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FORMULATION AND EVALUATION OF CONTROLLED RELEASE FLOATING MICROSPHERES OF VALSARTAN

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ABSTRACT The aim of the present investigation was to prepare and evaluate the Valsartan floating microspheres for gastro retentive drug delivery. Eudragit RS 30D, HPMC grades, Guar Gum Sodium alginate and calcium chloride were used as polymers. Fourteen formulations were prepared using Ionotropic gelation technique. All the microspheres were evaluated for particle size, percentage yield, drug entrapment, % buoyancy, in vitro dissolution studies and release order kinetics. Based on the results, the formulation F13 was selected as optimized formulation. *In vitro* drug release study of optimized formulation showed 97.34 after 12 h in a controlled manner. The marketed product shows the drug release of 94.26 within 1 h. Drug and excipient compatibility studies were carried out by FT-IR and no interactions were observed. The SEM of microspheres shows a hollow spherical structure with a rough surface morphology. The drug release of Valsartan optimized formulation F13 followed zero order, Higuchi and Korsmeyer Peppas kinetics indicating diffusion controlled with non fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion.

KEYWORDS : Valsartan, Hypertension, Eudragit, Floating microspheres, HPMC

INTRODUCTION:

Oral delivery of the drug is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulation[1]. These controlled/sustained release preparations using alternative routes have been formulated but the oral route still remains preferable [2]. Gastroretentive Drug Delivery System (GRDDS) have been patented keeping in view its commercial success. To overcome this restriction and to increase the bioavailability of these drugs, controlled drug delivery systems with a prolonged residence time in the stomach can be used [3].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms[4]. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices [5]. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach [6]. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms [7].

Microspheres are multiparticulate drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined rate [8].

Floating drug delivery system (FDDS) promises to be a potential approach for gastric retention. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach [9]. Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs the increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability, and extensive first pass metabolism [6].

Valsartan is an angiotensin II receptor antagonist that is used for the treatment of hypertension. It treat the hypertension by blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II selectively by blocking the binding of angiotensin II and angiotensin I receptor in many tissues. The most preferred route for this drug is oral delivery in form of tablets. Valsartan have poor water solubility, low bioavaibility (approximately 20-25%), and shorter half-life of 6 h [10]. The aim of present work is to design and in vitro evaluation of Valsartan floating microspheres to enhance its bioavailability and prolonged residence time in stomach.

MATERIALS AND METHODS:

Floating microspheres

Formulation of Valsartan Floating microspheres – Formulation design:

Valsartan floating microspheres were prepared using polymers sodium alginate, calcium chloride, HPMC K4M, HPMCK100M, Eudragit RS 30D, Guar gum and sodium bicarbonate using Ionotropic gelation method. Different formulation trials were made using different concentrations of hydrophilic and hydrophobic polymers along with sodium bicarbonate summarized in the **Table 1.**

Table 1: Formulation trials of Valsartan Floating microspheres:

Formulation code	Valsartan (mg)	Sodium alginate	HPMC K 4M (mg)	Sodium bi carbonate (mg)	Calcium chloride	Eudragit RS 30D (mg)	Guar Gum (mg)
F1	80	2.5%	100	25	2.5%	40	10
F2	80	2.5%	125	50	2.5%	45	15
F3	80	2.5%	150	75	5%	50	20
F4	80	2.5%	175	100	5%	55	25
F5	80	5%	200	125	2.5%	60	30
F6	80	5%	225	150	2.5%	65	35
F7	80	5%	250	175	2.5%	70	40
Formulation code	Valsartan (mg)	Sodium alginate	HPMC K 100M (mg)	Sodium bi carbonate (mg)	Calcium chloride	Eudragit RS 30D (mg)	Guar Gum (mg)
F8	80	2.5%	100	25	2.5%	40	10
F9	80	2.5%	125	50	2.5%	45	15
F10	80	2.5%	150	75	5%	50	20
F11	80	2.5%	175	100	5%	55	25
F12	80	5%	200	125	2.5%	60	30
F13	80	5%	225	150	2.5%	65	35
F14	80	5%	250	175	2.5%	70	40

Procedure:

Fourteen formulations of Valsartan floating microspheres were prepared by ionotripic gelation technique using different proportion of polymers as shown in table 1. A solution of sodium alginate is prepared by weighed quantity of sodium alginate, drug (Dose is 80mg of Valsartan) and HPMC K4, HPMC K100 with other polymers were added and was triturated to form fine powder, and then added to above solution. Sodium bicarbonate, a gas forming agent was added to this mixture. Resultant solution was extruded drop wise with the help of syringe and needle into 100ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 minutes the obtained microspheres were washed with water and dried at 60 degrees -2 hours

in a hot air oven and stored in dessicater [11].

Evaluation of Valsartan floating microspheres:
Micromeretic properties like particle size, angle of repose, bulk density, Tapped density, Compressibility index, Hausner's ratio and evaluation parameters like Swelling index, Drug entrapment efficiency and % yield, In vitro dissolution studies and percentage buoyancy studies were performed [1].

In vitro drug release studies:
In vitro drug release studies for developed Valsartan microspheres were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900 ml of 0.1 N HCl at 37± 0.50C temperature at 100 rpm. The amount of drug release was determined at different time intervals of 0, 1, 2, 3, 4, 6, 8, 10 & 12 hours by UV visible spectrophotometer (Shimadzu UV 1800) at 250nm.

Kinetic modeling of drug release:
In order to understand the kinetics and mechanism of drug release, the result of the in vitro dissolution study of floating microspheres were fitted with various kinetic equations like Zero order as cumulative percentage released Vs. time, First order as log percentage of drug remaining to be released Vs. time, Higuchi's model cumulative percentage drug released Vs. square root of time.r^2 and K values were calculated for the linear curves obtained by regression analysis of the above plots. To analyze the mechanism of drug release from the tablets the in vitro dissolution data was fitted to zero order, first order, Higuchi's release model and Korsmeyer – Peppas model.

Drug excipient compatibility studies
The drug excipient compatibility studies like Fourier Transmission Infrared Spectroscopy (FTIR) and SEM were performed.

Stability studies
The stability study of the optimized formulation was carried out under different conditions according to ICH guidelines. The optimized microspheres were stored in a stability chamber for stability studies (REMI make). Accelerated Stability studies were carried out at 40 0C / 75 % RH for the best formulations for 6 months. The microspheres were characterized for the percentage yield, entrapment efficiency and cumulative % drug released during the stability study period.

RESULTS AND DISCUSSION:
All the formulations were evaluated for their various physical parameters like particle size, bulk density, tapped density, angle of repose, Carr's index and found to be within the limits (Table 2).

Table 2: Percentage yield, entrapment efficiency, in vitro cumulative % drug release of Valsartan microspheres

Formulation code	Percentage Yield	Entrapment efficiency	Swelling index	% Buoyancy
F1	81.11%	80.01%	72.14%	82.50%
F2	82.14%	83.26%	74.48%	85.20%
F3	84.22%	85.51%	78.32%	88.56%
F4	86.17%	88.10%	82.63%	89.90%
F5	88.30%	90.18%	86.10%	91.24%
F6	92.34%	93.60%	91.72%	92.50%
F7	93.12%	94.20%	92.82%	93.90%
F8	83.26%	81.20%	81.13%	79.10%
F9	86.52%	83.26%	85.30%	81.40%
F10	87.73%	85.88%	89.25%	85.28%
F11	89.26%	88.24%	90.89%	88.30%
F12	92.40%	92.50%	93.15%	93.56%
F13	96.62%	95.98%	97.80%	98.17%
F14	94.40%	93.98%	92.90%	94.18%

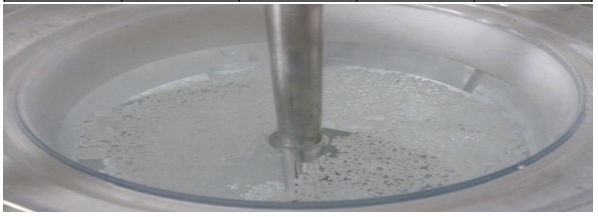


Figure 1: In vitro buoyancy study of Valsartan floating microspheres (F13)

The results of Percentage yield, entrapment efficiency, swelling index and % buoyancy of floating microspheres of all formulations were shown in **Table 2 & Figure 1**. The Percentage yield, entrapment efficiency, swelling index and % buoyancy of F13 was found to be 96.62%, 95.98%, 97.80% and 98.17% respectively.

In vitro drug release studies:
The In vitro drug profile of Valsartan from different formulations was carried and the results are depicted in **Table 3 & 4.** The highest drug release was found in the formulation F13 i.e 97.34%within 12hrs. F13 was found to be optimized formulation based on the dissolution and other evaluation parameters. The in vitro drug release profile from reference standard conventional tablet was found to be 94.26% within 60min.

Table 3: *In vitro* cumulative % drug release of Valsartan floating microspheres F1-F7

Time (h)	F1	F2	F3	F4	F5	F6	F7
0	0%	0%	0%	0%	0%	0%	0%
1	18.08%	20.23%	19.11%	17.08%	21.02%	18.40%	19.56%
2	30.17%	31.15%	28.14%	27.17%	32.13%	27.10%	30.13%
3	37.96%	39.25%	41.96%	38.93%	41.36%	37.71%	40.29%
4	49.68%	48.22%	49.28%	50.28%	51.28%	39.40%	52.13%
6	60.91%	62.35%	58.21%	61.25%	63.11%	53.42%	61.78%
8	72.15%	73.53%	75.32%	70.25%	75.52%	68.21%	74.43%
10	80.90%	82.13%	84.10%	81.10%	84.22%	80.46%	84.21%
12	89.23%	90.25%	92.25%	91.43%	92.73%	91.95%	92.16%

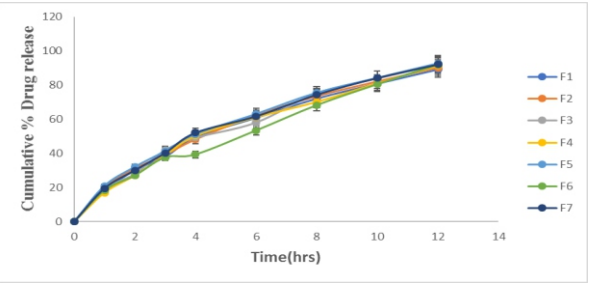


Figure 2: In vitro cumulative % drug release of Valsartan floating microspheres F1-F7

Table 4: *In vitro* cumulative % drug release of Valsartan floating microspheres F8-F13 with Reference standard

Time (h)	F8	F9	F10	F11	F12	F13	F14	Reference standard
0	0%	0%	0%	0%	0%	0%	0%	0
1	17.22%	18.25%	20.11%	19.13%	16.40%	13.80%	16.10%	94.26
2	26.15%	30.15%	32.15%	27.28%	28.13%	26.25%	25.05%	
3	37.23%	43.28%	40.03%	41.22%	40.33%	38.46%	40.41%	
4	47.15%	55.49%	51.23%	50.38%	56.42%	50.15%	52.17%	
6	58.23%	67.11%	62.60%	61.26%	65.18%	61.18%	63.78%	
8	70.32%	72.67%	73.15%	71.66%	77.28%	72.58%	75.28%	
10	79.29%	80.58%	81.02%	83.29%	86.36%	84.19%	83.19%	
12	88.26%	90.92%	91.25%	92.68%	93.16%	97.34%	94.26%	

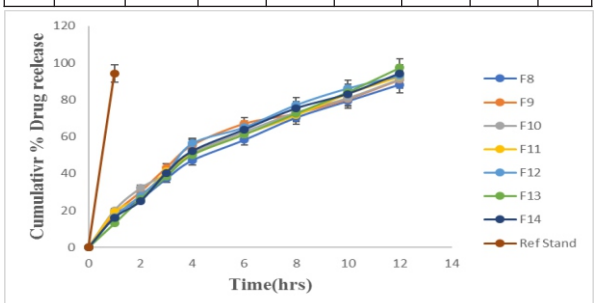
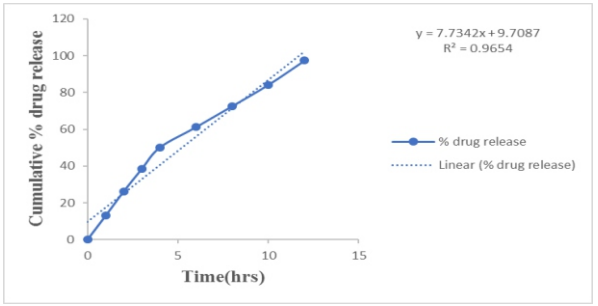
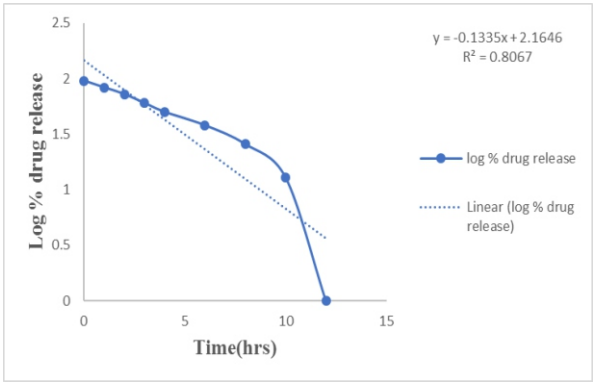


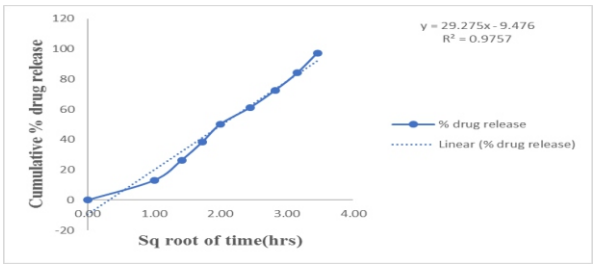
Figure 3: In vitro cumulative % drug release of Valsartan floating microspheres F8-F13 with Reference standard



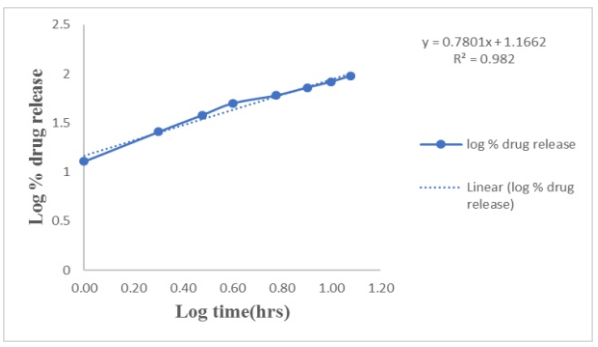
Zero order



First order



Higuchi



Korsmeyer-Peppas

Figure 4: Release order kinetics of Valsartan optimized floating microspheres (F13)

Table 5: Release order kinetics of optimized floating microspheres (F13)

Formulation code	Zero order	First order	Higuchi	Korsmeyer-Peppas	
F13	R^2	R^2	R^2	R^2	n
	0.965	0.806	0.975	0.982	0.780
Reference standard		0.893±0.0619			

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.965 indicates that the drug release follows a zero order mechanism (**Table 5**). This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics.

Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsemeyer-Peppas plots.

The mass transfer with respect to square root of the time has been plotted, revealed a linear graph with regression value close to one i.e. 0.975 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsemeyer-Peppas plots i.e. 0.780 suggest that the drug release from floating tablet was anomalous Non fickian diffusion.

Drug excipient compatibility studies:
Fourier Transform Infrared Spectroscopy (FTIR)

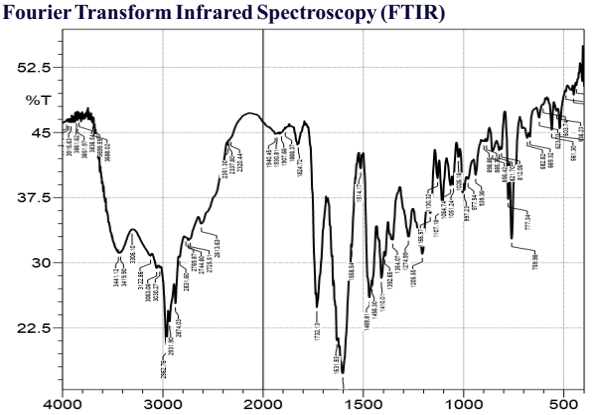


Figure 5: FT-IR spectrum of pure drug Valsartan

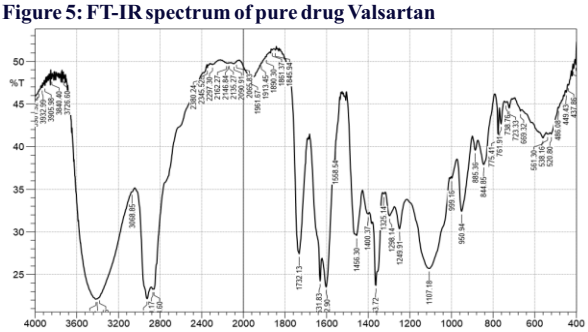
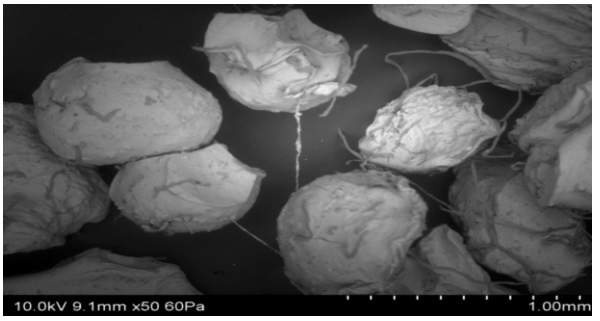


Figure 6: FT-IR spectrum of Valsartan optimized formulation F13

The FTIR spectra of pure Valsartan (Figure 5) displayed bands at 3419.9 cm-1 due to N-H stretch, at 2962.76 cm^{-1} due to C=N stretching, at 1732.13 cm^{-1} due to Carboxylate stretching. The spectra also showed bands at 1631.83 cm^{-1} due to C=O bending at 1107.18 due to C-N bonding. The FTIR spectrum of Valsartan optimized formulation (Figure 6) exhibited characteristic bands consistent with the molecular structure of Valsartan such as bands at 3416.05 cm^{-1} due to N-H stretch, at 2926.11 cm^{-1} due to C=N stretching, at 1732.13 cm-1 due to carboxylate stretching, at 1631.83 cm^{-1} due to C=O bending, at 1107.18 cm^{-1} due to C-N bonding. Thus, the presence of characteristic absorption bands of Valsartan and the Valsartan floating microspheres suggest that there is no interaction takes place between the drug and excipients used in the formulation.

Scanning electron microscopy studies:



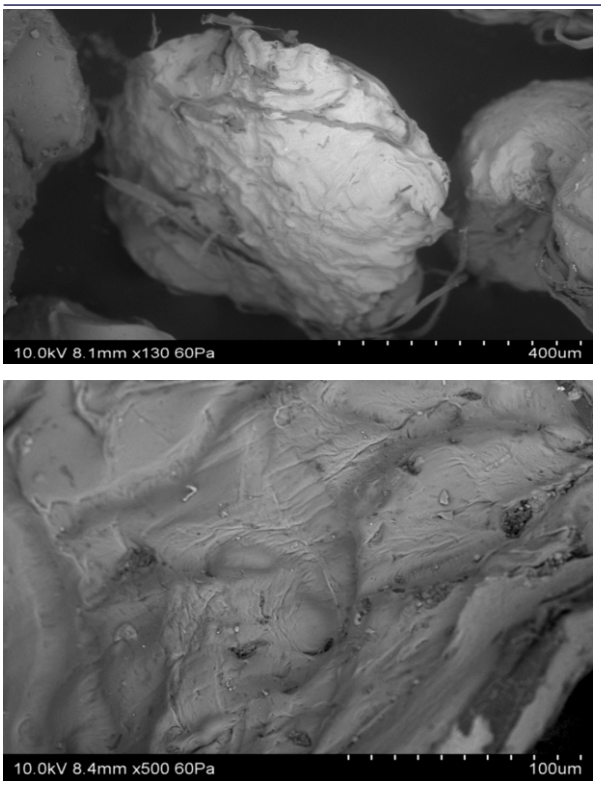


Figure 7: Scanning electron micrograph of Valsartan floating microspheres

The SEM of microspheres shows a hollow spherical structure with a rough surface morphology. Some of microsphere showed dented surface structure but they showed good floating ability on medium indicated intact surface (Figure 7). The shell of microspheres also showed some porous structure it may be due to release of carbon dioxide.

Stability studies:

Optimized formulation F13 was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From the results it was concluded that, optimized formulation is stable and retained their original properties with minor differences.

SUMMARY AND CONCLUSION:

In the present study, an attempt was made to prepare Valsartan floating microspheres, which were characterized for particle size, percentage yield, %drug entrapment, stability studies and found to be within the limits. Among all the formulations F13 was selected as optimized formulation. In vitro release study of formulation F13 showed 97.34% release after 12 h in a controlled manner. The in vitro release profiles from optimized formulations were applied on various kinetic models suggest that the drug release from floating tablet was zero order with anomalous Non fickian diffusion. FT-IR analyses confirmed the absence of drug-polymer interaction. The SEM of microspheres shows a hollow spherical structure with a rough surface morphology. The shell of microspheres also showed some porous structure it may be due to release of carbon dioxide. Optimized formulation F13 was selected for stability studies on the basis of high cumulative % drug release. F13 was stable and retained their original properties with minor differences.

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