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FORMULATION DEVELOPMENT AND EVALUATION OF VALSARTAN FLOATING MICROSPHERES USING PSYLLIUM HUSK POWDER BY MODIFIED EMULSION SOLVENT DIFFUSION METHOD

Boda Veeru Naik[1]*, Balla Rmakrishna[1], Purushothaman M[2]

[1]Glocal University, Mirzapur, Saharanpur, Uttar Pradesh-247001, India.
[2]KLR Pharmacy College, Paloncha, Bhadradri Kothgudadm, Telangana- 507115, India.

ABSTRACT

A sustained release system for Valsartan designed to increase its residence time in the stomach without contact with the Microspheres was achieved through the preparation of floating Microspheres by the Modified Emulsion solvent Diffusion method. In the present study attempt has been made to develop sustained released drug delivery system by formulating the floating Microspheres of Valsartan using psyllium husk powder as a natural polymer which is biodegradable, biocompatible, nontoxic, economically cheap cost, devoid of adverse and side effects and easily availability. Valsartan N-(1-oxopentyl)-N-[[2-(1H-tetrazol-5-yl) [1,1'-biphenyl] -4[-yl] methyl] L Valine used as an Anti-hypertensive agent. The 12 batches of floating Microspheres (VF1 to VF12) were formulated by Modified Emulsion solvent Diffusion method using different ratio of polymers like Psyllium husk power, HPMC K4M and Carbopal. The formulated Microspheres were evaluated by means of different parameters like shape and density of Microsphere, drug content uniformity, Invitro buoyancy, swelling Index, Invitro dissolution studies. The formulation VF7 has better sustained release when compared other formulations, hence we conclude that the combination of Psyllium husk powder, HPMC K4M shows better Gastric retention time which sustains the release of the dosage form.

KEY WORDS: Valsartan, Floating Microspheres, Psyllium Husk Powder, Natural Polymer.

INTRODUCTION

Valsartan chemically N-(1-oxopentyl)-N-[[2-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4[-yl] methyl] L Valine used as an Anti-Hypertensive agent. When dose is missing it may cause nocturnal attack, so attention was made to develop the extended release Microspheres of Valsartan by utilizing hydroxyl propyl methyl cellulose K4M, Carbopol and Psyllium Husk Powder.

To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of Valsartan is desirable. The drug is freely soluble in water and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug. The most commonly used method of modulating the drug release is to include it in a matrix system [1].

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The purpose of controlled release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible. In other words, they are able to exert a control on the drug release rate and duration. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery system because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance [2].

The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems.

Prolonging the gastric residence of a dosage form may be of therapeutic value. Amongst the methods available to achieve this, floating dosage forms show considerable promise [3]. The basic idea behind the development of such a system is to maintain a constant level of drug in the blood

Corresponding Author: - **Boda Veeru Naik Email**: Veerunaikboda@gmail.com

plasma in spite of the fact that the drug does not undergo disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood [4].

Several approaches are used for the formulation of gastroretentive systems such as mucoadhesion, flotation, sedimentation, expansion and modified shape systems. Both single-unit systems (Microspheres) and multiple unit systems (Multiparticulates systems) have been reported in the literature. Among these, FDDS offer the most effective and rational protection against early and random gastric emptying compared to the other methods proposed for prolonging the gastric residence time (GRT) of solid dosage forms.

Extended-release dosage forms with prolonged residence time in the stomach are also highly desirable for drugs that are locally active in the stomach and those are unstable in the intestinal or colonic environment or which have low solubility at higher pH values. FDDS has a lower density than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [5].

Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. Effervescent floating dosage forms prepared with the help of swellable polymers such as methylcellulose and various effervescent compounds such as sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms [6].

The objective of present work was to develop gastro retentive formulation using Psyllium husk powder as a natural polymer which releases drug in the stomach and upper gastrointestinal (GI) tract, and form an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract [7].

Materials and Methods:

Valsartan, HPMC K4M, Carbopol, Sodium Carbonate, Magnesium stearate and talc were obtained from Madras Pharmaceuticals, Chennai. All reagents and solvents used were of analytical grade satisfying pharmacopeial standards

Preparation of gastro retentive floating Microspheres

Floating Microspheres contains were prepared by Modified Emulsion solvent Diffusion technique using variable concentrations of Psyllium husk power, HPMC K4M and Carbopal with sodium bicarbonate. Different Microspheres formulations were prepared by Modified Emulsion solvent Diffusion technique. A solution of Sodium alginate Solution and Psyllium Husk solution is prepared weighed quantity of the sodium-bi-carbonate, Carbopal and HPMCK4 was triturated to form a fine powder, and then added to above solution. Valsartan was missed with the proportionate ratio of sunflower oil to form the drug oil mixture to form the oil phase.

The Valsartan oil phase was added in to the above prepared polymer solution to form the Homogenous solution. The solution was mixed using the Magnetic stirrer at rpm 1500 for about 30 min. Resultant solution was extruded drop wise with the help of syringe and needle into 100 ml 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 desiccators.

Evaluation of Microspheres

Compatibility studies:

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. Drug-excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used.

Percentage Yield:

Percentage yield of different formulation was determined by weighing the floating microspheres after drying. The percentage yields of different formulation were in range of 60.23 – 62.57% as shown in ***table no: 2***and percentage yield for all formulations were almost similar.

Drug Entrapment:

The drug entrapment efficacy of different formulations was in range of 57.52 – 63.70 % w/w as shown in ***table no: 2***. The percentage entrapment of Valsartan was found to be good at all different batches and was similar.

Drug content:

Practical drug loading was determined and the various batches showed in a range of 61.56 -63.60% of the drug content in the microspheres.

Content uniformity:

Content uniformity was determined according to the procedure and it was found that the various batches of floating microspheres were found in the range of 62.75-64.87.

In Vitro dissolution studies

The release rate of Valsartan from floating Microspheres was determined using *The United States Pharmacopoeia* (USP) XXIV dissolution testing apparatus

II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 50 rpm A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 8 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 250 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

In vitro buoyancy studies

The in vitro buoyancy was determined by floating lag time method described by Dave B.S. The Microspheres were placed in 250 ml beaker containing 0.1 N HCl. The time required for the Microspheres to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured.[8] The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Stability Studies on Selected Floating Microspheres Of Valsartan

Valsartan floating microsphere containing combination of Psyllium Husk powder, HPMC and Carbopal (i.eVF7). In order to test the stability of the products, the storage conditions for accelerated testing (as per ICH and WHO) are 40°C±2°C and 75 % RH ± 5% RH for solid dosage forms for 6 months. If the product is unstable in the above testing conditions, intermediate conditions, 30°C ± 2°C /80% RH ± 5% RH are recommended. . WHO prescribed testing at 0, 1, 2, 3- and 6-months during storage.

In the present study, as the formulations developed are solid oral dosage forms, a storage condition of 40^0 C±2^0C, 75 % ±5% RH for 6 months was used for accelerated testing. Floating Microspheres of Valsartan (VF7) were tested for physical observation, hardness, drug content and drug release rate at 0, 1, 3 and 6 months. The floating Microspheres of Valsartan (VF7) were showed the desired, optimum drug release profile, and were hence chosen for further studies. [9]

In each case, 20 Microspheres were packed in screw capped HDPE bottles sealed with aluminium seals and were stored at 40°C/75% relative humidity (RH) in the stability chamber for 6 months. Samples were taken at 0, 1, 3 and 6 months during the testing period and these samples were tested for physical appearance, hardness, drug content [4] and drug release studies [5] as per the methods described earlier

RESULTS AND DISCUSSION:

Percentage Yield, Entrapment efficiency, Drug content and content uniformity of different batches of floating microspheres.

In vitro Buoyancy Study:-

On immersion in 0.1N HCl solution pH (1.2) at 37^0C, the Microspheres floated, and remained buoyant without disintegration.[10] Table 3 shows the results of Buoyancy study shows Buoyancy character of prepared Microsphere.

From the results it can be concluded that the batch containing only HPMC polymer showed good Buoyancy lag time (BLT) and Total floating time (TFT). Formulation containing showed good BLT of 45 sec, while the formulation containing Psyllium powder, drumstick powder (alone) did not float more than 1.5 hrs. This may be due to the nature of polymer and gas generating agent, which were kept constant in the present study.[11] But the different combination of different natural and synthetic polymers gives the greater floating time more than 24 hrs also. The gas generated cannot be entrapped inside the gelatinous layer, and it escapes leading to variation in BLT and TFT.

In-vitro Dissolution Study

All the Nine formulation of prepared floating Microspheres of Valsartan were subjected to invitro release studies these studies were carried out using dissolution apparatus, 0.1N HCL (PH 1.2)

The release data obtained for formulations VF1 to VF12 were tabulated in table 4 and fig no 7.2 shows the plot of cumulative % drug released as a function of time for different formulations. [12] The invitro release of all nine batches of floating Microspheres showed the release with an initial effect. In the first hour % drug released were 22.1, 23.5, 30.1, 28.6, 28. 7, 23.2, 23.5, 30.1, 28.6, 40.2, 36.4 and 33.6 For VF1, VF2, VF3, VF4, VF5, VF6, VF7, VF8, VF9, VF10, VF11 and VF12 respectively.

From the in-vitro dissolution data it was found that formulation VF1, VF2, VF3, VF4, VF5, VF6, VF7, VF8 VF9, VF10, VF11 and VF12released more than 60% of drug before 8 hrs of the study indicating that the polymer amount is not sufficient to control the drug release. [13] While VF1, VF4, VF5, VF6 and VF9 containing all polymers released more than 60% of drug within 8 hr. It concludes VF7 had better controlled release than the other formulation.

Table no 1: - Composition of the Floating microspheres of Valsartan

Formulation Code	Valsartan (mg)	Sodium alginate	psyllium husk	HPMCK4 (mg)	Sodium-bi-carbonate (mg)	Calcium chloride	Oil and polymer Ratio
VF1	0.5	1%	0%	0	25	1%	1:3

VF2	0.5	1.5%	0%	0	75	1%	1:3
VF3	0.5	2%	0%	0	150	1%	1:3
VF4	0.5	3%	0%	0	300	1%	1:3
VF5	0.5	0%	1%	0	25	1%	1:3
VF6	0.5	0%	1.5%	0	75	1%	1:3
VF7	0.5	0%	2%	0	150	1%	1:3
VF8	0.5	0%	3%	0	300	1%	1:3
VF9	0.5	0%	0%	50	25	1%	1:3
VF10	0.5	0%	0%	150	75	1%	1:3
VF11	0.5	0%	0%	200	150	1%	1:3
VF12	0.5	0%	0%	300	300	1%	1:3

Table No 2: Percentage Yield, Entrapment efficiency, Drug content and content uniformity of different batches of floating microspheres.

S.no	Formulation code	Percentage Yield	Entrapment efficiency (% w/w)	Drug content	Content uniformity
1	VF1	62.28	57.52	63.60	62.75
2	VF2	62.43	59.58	61.6	64.11
3	VF3	60.23	62.86	62.25	61.87
4	VF4	60.02	68.50	64.46	65.89
5	VF5	61.64	56.85	62.12	66.12
6	VF6	61.57	60.70	64.86	61.86
7	VF7	60.28	64.52	61.60	64.75
8	VF8	60.43	69.58	65.56	63.11
9	VF9	63.23	58.86	63.25	65.87
10	VF10	63.57	61.50	61.46	61.89
11	VF11	61.64	63.85	62.12	62.12
12	VF12	61.57	67.70	61.86	65.86

Table No 3 :-Buouancy studies of Valsartan Floating Microspheres

S.No	Formulations	Floating Lag time	Floating time
1	VF1	9±0.22	15.00±0.55
2	VF2	15±0.66	14.50±0.47
3	VF3	16±0.24	17.00±0.28
4	VF4	8±0.14	16.50±0.73
5	VF5	11±.44	13.50±0.29
6	VF6	4±033	16.00±0.32
7	VF7	16±0.16	15.00±0.25
8	VF8	12±0.85	17.00±0.77
9	VF9	5±0.22	15.00±0.58
10	VF10	16±0.93	17±0.52
11	VF11	12±0.41	16±0.46
12	VF12	14±0.81	15±0.46

Table no 4 :-Standard calibration curve of Valsartan

Concentration(µg/ml)	Absorbance
0	0
1	0.019
2	0.041
3	0.062
4	0.084
5	0.105
6	0.123
7	0.141
8	0.163

9	0.180
10	0.201
Slope value(b)	**0.020**
R^2 Value	**0.999**

Table No 5:- Release profiles of Valsartan floating Microspheres (VF7) during the stability studies.

Time (Hrs)	Percent of Valsartan released ($\overline{X}$ ± S.D) n=3			
	Before storage	After storage		
		1 Month	3 Months	6 Months
0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
1	27.60±0.15	28.20±0.23	27.26±0.17	26.90±0.28
2	37.55±0.19	37.97±0.41	36.79±0.28	36.50±0.21
3	44.70±0.43	43.62±0.25	44.60±0.33	43.95±0.23
4	54.70±0.28	55.15±0.31	54.85±0.42	55.25±0.28
5	66.15±0.35	66.80±0.18	65.95±0.44	65.16±0.36
6	77.55±0.17	76.75±0.27	77.10±0.29	76.35±0.38
7	84.70±0.58	85.95±0.33	85.40±0.33	83.24±0.18
8	89.00±0.22	90.55±0.24	90.10±0.19	91.25±0.23

Figure no 1 :- Standard Calibration Curve of Valsartan

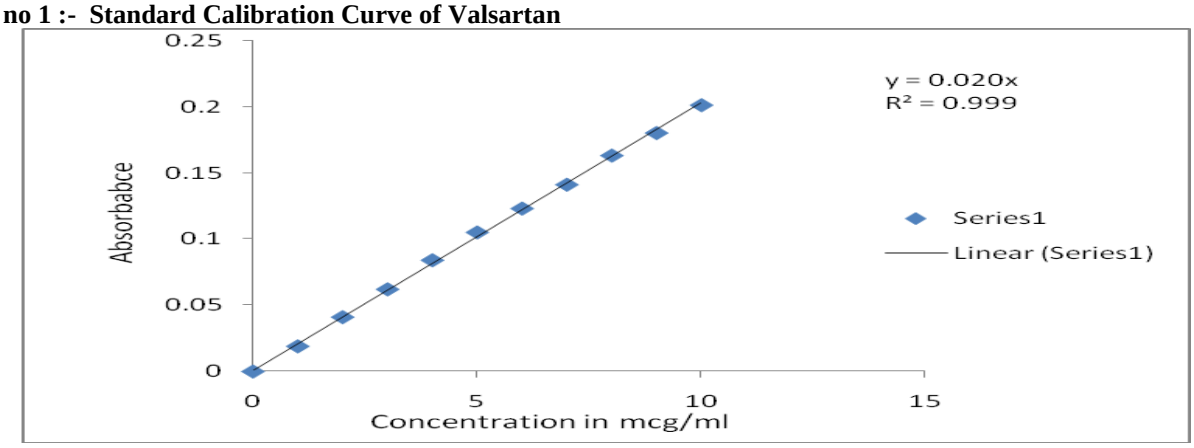


Figure No 2 :- Dissolution of Valsartan floating Microspheres Batches VF1 to VF12.

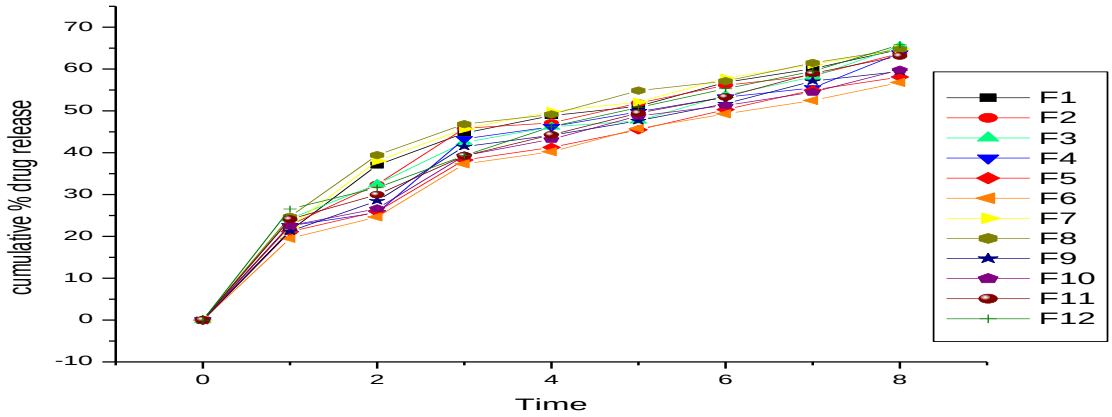
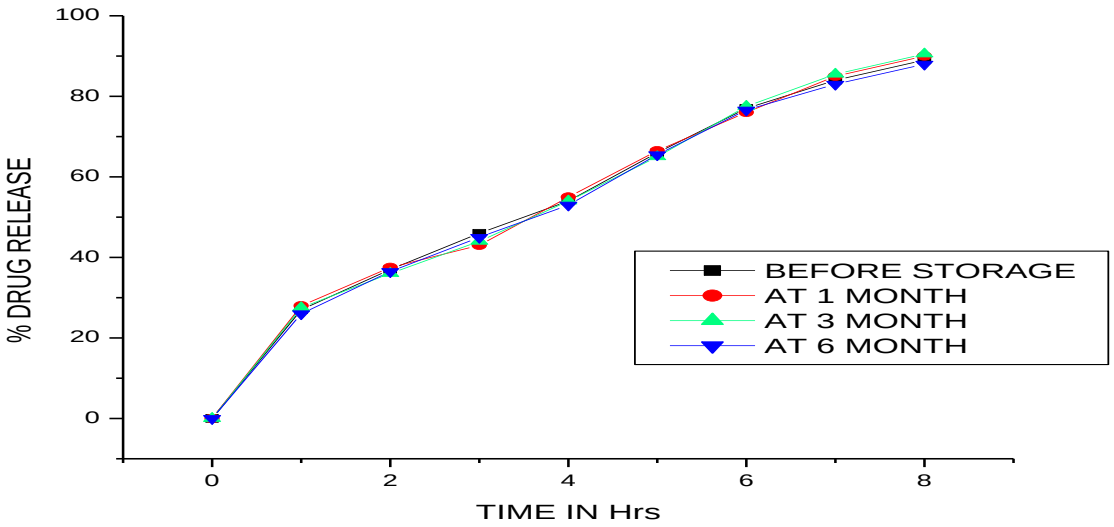


Figure No 3 :- Release profiles of Valsartan floating Microspheres (VF7) during the stability studies.



STABILITY STUDIES ON SELECTED FLOATING MICROSPHERES OF Valsartan

Selected floating Microspheres of Valsartan (VF7) were packed into screw capped container and were stored at40°C and 75% relative humidity (RH) for 6 months.[14] Physical observation and drug release studies were conducted after one month, after 3 months of storage and after 6 months. The stored Microspheres were evaluated for physical changes, drug content and drug release studies were conducted. The results are shown in Tables 4. No color change was observed during the storage.[15] No significant difference was observed in the hardness and drug content between before and after storage of Microspheres for 6 months at 40°C and 75% relative humidity (RH). The drug release profiles of floating Microspheres of Valsartan (VF7) were before and after storage are given in Tables 5 and are shown in Fig. 3. The drug release characteristics of all the Microspheres tested remained unaltered during the storage period.[16] The results thus indicated that formulations were quite stable and the sustained release characteristics of the prepared floating Microspheres remained unaltered.[17] Since the Microspheres were packed into screw capped bottles, this study indicates the protective ability of the screw capped bottle.

CONCLUSION:

It was concluded that the Valsartan floating Microspheres can be formulated using Psyllium Husk Powder with good release profile for a prolonged period of time up to 12 hours. It could decrease the frequency of dose administration, prevent nocturnal attack and improves patient compliance. Further in vivo studied are required to correlate in vitro release data.

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