The result was showed in the table no.1 and figure no.1.

Table 1: Standard Curve of Valsartan in 0.1 N HCl solution

S. No.	Concentration (µg/ml)	Absorbance			Average Absorbance	Calculated Absorbance
		1	2	3		
1	0	0	0	0	0	0.002
2	10	0.042	0.041	0.042	0.042	0.038
3	20	0.078	0.079	0.079	0.079	0.074
4	40	0.149	0.149	0.150	0.149	0.148
5	60	0.212	0.214	0.215	0.214	0.216
6	80	0.268	0.269	0.268	0.268	0.270
7	100	0.365	0.366	0.366	0.366	0.370
Correlation Co-efficient : 0.9984 Absorbance= 0.0038x conc. + 0.0021						

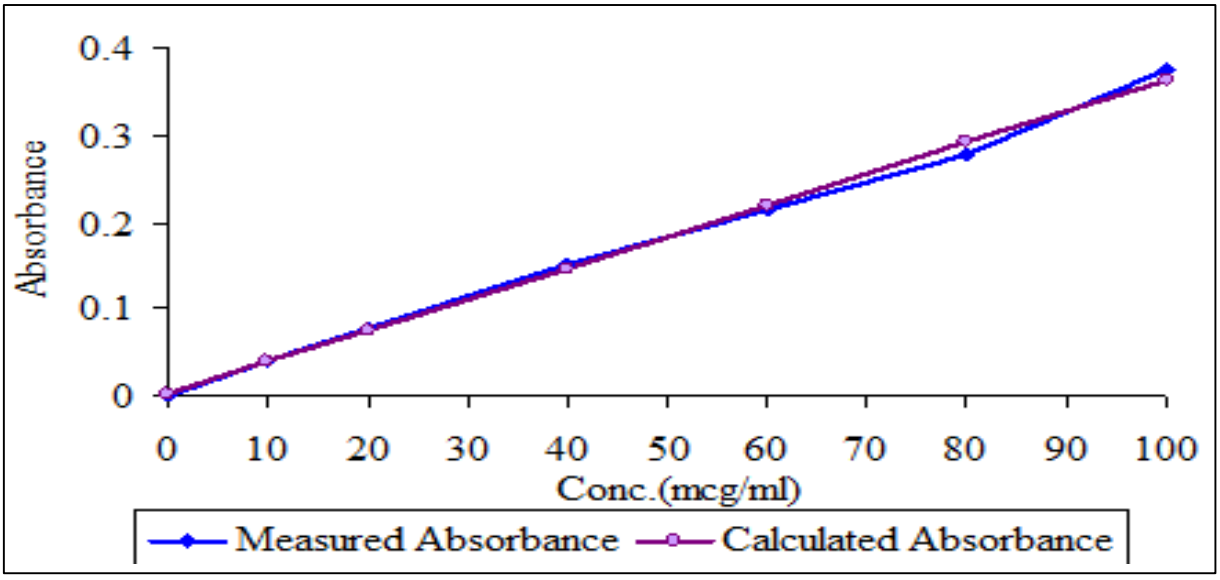


Fig 1: Standard calibration curve of drug in 0.1 N HCl Solution

Drug- excipients compatibility studies

Drug- excipients interactions play a vital role with respect to release of drug from the formulation amongst others. It has been observed that there is no chemical interaction between Valsartan and the polymers used. The functional group present in drug give peaks to specify the presence of 5-cyclic ring with oxygen atom, 2- diamine, and alkene, and other peaks for nitro groups. Form the figure it was observed that there was no incompatibility between drug and other excipients. The FTIR 8400S model instrument was used for the compatibility study of drugs with other excipients which were used in formulation of tablets.

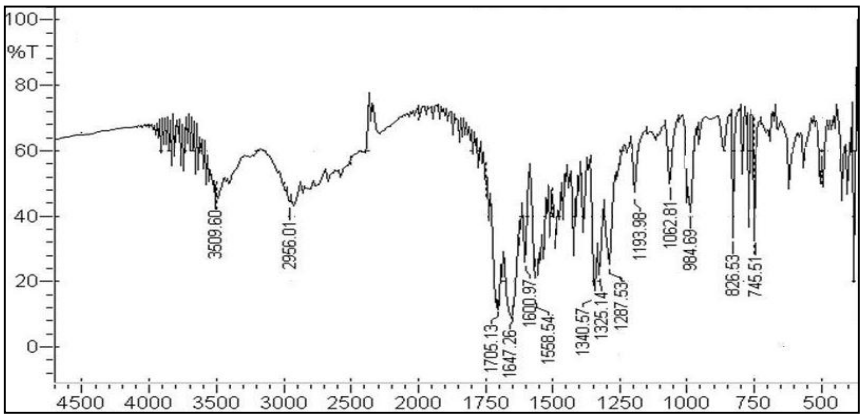


Fig 2: Infrared spectra of Valsartan

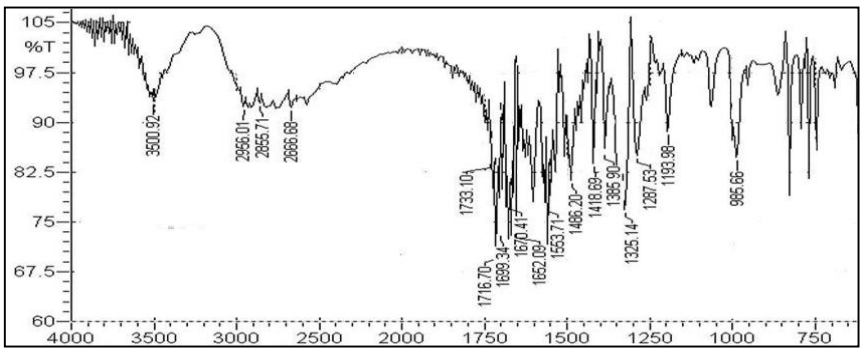


Fig 3: Infrared spectra of Chitosan

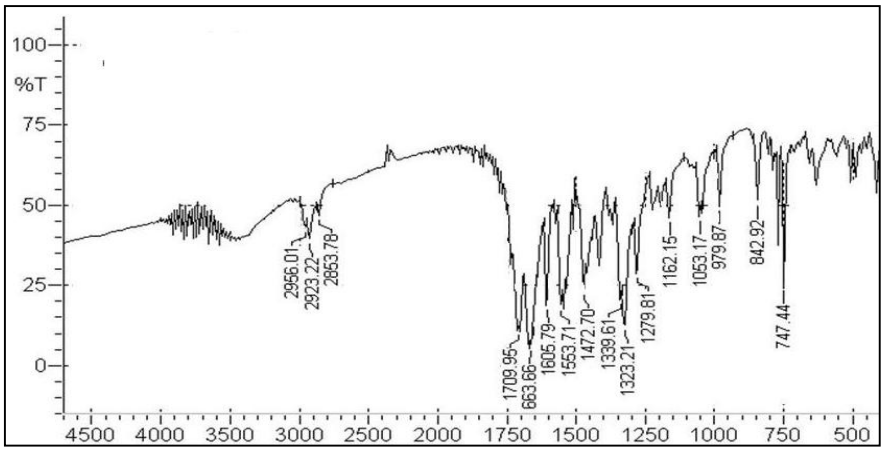


Fig 4: Infrared spectra of Carbopol 940

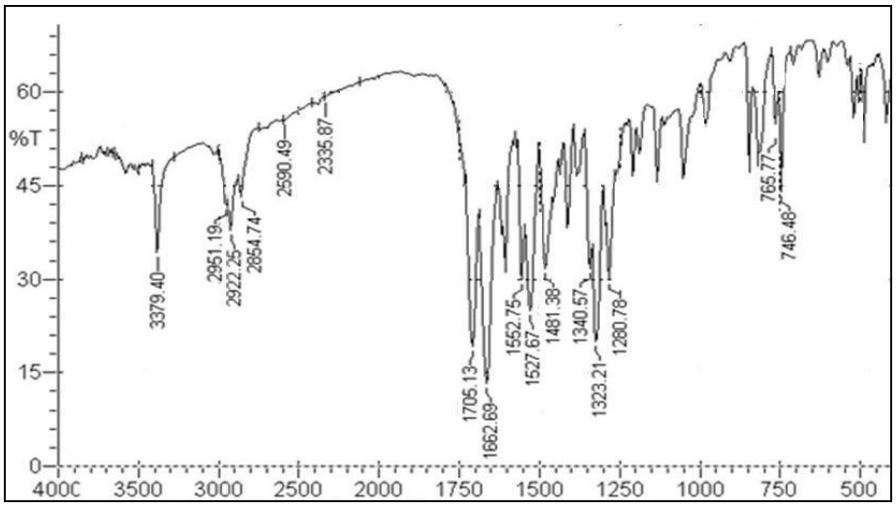


Fig 5: Infrared spectra of Poly (Styrene-divinylbenzene)

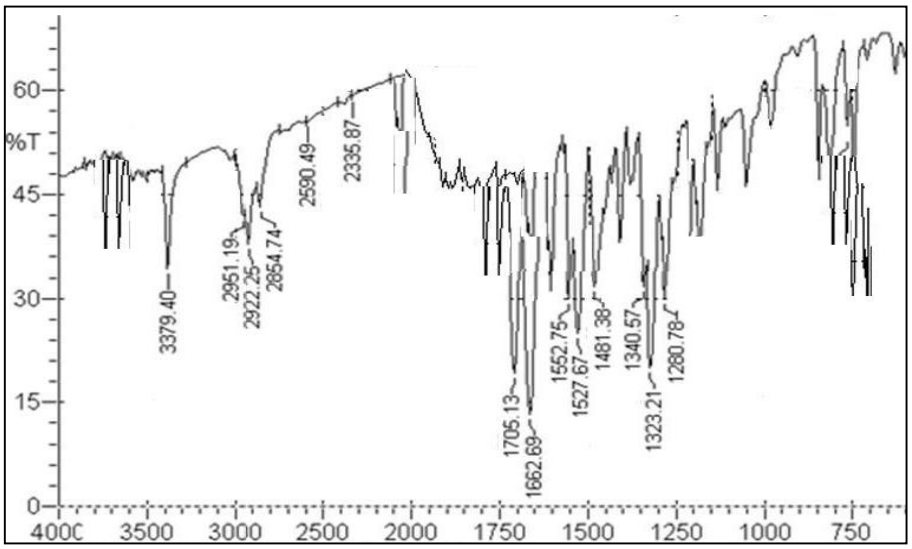


Fig 6: Infrared spectra of best batch (F-13)

Pre-compression parameters of powder mixture

The prepared blend of the formulations was evaluated for the parameters like angle of repose, bulk density, tap density, compressibility index and hausner's ratio. After granulation, angle of repose was improved. All these values indicated that the granules have good flow property and hence the granulation process has improved the flow property. For uniform tablet compression, good flow property is the major criteria.

Table 2: Physical Characteristics of powder blend

Formulation code	Angle of Repose (º)	Bulk density	Tap density	Hausner ratio	Carr's Index
F1	20 º 09 ± 0.4580	0.351 ± 0.014	0.410± 0.003	1.17± 0.002	14.41± 0.603
F2	21 º 13 ± 0.4670	0.356 ± 0.012	0.420± 0.004	1.18± 0.001	15.20± 0.520
F3	20 º 22 ± 0.2654	0.361 ± 0.015	0.434± 0.005	1.18± 0.002	15.35± 0.109
F4	20 º 36 ± 0.3564	0.371 ± 0.018	0.421± 0.001	1.19± 0.003	16.69± 0.211
F5	21 º 09 ± 0.8547	0.358 ± 0.019	0.442± 0.004	1.17± 0.003	15.80± 0.309
F6	20 º 18 ± 0.5226	0.353 ± 0.011	0.424± 0.002	1.19± 0.004	14.78± 0.408
F7	20 º 54 ± 0.6548	0.364 ± 0.014	0.438± 0.006	1.20± 0.001	15.92± 0.554
F8	22 º 16 ± 0.5547	0.376 ± 0.016	0.415± 0.002	1.18± 0.001	16.55± 0.612
F9	20 º 26 ± 0.6321	0.366± 0.012	0.428± 0.005	1.19± 0.001	14.69± 0.469
F10	20 º 28 ± 0.4568	0.374 ± 0.017	0.446± 0.002	1.18± 0.002	15.23± 0.532
F11	21 º 22 ± 0.5449	0.352 ± 0.013	0.423± 0.003	1.17± 0.004	14.64± 0.368
F12	20 º 17 ± 0.4225	0.380 ± 0.014	0.417± 0.001	1.18± 0.003	14.20± 0.398
F13	20 º 14 ± 0.3326	0.360 ± 0.011	0.445± 0.004	1.17± 0.001	14.42± 0.215
F14	22 º 12 ± 0.4569	0.359 ± 0.012	0.433± 0.003	1.20± 0.002	16.36± 0.276
F15	21 º 14 ± 0.5698	0.372 ± 0.016	0.416± 0.002	1.19± 0.001	16.66± 0.604
F16	20 º 12 ± 0.7254	0.365 ± 0.013	0.448± 0.006	1.18± 0.003	14.90± 0.401

*Values mentioned are average of 3 determinations

Preparation of floating matrix tablets

Various formulations were prepared by direct compression method. 80 mesh sieve used for powder sieving. Drug, matrix polymer and low-density copolymer were mixed thoroughly according to required quantity. As a glident and lubricant talc and magnesium stearate were added as respectively. By the using of multi punch tablet compression machine (Cadmach, Ahmedabad, India) blend was compressed (12 mm diameter, flat punches) & 80 mg of Valsartan present in each tablet and other pharmaceutical ingredients as listed in table in each section.

Formulation tables

Table 3.1: Polymer concentration formulation F-1 to F-8

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Valsartan	80	80	80	80	80	80	80	80
Chitosan	90	80	70	60	50	40	30	20
Carbopol-940	20	30	40	50	60	70	80	90
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5

Table 3.2: Poly (Styrene-divinylbenzene) copolymer concentration (F-9 toF-12)

Ingredients	F-9	F-10	F-11	F-12
Valsartan	80	80	80	80
Chitosan	40	40	40	40
Carbopol-940	20	30	40	50
Poly (Styrene-divinylbenzene)	50	40	30	20
Magnesium stearate	5	5	5	5
Talc	5	5	5	5

Table 3.3: PSDVB copolymer concentration (F-13 to F-16)

Ingredients	F-13	F-14	F-15	F-16
Valsartan	80	80	80	80
Chitosan	30	30	30	30
Carbopol-940	30	40	30	40
PSDVB	30	20	30	20
Lactose	20	20	-	-
DCP	-	-	20	20
Magnesium Stearate	05	05	05	05
Talc	05	05	05	05

Post-compression parameters of the prepared floating tablets

After formulation of tablets by direct compression method, different evaluations were done and results obtained were as following table:

Table 4: Post Compression Parameter

Formulation code	weight variation (mg) ± S.D	Hardness (Kg/cm^2) ± S.D	Friability (%) ± S.D	Thickness (mm) ± S.D	Content uniformity (%)
F1	200 ± 1.10	5.2 ± 0.218	0.31 ± 0.06	2.88±0.011	99±0.65
F2	200 ± 1.52	5.4 ± 0.225	0.33 ± 0.04	2.45±0.013	98±0.14
F3	201± 1.08	6.1 ± 0.363	0.36± 0.08	2.37±.012	98±0.95
F4	201 ± 1.32	5.9 ± 0.106	0.38± 0.09	2.65±0.018	98±0.09
F5	200 ± 1.48	5.5 ± 0167	0.32± 0.03	2.11±0.013	99±0.02
F6	200 ± 1.56	6.2 ± 0.412	0.37± 0.07	2.54±0.016	99±0.19
F7	200 ± 1.22	5.7 ± 0.332	0.36± 0.11	2.44±0.012	98±0.72
F8	202± 1.07	5.9 ± 0.423	0.28± 0.13	2.75±0.075	99±0.45
F9	201 ± 1.23	5.6 ± 0.154	0.29± 0.06	2.45±0.19	98±0.10
F10	201 ± 1.03	5.8 ± 0.213	0.35± 0.15	2.64±0.017	99±0.07
F11	200 ± 1.16	5.6 ± 0.321	0.31± 0.09	2.19±0.013	98±0.65
F12	200 ± 1.22	5.7 ± 0.112	0.33± 0.08	2.86±0.018	98±0.25
F13	200 ± 1.04	5.9 ± 0.101	0.32± 0.03	2.99±0.005	99±0.01
F14	201± 1.18	6.1 ± 0.325	0.35± 0.05	2.11±0.019	99±0.35
F15	201± 1.17	6.4 ± 0.224	0.28± 0.09	2.54±0.016	98±0.74
F16	200 ± 1.18	6.6 ± 0.423	0.34± 0.19	2.44±0.012	98±0.30

The thickness was found in the range of 2.11 ± 0.13 to 2.99 ± 0.005. In each formulation, weight variation was within the I.P limit. Mostly, the variation was within ± 5%. The hardness of the different formulations ranged from 5-7 kg / cm^2. All the formulations exhibited less than 1% friability and drug content was in permissible limit.

***In vitro* dissolution studies**

As *United States Pharmacopoeia* (USP) XXIV states, dissolution testing apparatus-II (paddle type) was used for dissolution study of Valsartan for floating matrix tablet. Test was performed by use of 0.1 N HCl solution (900ml) at temperature 37 ± 0.5 °C and speed was set at75 rpm [9]. During the 18 hrs. 10 ml of sample was withdrawn at specific time interval, drug samples was filter through 0.45 µ membrane filter and dissolution medium used for dilution purpose. Shimadzu UV-1601 UV/Vis double beam spectrophotometer was used for measure the absorbance at 250 nm and Cumulative% release of drug was calculated by equation which was obtained from standard Calibration Curve.

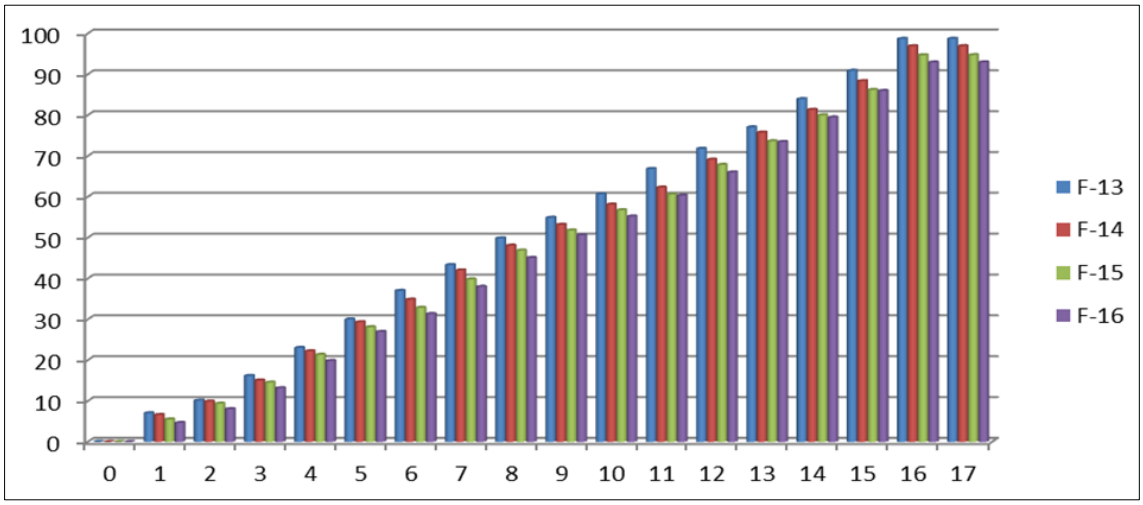


Fig 7: Comparison of drug release (F-13 to F-16)

Table 5: Cumulative % Drug Release (F-13 to F-16)

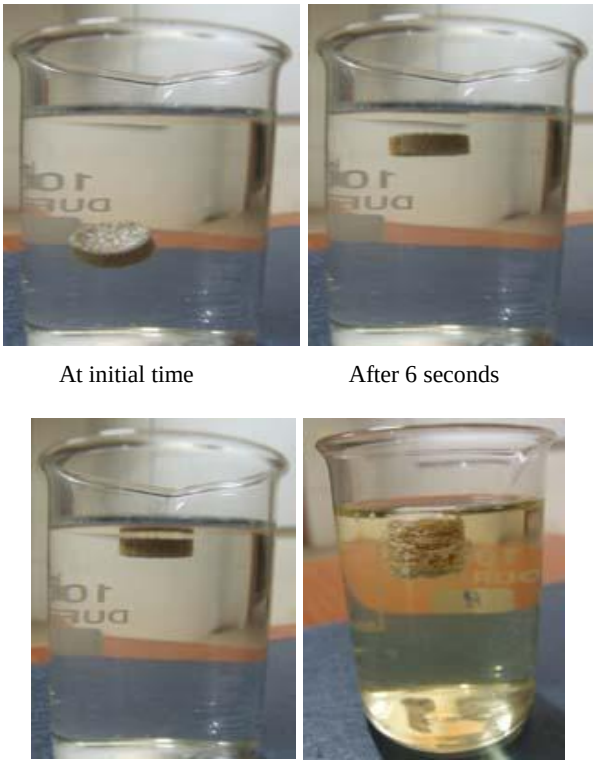
Time (hr)	F-13	F-14	F-15	F-16
0	0.0	0.0	0.0	0.0
1	7.02	6.59	5.51	4.65
2	10.11	9.89	9.36	8.03
3	16.16	15.04	14.53	13.15
4	23.04	22.19	21.33	19.84
5	30.01	29.32	28.09	26.93
6	36.99	34.85	32.84	31.32
7	43.31	41.99	39.81	37.97
8	49.83	48.07	46.86	45.06
9	54.89	53.16	51.78	50.61
10	60.65	58.13	56.72	55.21
11	66.84	62.28	60.59	60.31
12	71.78	69.11	67.84	66.01
13	77.03	75.74	73.62	73.44
14	83.94	81.33	79.99	79.46
15	90.88	88.35	86.19	85.95
16	98.69	96.89	94.68	92.91
17	98.71	96.92	94.71	92.94

Drug release profile was checked for the effect of PSDVB copolymer on formulations containing PSDVB copolymer concentrations 30, 20 mg. According to observable data for *in vitro* dissolution profile I concluded that 98.71% of drug was released from optimized formulation containing PSDVB 30 mg and lactose 20 mg (F-13). For *in- vitro* buoyancy test, a major changes were observed in view of floating lag time of the formulation if increased amount of PSDVB. So all the parameters of batch F-13 were evaluated and select as the optimized batch.

Selection of the best batch

The Formulation with batch F-13 different polymer concentration incorporated like Chitosan, Carbopol-940 (30 mg) used and PSDVB copolymer 30 mg showed 98.71% of drug release after 17 hour. This shows that the formulation should release drug in predictable and controlled manner and have FLT less than 15 sec.

1 *In-vitro* buoyancy studies

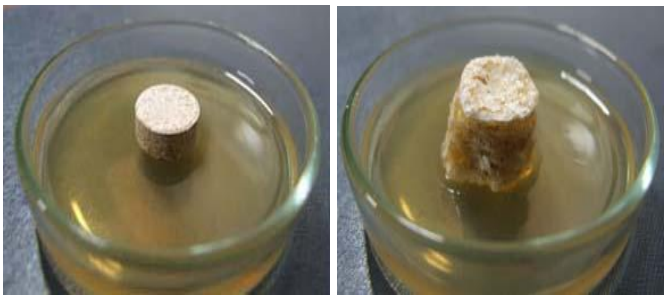


At initial time | After 6 seconds

After 10 seconds | After 17 hours

Fig 8: *In vitro* buoyancy studies of batch F-13

2 Swelling index



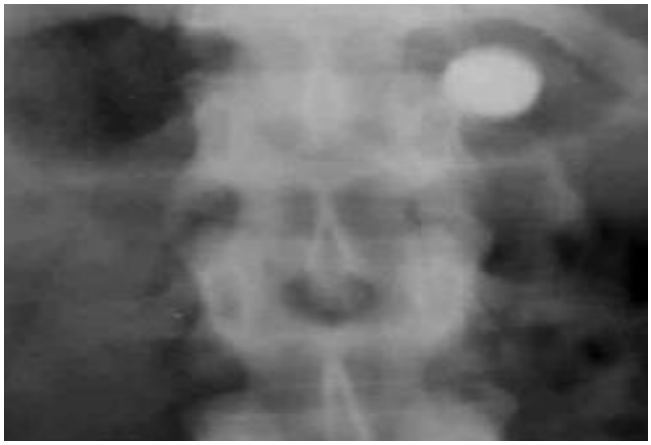
At initial time (0.1 N HCl) | After 17 hour (0.1 N HCl, swelling)

Fig 9: Swelling index of batch F-13

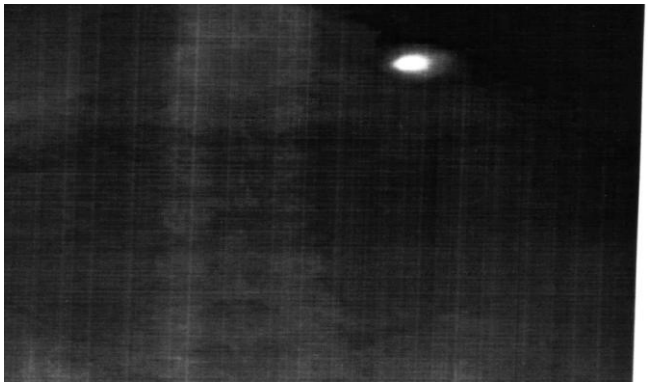
As swelling and water acceptance must balance between both to achieve floating property, which will be restored (10, 11). The swelling behavior of the tablets was determined according to the method describe by Ramji *et al.* [12]. After 17 hrs, swelling index was found 1.289, which may be due to carbopol-940 having high viscosity and water retention property.

***In vivo* studies**

The study was carried out by administering the gastro retentive tablets to rabbit. The tablet was administered in the fasting state. The x ray opaque formulation was administered along with 25 ml of water. The subjects were allowed to remain in sitting or up-right position. A light meal was given to rabbit 2 hour after administration of the tablet to evaluate effect of food of gastro retentive property. The position of tablet was monitored by X-Ray screening technique X-Ray photographs were taken after 6 hours and 12 hours to monitor tablet position in gastrointestinal tract. The X-Ray photographs revealed that the tablet remained buoyant in stomach after 6 h., which indicated that there is no significant effect of food on floating property of tablet. This behavior may be attributed to bioadhesive and insolubility property of carbopol 940 & low density polymer in stomach fluid.



After 6 hour



After 12 hour

Fig 10: X-ray Photographs of *in vivo* study

Drug release kinetics

According to data kinetic modeling of drug release of the dissolution profile of the best batch was follow to zero-order, first-order, Higuchi and Hixon-Crowell models. Mechanism of drug release from the matrix tablets were analyzed and the results were as followings:

Table 6: Observation data of model fitting of batch F-13

	Intercept	Slope	R^2	F-value
Zero-order plot	+ 18.518	+ 0.188	0.9115	105.69
First-order plot	+ 4.843	+ 0.756	0.5297	140.12
Higuchi plot	- 1.487	+ 4.587	0.9944	5.98
Hixon Crowell	+ 5.571	+ 0.384	0.9584	10.03

According to data observed for the selection of the appropriate model used F-Statics. F-13 batch selected as best batch according to release profile, it showed higher similarities factor, for Higuchi model there was F= 5.98 found. According to Hixon Crowell model F was found 10.03) according to Zero order model F was found 105.69. Which shown by the goodness of fit test (F-ratio test). The models give least F-value have higher priority. So Higuchi model give 4.587 as slope value and – 1.487 as intercept values.

Stability Studies

For accelerated stability studies the temperature and humidity was set as temperature at 40° C and humidity was 75% RH. The tablet of Batch F-13 was kept for accurately 12 weeks in a humidity Chamber. After 12 weak we calculated the floating lag time and drug dissolution profile. During the stability studies similarity factors were calculated for evaluate the dissolution release profile at both times as before and after study. If Similarity factor i.e. f-2 value was higher than 50, it's a clearly indication of a better similarity between both the dissolution profiles. According to observation data the value of f-2 was found ~ 77.251. So in our formulation dissolution profile and floating lag time after stability studies, there was no difference observed, the results of stability studies said that the formulation possess good stability.

Conclusion

Sustained release floating matrix tablets of Valsartan were successfully prepared by use of chitosan, carbopol 940 and low density polymer Poly (Styrene-divinylbenzene). For the preparation of hydrophilic matrix chitosan – carbopol 940 mixed matrices were used. By the use low density polymer Poly (Styrene-divinylbenzene), it was possible to reduce the floating lag time and increase the floating time after the 8 hrs. By use of 16% low density polymer for preparation it was reduced the lag time to 10 sec. Release behavior of matrices were also controlled by the adjustment of the different parameter, that is selection of the hydrophilic matrices, drug diffusion from the matrices core. It was a better approach to achieve *in vitro* buoyancy and to improve the absorption of Valsartan. The results obtained from the experiment concluded that the release of drug from the optimized formulation F13 occur by non-Fickian diffusion. Based on the series of investigations, formulation F13 was found to offer optimum release and buoyancy. According to the results of *in vivo* study of the X-ray imaging in albino rabbits, formulation F13 showed the floatability of the tablet in gastric content and prolonged the GRT to approximately 12 h. Therefore, developed floating matrix tablets could be successfully used for the sustained release of Valsartan which has a narrow window of absorption in the stomach or in the upper part of the gastrointestinal tract.

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