Research Article

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PREPARATION OF FLOATING MICROSPHERES OF VALSARTAN: *IN-VITRO* CHARACTERIZATION

Avinash Y Kaushik[1]*, Ajay K Tiwari[1], Ajay Gaur[2]

[1]Department of Pharmaceutics, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India

[2]Department of Pharmaceutics, Lachoo Memorial College of Science and Technology, Jodhpur, Rajasthan, India

Received on: 04/08/14 Revised on: 25/09/14 Accepted on: 22/10/14

***Corresponding author**

Mr. Avinash Y Kaushik, Department of Pharmaceutics, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India

E-mail: lavi1191@gmail.com

DOI: 10.7897/2277-4343.06126

ABSTRACT

The objective of the present work was to formulate and characterize floating microspheres of valsartan to improve gastric-retention and provide controlled release with less degradation. Valsartan floating microspheres were prepared by solvent evaporation emulsification method using two polymers ethylcellulose and eudragit in different concentration and two different surfactant poly vinyl alcohol and tween 80. Studies were carried out on floating behavior and influence of type of polymer on drug release rate. *In-vitro* release and stability of formulation were also conducted. The valsartan floating microspheres F4 and F7 formulations followed first order kinetics and F8 formulations followed higuchi drug release kinetics with erosion as the dominant mechanism of drug release. Ethylcellulose with poly vinyl alcohol and eudragit with tween 80 were formulations with good physical appearance. On the basis of results it can be concluded that valsartan floating microspheres prepared by less concentration of polymers given uniform floating microspheres in aspect of particle size, good floating ability and good flow property.

Keywords: Valsartan, Ethylcellulose, Floating, Surfactant

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process.[1] Oral drug delivery systems can be classified into three categories like; immediate release preparations, targeted release preparations and controlled release preparations.[2] Gastric retention is an approach to overcome the several problems associated with the oral formulations such as; first pass metabolism, ionization in gastric pH etc.[3] Floating microspheres are the systems which are based on the concept of low density system to provide gastric retention to the drugs having instability problem in intestinal medium.[3] It can be formulated by using gas generating agents or hydrocolloids (swelling agents).[4] Valsartan is an angiotensin receptor antagonist, which is latest category after angiotensin converting enzyme inhibitors.[5] It has several characteristics which are suitable for the formulation of floating drug delivery system. It has bioavailability of 25 % and has small dose (40 to 160 mg/day on the basis of severity).[6] The dissociation constant is also 4.9 which is a characteristic of valsartan favor its fabrication in controlled and floating drug delivery systems.[7] Valsartan has some additional advantages over other anti-hypertensive drugs that it may also help in diabetic patients (1 %).[8] Valsartan is already formulated for the other floating dosage forms such as; floating tablets and floating beads.[9,10] The floating microspheres have many advantages over those dosage forms such as no risk of dose dumping, increase solubility due to micron size etc.[11] We have utilized eudragit and ethylcellulose as hydrocolloids (swelling polymer) and formulation of floating microspheres were formulated using solvent evaporation extraction method which is most simple and of high yield method. We studied the effect of two different surfactants (poly vinyl alcohol and tween 80) on formulations.

MATERIAL AND METHODS

Valsartan was obtained from Alembic Pharmaceuticals Ltd. as a gift sample. Eudragit (Chemdyes Ltd, India), Ethylcellulose (Chemdyes Ltd, India), Poly vinyl alcohol (Chemdyes Ltd, India), Tween 80 (Merck Specialties P Ltd, India), Dichloromethane (Merck Specialties P Ltd, India) and Ethanol (Merck Specialties P Ltd, India) were of analytical grade and purchased for carrying out various experiments.

Preparation of ethylcellulose and eudragit based floating microspheres

The floating microspheres were formulated by solvent evaporation emulsification method. In this ethylcellulose/eudragit and active pharmaceutical ingredient were dissolved in dichloromethane and ethanol (1:1) solution to prepare solution A. Solution B was prepared by mixing tween 80/poly vinyl alcohol as surfactant in water. Solution A was constantly mixed in solution B drop wise with continuous stirring at 1000 rpm for three hours with continuous heating at 60^{o}C. After that prepared microspheres were separate out by filtration of mixture and dried at room temperature.[12] (Table 1)

Evaluation of Prepared Floating Microspheres
Compatibility study between drug and polymer using infrared spectrum

Drug with different polymer in 1:3 were mixed. These prepared samples were mixed with potassium bromide in 1:5 ratio and pallets were prepared for evaluation. Then the samples were evaluated in infra-red spectroscope and spectrums were compared with the infra-red spectrum of pure drug.[13]

Percentage yield

The percentage yield of different formulations was determined by weighing the floating microspheres after drying and comparing with total weight of drug and polymer required to formulate those formulations.[14] The percentage yield was calculated as follows.

% Yield = Total weight of floating microspheres / Total weight of drug and polymer x 100

Entrapment efficiency

The various batches of the floating microspheres were subjected to estimation of drug content. The floating microspheres equivalent to 50 mg of Valsartan from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved in ethanol (5 ml) in volumetric flask (100 ml) and made the volume with 0.1 N HCl. This solution is then filtered through Whatmann filter paper No. 45. After filtration, the sample was observed in UV spectrophotometer and the absorbance was measured at 249 nm against 0.1 N HCI as a blank.[15] The percentage drug entrapment was calculated as follows.

% Drug entrapment = Calculated drug concentration / Theoretical drug concentration x 100

Floating lag time and floating time of microspheres

Floating microspheres (50 mg) were placed in 0.1 N HCI (100 ml) containing 0.02 % Tween 20. The mixture was stirred at 100 rpm in a magnetic stirrer. The time taken by the microspheres start floating was noted down as floating lag time and the floating ability of microspheres were observed up to 24 hours.[16]

Micromeretics of floating microspheres
Angle of repose

It is a technique to determine the flow property of microspheres. In this technique, Microspheres were filled in the funnel and were dropped from a specific height. The height and the radius of the of generated cone to calculate the angle.[17]

$$\Theta = \tan^{-1} h/r$$

Where h is height of cone and r is radius of circle.

Hausner ratio

The Hausner ratio is a number that is correlated to the flow-ability of a powder or granular material. It is named after the engineer Henry H. Hausner (1900–1995). The Hausner ratio is calculated by the formula;

$$H = \rho T/\rho B$$

Where ρB is the freely settled bulk density of the powder, and ρT is the tapped bulk density of the powder.[17]

Carr's compressibility index

Carr's compressibility index is an indication of the compressibility of a powder. It is named after the pharmacologist Charles Jelleff Carr (1910–2005). It measures the relative significance of inter-particle interactions. The Carr index is calculated by the formula;

$$C = 100 \text{ X } (1 - \rho B/\rho T)$$

Where ρB is the freely settled bulk density of the powder, and ρT is the tapped bulk density of the powder.[17]

***In-vitro* dissolution study**

In vitro dissolution study was performed in paddle type dissolution apparatus of Veego Instruments Corporations, India. Accurately weighed microsphere equivalent to 40 mg of valsartan were taken in gelatin capsule and placed in dissolution vessels. Dissolution study was carried out in 900 ml 0.1 N HCl (pH 1.2) at 100 rpm at temp 37 ºC ± 0.5 ºC. During dissolution study 10 ml aliquot was withdrawn at a time intervals of 0.5 to 24 h and same was replaced with equal volume of fresh medium. The withdrawn samples were filtered through Whatmann filter paper and Absorbance's were measured at 249 nm. Drug concentration in the samples was determined from the standard calibration curve. Cumulative percent of drug released was found out at each time point.[18]

Size, shape and surface morphology of floating microspheres

This study was performed by microscopy using scanning electron microscope of Carl Zeiss P Ltd, India at University Science Instrumentation Centre, University of Rajasthan, Jaipur, India. In this, the microspheres of final selected formulations were coated with gold by ion sputtering. The microspheres were kept on the sample holder and the scanning electron micrographs were taken at different scale.[19]

Kinetic studies

The *in vitro* release data obtained was treated to zero order kinetics, first order kinetics, higuchi model and korsemeyer peppas model to know precisely the mechanism of drug release of the floating microspheres.[20]

Stability study

A study of stability of pharmaceutical product is essential. These studies were designed to increase the rate of

chemical and physical degradation of the drug substance or product by using exaggerated storage condition. Optimized formulations were packed in amber colored bottles, which were tightly plugged with cotton and capped. They were then stored at 45 ± 2°C / 75 ± 5 % relative humidity for 3 months and evaluated for the physical appearance and drug content, % buoyancy and entrapment efficiency at specific interval of time. Finally, at the end of 3 months and *in vitro* release studies were also conducted.[21]

RESULTS AND DISCUSSION

In this study the formulation containing eudragit and poly vinyl alcohol was also not formulated due to its melting ability at low temperature between 45-60° C and form film with poly vinyl alcohol on drying in Petri-dish. Ethylcellulose formulations with tween 80 were formulated but were not in shape and has sticky in nature. The final formulations accepted for the evaluation batches were formulation of ethylcellulose microspheres with 0.75 % poly vinyl alcohol and eudragit microspheres with tween 80 as surfactant.

Drug excipients compatibility study

As per the IR spectrum and physical appearance, the result showed that there was no evidence of valsartan and polymer interactions which allow us to formulate the formulations with this polymer and drug. (Figure 1-3)

Percentage yield

Percentage yield was found to be between 84.37 ± 2.41 to 93.15 ± 1.94. It shows that the utilized method provides good yield of microspheres. (Table 2)

Entrapment efficiency

The entrapment efficiency was observed and found to be between 69.45 ± 1.10 and 81.67 ± 1.68. As per the results, it has been observed that the formulation with high concentration of polymer has high entrapment efficiency. (Table 2)

Floating lag time and floating time of microspheres

Floating lag time is the time required for the floating of more than 90 % microspheres, was noted down and found to be 11 ± 1.63 to 128 ± 3.78 seconds and the floating time was found to be more than 24 hours for all formulations (except F3) in which more than 90 % microspheres float on the surface of simulated gastric fluid this is due to the ability of polymers to swell after contacting with simulated gastric fluid. (Table 2)

Micromeretics of floating microspheres (Table 3)

Angle of repose

Angle of repose of final formulations were found to be in range of 24°58' to 41°54'. The flow property of F4, F7 and F8 shown its excellent/good flow property of floating microspheres. This feature of excellent flow helped in flow of microspheres through hopper. (Table 3)

Carr's compressibility index

Carr's index was found to be in range of 7.31 ± 0.03 to 17.24 ± 0.12. The index of F4, F6, F7 and F8 shown excellent and good flow property range. (Table 3)

Hausner ratio

Hausner ratio also provided an evidence of good flow properties by resulting in range of 1.07 to 1.21. The F5 and F9 were the exception which did not provide the good flow property. (Table 3) The F4, F7 and F8 were the formulations which had best flow property over other formulations.

In-vitro release study

In-vitro release was studied through the dissolution of 40 mg valsartan microspheres. Cumulative % drug release was calculated for all the formulation and compared. The release profile was compared and F4 formulation shown maximum release in constant manner till 24 hours and near 24 hours it released in controlled manner. Formulations prepared by using eudragit were analyzed for *in-vitro* release study and results showed that F7 and F8 formulations were better than F9 due to higher release (more than 90 %) in 24 hours. All formulations were analyzed for the above evaluation parameters and formulation F4, F7 and F8 were considered as final formulations. (Table 4)

Size and shape floating microspheres

The F4 formulations had smoother surface and spherical in shape when observed in scanning electron micrographs. The size of ethylcellulose microspheres had 1-30 µm size which is smallest and in required range. (Figure 6)
In case of eudragit based formulations, F7 and F8 formulations were also observed for size and shape with the help of scanning electron micrographs. F7 and F8 microspheres were found to be spherical in shape. Sizes of F8 microspheres were varying between 2–30 µm but in case of F7 microspheres size has increased between 5-200 µm. (Figure 7,8)

Release kinetics of final formulations

Drug release mechanism and kinetic are the two important characteristics of a drug delivery system in describing drug dissolution profile. As shown results r^2 values for different kinetics model, F4 (r^2 - 0.9956) and F7 (r^2 - 0.9763) followed first order kinetics which showed that the release of drug from floating microspheres were dependent to the concentration and F8 followed the higuichi model on the basis of r^2 value 0.9940, which shows that release of drug from formulation follows diffusion mechanism. Release mechanism of formulation F4 (r^2 - 0.9894, n - 1.632), F7 (r^2 - 0.9612, n - 1.634) and

was F8 (r^2 – 0.9901, n – 1.648) followed the polymeric chain erosion mechanism it was calculated on the basis of korsmeyer peppas model. (Table 5)

Stability study

Stability study was performed on all three formulations for three months at accelerated conditions. Results obtained after three months study were satisfactory. There was no change in size, shape and colour. The releases of formulations were also more than 90 % in 24 hours at the end of three months which shows that the formulations F4, F7 and F8 were stable and can be utilized for the further industrial formulation development.

Table 1: Composition of Floating Microspheres of valsartan

FORMULATIONS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ethylcellulose*	1%	2%	3%	1%	2%	3%	-	-	-	-	-	-
Eudragit RS100*	-	-	-	-	-	-	1%	2%	3%	1%	2%	3%
Poly Vinyl Alcohol*	-	-	-	0.75%	0.75%	0.75%	-	-	-	0.75%	0.75%	0.75%
Tween 80**	1%	1%	1%	-	-	-	1%	1%	1%	-	-	-
Drug : Polymer	1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2	1:3
Ethanol : DCM	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1

* Concentration in % w/v, **In case of Tween 80 % v/v

Table 2: Percentage yield, entrapment efficiency, floating lag time and floating time of all formulations, where n = 3

Formulation	Parameters			
	Percentage yield (%)	Entrapment efficiency (%)	Floating lag time (Seconds)	Floating time (Hours)
F4	84.37 ± 2.41	78.31 ± 3.88	11 ± 1.63	>24
F5	88.72 ± 0.89	69.45 ± 1.10	40 ± 1.14	>24
F6	86.97 ± 1.91	79.81 ± 2.18	128 ± 3.78	≈18
F7	86.61 ± 0.43	72.71 ± 1.89	17 ± 0.25	>24
F8	93.15 ± 1.94	74.82 ± 3.03	28 ± 4.57	>24
F9	92.62 ± 1.53	81.67 ± 1.68	26 ± 2.78	>24

Table 3: Micromeretics of prepared formulations

Formulation	Angle of Repose	Bulk Density	Tapped Density	Compressibility Index	Hausner Ratio
F4	24°58’	0.41 ± 0.03	0.44 ± 0.02	7.31 ± 0.03	1.07
F5	35°48’	0.48 ± 0.14	0.58 ± 0.10	17.24 ± 0.12	1.21
F6	41°54’	0.54 ± 0.18	0.59 ± 0.11	8.48 ± 0.21	1.09
F7	25°41’	0.47 ± 0.03	0.52 ± 0.02	10.63 ± 0.03	1.11
F8	33°50’	0.49 ± 0.01	0.54 ± 0.01	10.20 ± 0.02	1.10
F9	38°67’	0.52 ± 0.12	0.61 ± 0.08	14.76 ± 1.09	1.17

Table 4: Mean of Cumulative percentage drug release of prepared formulation, where n = 3

S. No.	Time (H)	%CDR ± SD (F4)	%CDR ± SD (F5)	%CDR ± SD (F6)	%CDR ± SD (F7)	%CDR ± SD (F8)	%CDR ± SD (F9)
1.	0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
2.	0.5	13 ± 1.2	7 ± 1.7	8 ± 0.6	12 ± 0.6	10 ± 0.6	6 ± 0.6
3.	1	20 ± 2.5	13 ± 0.6	14 ± 1.5	24 ± 0.6	18 ± 0.6	18 ± 0.6
4.	2	28 ± 2.1	19 ± 1.0	20 ± 1.7	37 ± 1.5	27 ± 1.5	29 ± 0.6
5.	4	42 ± 0.6	33 ± 1.2	31 ± 1.2	51 ± 1.5	41 ± 1.5	45 ± 1.5
6.	8	62 ± 2.5	56 ± 1.7	47 ± 0.6	70 ± 2.0	60 ± 1.0	66 ± 3.2
7.	12	73 ± 1.5	69 ± 2.6	59 ± 1.2	80 ± 2.1	74 ± 0.6	73 ± 2.6
8.	18	84 ± 1.0	81 ± 1.6	69 ± 1.2	87 ± 2.1	89 ± 0.6	79 ± 0.6
9.	24	91 ± 2.0	88 ± 1.0	75 ± 1.5	92 ± 1.5	96 ± 1.0	83 ± 1.0

Table 5: Regression values (r^2) for all kinetic models for F4, F7 and F8

Formulations	Zero order kinetics r^2	First order kinetics r^2	Higuichi model r^2	Korsmeyer peppas model	
				r^2	n
F4	0.8820	0.9956	0.9932	0.9894	1.632
F7	0.8100	0.9763	0.9529	0.9612	1.634
F8	0.9088	0.9909	0.9940	0.9901	1.648

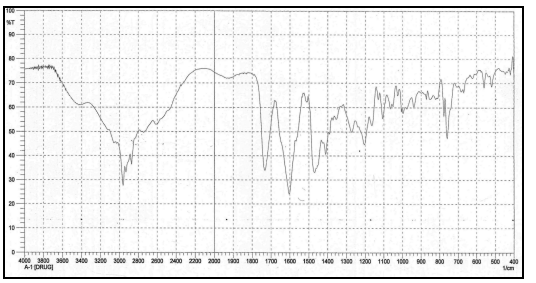

Figure 1: IR spectrum of pure drug (valsartan)

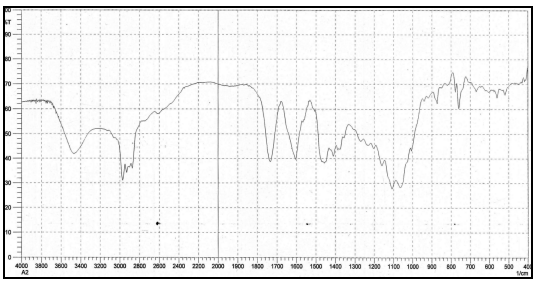

Figure 2: IR spectrum of mixture of drug (valsartan) and ethylcellulose

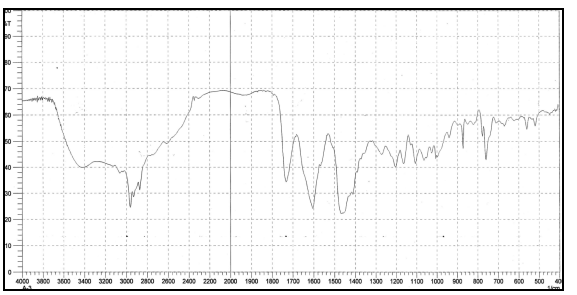

Figure 3: IR spectrum of mixture of drug (valsartan) and eudragit

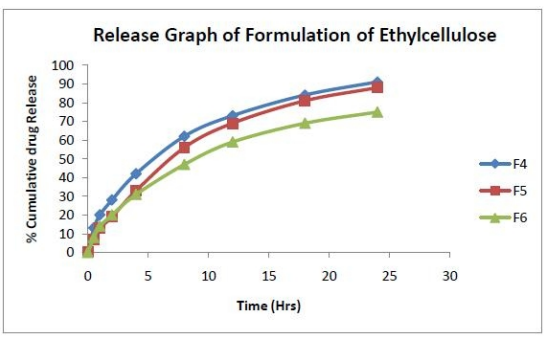

Figure 4: Dissolution release profile of ethylcellulose based formulations

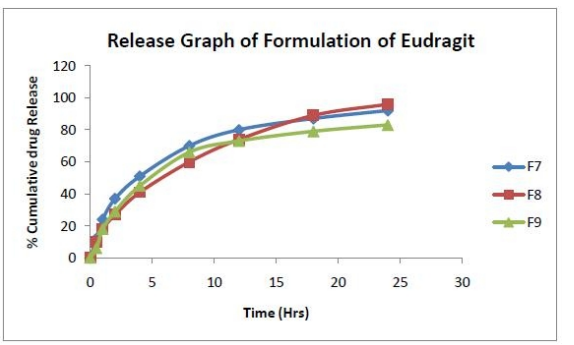

Figure 5: Dissolution release profile of eudragit based formulations

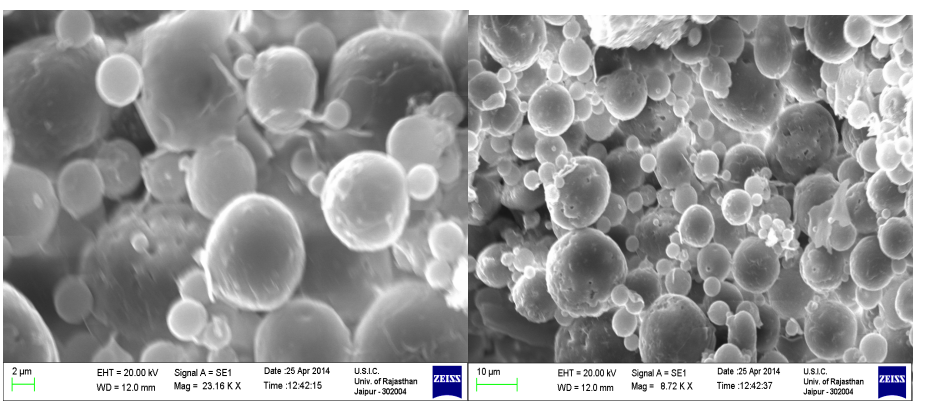

Figure 6: Scanning electron micrographs of F4 formulation

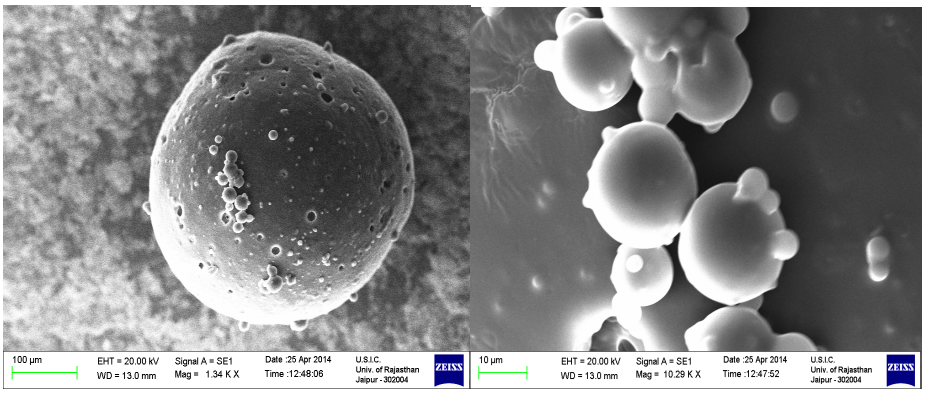

Figure 7: Scanning electron micrographs of F7 formulation

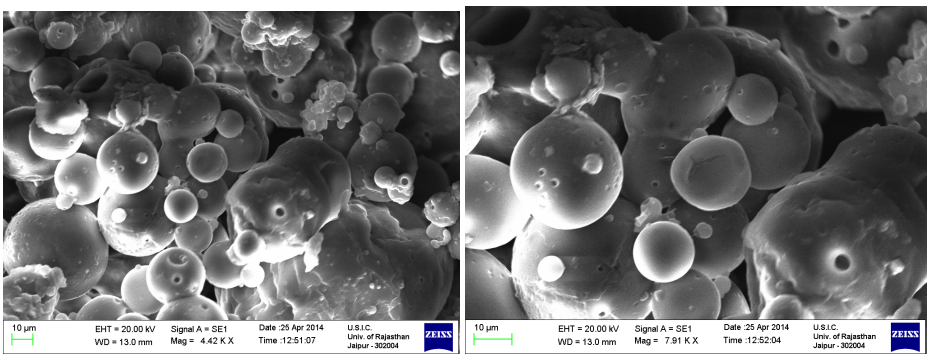

Figure 8: Scanning electron micrographs of F8 formulation

CONCLUSION AND FUTURE PROSPECTS

The floating microspheres of valsartan were prepared by both polymers eudragit and ethyl cellulose but we have different efficiency with poly vinyl alcohol and tween 80. The formulations prepared of eudragit and ethyl cellulose were evaluated. The formulation of ethylcellulose : tween 80 and eudragit : poly vinyl alcohol are rejected due to their sticky nature and melting property respectively. The stirring speed around 500 rpm causes increase in particle size of floating microsphere and also the concentration of polymers affect the entrapment efficiency and floating property of prepared formulation. The F4, F7 and F8 formulations were considered to be final with all good properties including floating ability and continuous release till 24 hours. These formulated dosage forms can also be compared with the marketed formulations and further in vivo - in vitro correlation and *in-vivo* study can be performed for future purpose. At the end, the formulations showed good stability data for three months which can be extended to develop a cheap commercial dosage form to increase the oral bioavailability by controlled release of valsartan.

ACKNOWLEDGEMENT

The authors are grateful to University of Rajasthan, India for providing scanning electron microscope facility for particle size and shape study and Alembic Pharmaceuticals Ltd. for gift sample of valsartan.

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Cite this article as:
Avinash Y Kaushik, Ajay K Tiwari, Ajay Gaur. Preparation of floating microspheres of Valsartan: In-vitro characterization. Int. J. Res. Ayurveda Pharm. 2015;6(1):124-130 http://dx.doi.org/10.7897/2277-4343.06126

Source of support: Nil, Conflict of interest: None Declared