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Original Article

Development and Evaluation of Gastroretentive Floating Microspheres of Valsartan.

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Abstract

Valsartan, a widely prescribed anti-hypertensive drug which is belongs to BCS class II. It shows absorption window in stomach area, which makes it a good candidate for gastro retentive dosage forms. The floating microspheres release the drug in the stomach and upper part gastrointestinal tract and thereby improve the bioavailability (25%). In the present study, nine formulation of valsartan were prepared as a gastroretentive floating microspheres by non aqueous solvent diffusion method using polymers such as ethyl cellulose (EC) and hydroxypropylmethylcellulose (HPMC K100M and HPMC K15M) in different concentration. The prepared microspheres were evaluated for different physicochemical tests such as characterization of drug polymer complex, particle size, percentage yield, percentage buoyancy, entrapment efficiency and *in vitro* release. The results of all the physicochemical tests of all formulations were found to be satisfactory. The formulation F6 is an optimized formulation. The FTIR confirmed the drug polymer complex. The average particle size of this formulation is 194.35µm, percent buoyancy were 90.15%, percent drug entrapment 94.25% and drug release up to 12 hrs is 89.64% shows better than other formulation. Developed formulation of floating microspheres can be used for prolonging its retention in the stomach for at least 12 hours, thereby improving bioavailability and patient compliance. The gastroretentive floating microspheres is a potential new delivery system for treatment of hypertension.

Keywords: Valsartan, gastroretentive floating microspheres, hydroxypropylmethylcellulose (HPMC), ethyl cellulose (EC).

Introduction

Oral route has been the most popular and successfully used route for controlled delivery of drugs due to some reasons like convenience, ease of production, ease of administration and low cost of such system[1]. Gastroretentive drug delivery systems (GRDDS) are a topic of interest within pharmaceutical formulation development for more than 40 years. Gastro retentive drug delivery system is oral drug delivery system in which dosage form is designed in such manner which can retained in the stomach to give controlled and sustained release of drug.

In another way gastroretentive drug delivery system is dosage form which enhances gastric residence time (GRT) and release drug without affecting the intrinsic rate of gastric emptying for several hours[2].

Several approaches have been proposed to retain the dosage forms in the stomach. Several techniques such as floating drug delivery system, low density systems, raft systems, mucoadhesive systems, high density systems, superporous hydrogels and magnetic systems have been employed. These methods include bioadhesive system, swelling system, expanding system, raft forming system, magnetic system, superporous hydrogels and floating system[3].

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Floating drug delivery system (FDDS) is low density systems that have sufficient buoyancy to float over the gastric content and remain buoy and in the stomach without affecting a gastric emptying rate for desire period of time. While the system is floating on gastric content, the drug is released slowly at desire rate from the system[4]. As in floating drug delivery formulation retain in stomach and increase residence time in stomach so it need to have a good fundamental understanding of the anatomic and physiological characteristics of the human stomach. Gastroretentive floating microspheres are drug delivery systems based on non-effervescent approach. Hollow microspheres are spherical shape particles and that particle core is empty [5, 6].

Valsartan is antihypertensive drug belonging to the family angiotensin II type I receptor antagonist. It mainly used in treatment of cardiac conditions including hypertension, diabetic nephropathy and heart failure. Valsartan has short Biological half-life (6 hrs) and bioavailability (25%). Valsartan is having the pKa 4.7. It is largely present in unionized form in acidic pH. Thus valsartan well absorbed from the acidic pH of the stomach than the basic pH condition of intestine [7, 8].

Materials and Methods

Materials

Valsartan was obtained as a gift from Wockhartd pharmaceuticals Ltd. (Aurangabad, India). HPMC K15M, HPMC K100M was obtained from Balaji Drugs. Surat, Gujrat. Ethanol, Dichloromethane was obtained from Research-Lab Fine Chem. Industries, Mumbai (India). All other reagents and solvents used were of pharmaceutical or analytical grade. USP dissolution apparatus, Mechanical stirrer (Remi India), FT-IR (Shimadzu Corp 00397, Japan) and UV-Visible spectrophotometer (UV-3000+, Lab, India Ltd) were the instruments employed in the current study.

Preformulation Study

Identification and Characterization of Drug:

The sample of Valsartan was studied for organoleptic properties such as colour, odour and appearance, melting point.

FTIR spectral studies:

FTIR spectral data were taken with a Bruker (Alpha series, Germany) instrument to study the structure of the drug as well as to find the chemical stability of drug with polymers. FTIR spectra of drug were obtained by it mixing with KBr to get pellets under a pressure of 600 kg/cm^2. Spectral scanning was done in the range between 4000 and 500 cm^{-1}.

Differential Scanning Calorimetry (DSC):

Differential Scanning Calorimetric studies of pure Valsartan samples were carried out at the 10^0C/min between temperature range 30^0C-300^0C under a nitrogen flow of 2-bar pressure.

UV Spectrophotometry:

UV spectrum of Valsartan solution in distilled water was scanned at 400 to 200 nm. The wavelength of maximum absorption (λ max) was determined.

Calibration Curve of Valsartan:

Accurately weighed 10 mg of Valsartan was transferred to 100 ml of volumetric flask and volume was made up to the mark with 0.1 N HCL pH 1.2 to obtained strength of 100mcg/ml. This was further diluted to give the solutions of concentration 2-20 mcg/ml. these solutions were measured for absorbance on UV spectrophotometer, plotted against the concentration to give the standard calibration curve**.**

Method of Preparation

The floating microspheres of Valsartan were prepared by Non aqueous solvent diffusion method. Drug (Valsartan) and polymers (Ethyl Cellulose, HPMC K15M and HPMC K100M) were mixed in ethanol and dichloromethane (ratio 1:1) by using blending solvent e.g. Isopropyl alcohol. The prepared slurry was introduced slowly into 200ml of liquid paraffin while being stirred at 1000 rpm by mechanical stirrer (paddle type) for 2 hours at room temperature. To allow for solvent evaporate completely and the microspheres were collected by filtration. For removal of oil the collected floating microspheres repeatedly washed with petroleum ether. The collected microspheres were dried for 2 h at room temperature[9, 10]. Formulation batches of drug and polymer were shown in the table 1.

Evaluation Of Gastroretentive Floating Microspheres

Confirmation of drug: polymer complex[11]

Confirmation of Drug: polymer complex was done using Fourier transform infra red (FTIR) studies.

FTIR Studies: drug- polymer complex formation was confirmed by FTIR studies. The IR spectrum of valsartan loaded microspheres was determined. In spectra observed functional groups. Sample preparation involved mixing of the sample with potassium bromide (KBr), triturating in glass mortal and finally placing in sample holder. Using KBr pellets as a blank sample were scanned over frequency range of 4000-400 cm^1.

Particle size analysis[12]

Determination of average particle size of floating microspheres of valsartan was carried by Motic microscope. A small quantity 50-100 number of microspheres were spread on clean glass slide and average particle size was determined in each batch.

Micromeritic properties of microspheres

The floating microspheres are characterized by their micromeritic properties such as bulk density, compressibility index, Hausner's ratio and angle of repose.

Percentage yield of microsphere[12,13]

Percentage of practically found gastroretentive floating microspheres of valsartan is calculated to know about percentage yield or methods efficiency used in formulation, thus it helps in selection of appropriate method of production. Microspheres were completely dried in an oven and maintained at 37^0C for 24 hrs and then weight. Practical yield was calculated as the weight of microspheres recovered from each batch in relation to sum of starting material. The percentage yield of prepared floating microspheres of valsartan was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Weight of microspheres}}{\text{Weight of drug and polymers}} \times 100$$

Percentage buoyancy[14, 15]

Floating microspheres were dispersed in 900ml of 0.1N hydrochloric acid solution (pH 1.2) containing tween 80 (0.01 W/V %) / tween 20 (0.02 W/V %) to simulate gastric fluid at 37^0. The mixture was stirred with a paddle at 100 rpm and after 12 hr, the layer of buoyant microspheres (W_f) was pipette and separated by filtration simultaneously sinking microspheres (W_s) was also separated. Both microspheres type were dried at 40^0C overnight. Both the fraction of calculated by the weight ratio of floating particles to the sum of the floating and sinking particles, as per the following formula:

$$\text{Percentage buoyancy (\%)} = \frac{\text{Weight of microspheres floated on medium}}{\text{Weight of total microspheres taken}} \text{ x } 100$$

Determination of percentage drug entrapment [16, 17]

The various batches of the floating microspheres of valsartan were subjected to estimation of drug content. 80 mg of drug equivalent floating microspheres from all batches were accurately weight 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. Then solution filtered through Whatmann filter paper. After filtration, the sample was observed in UV spectrophotometer and the absorbance was measured at 249 nm 0.1 N HCL as a blank. The percentage drug entrapment was calculated as follows.

$$\text{Drug entrapment}(\%) = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \text{ x } 100$$

In vitro dissolution study [18, 19]

In vitro dissolution study was performed dissolution apparatus USP dissolution tester. Accurately weighed microspheres equivalent to 80 mg of valsartan were taken in gelatin capsule and placed in dissolution jar. Dissolution study was carried out in 900 mi (pH 1.2) 0.1 N HCL at 100 rpm at temp 37^0C ± 0.5^0C. The sample was withdrawn with 1 hr intervals up to 12 hours. The Aliquots were withdrawn and the same volume of fresh medium was refilled for the maintenance of sink condition. The withdrawn samples were filtered absorbance was measured. Drug concentration in the sample was determined from the standard calibration curve.

Release kinetics[19]

In order to establish the mechanism of drug release the in-vitro drug release data was fitted to four popular exponential equations (zero order, first order, Higuchi and Kosermeyer Peppas)

Results and Discussion

Preformulation study:

In Preformulation study, Valsartan was identified by performing official identification tests as per I.P& U.S.P. Model drug was characterized such as color, odor, appearance and melting point. The results are presented (Table 2). The estimation of valsartan was carried out by Waters UV spectrophotometer at λ max 258 nm using 0.1 N HCL as solvent (table 3) and UV spectra and absorbance curve shown in figure 1 and 2 respectively, which had a good reproducibility and this method was used in the entire study. The FTIR (figure 3) and DSC (figure 6, 7)) spectra of pure valsartan were presented. The FTIR spectra revealed that, there was no interaction between polymers and valsartan. The polymers were compatible with the valsartan.

Evaluation of floating microspheres of Valsartan:

An attempt was made to prepare floating microspheres of valsartan by non aqueous solvent diffusion techniques using polymers like HPMC K15M, HPMC K100M and EC achieve an oral controlled release of the valsartan. In the present study nine formulations were formulated by using HPMC K15M, HPMC K100M and EC in various proportions. All the formulations were subjected to evaluation. FTIR, Motic microscopy, particle size, percentage yield, percentage drug entrapment, buoyancy time, *in vitro* dissolution study and release kinetics had shown satisfactory results.

FTIR spectra were obtained for Valsartan pure drug, physical mixture of Valsartan and polymer and Valsartan floating microspheres (figure 3, 4, 5) were presented in the figure, the characteristic peaks of the Valsartan were compared with the obtained formulation. The principle peaks for the formulation were almost similar to that of drug.

Determination of Average Particle Size:

The size and shape analyses of floating microspheres, studied by Motic Microscopy, show differences among floating microspheres based on the same polymer but with different concentrations. The floating microspheres exhibited spherical shape and smooth surface. The results showed that the drug/polymer ratio affected the morphological characteristics of the floating microspheres extensively. Average particle size of each batch is shown in Table 4 and microphotographs are shown figure 8.

Determination of Percentage Buoyancy (%):

The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. As the polymer concentration increases the buoyancy time increases. Percentage buoyancy of the floating microspheres was in the range 59.34% to 81.12% after 12 hrs (table 4).

Determination of Yield (%) and Drug Entrapment (%):

The percentage yields for floating microspheres were 71.54%. 89.21%, 76.75%, 84.15%, 85.45%, 92.19%, 80.15%, 81.25% and 79.95% for formulation batches F1, F2, F3, F4, F5, F6, F7, F8 and F9.

The drug entrapment efficiency was found to be in the range of 78.20 to 94.40% for the polymers studied. The results of drug entrapment are shown in the Table 8.12. Formulation F6 showed highest entrapment of 94.40 %, while lowest drug entrapment of 78.20 % was observed in formulation F9. Drug entrapment was attributed to the permeation characteristics of polymers used, that could facilitate the diffusion of part of the entrapped drug to the surrounding medium during preparation of floating microspheres (table 4).

Micromeritic properties:

All the formulations showed angle of repose value within the range of 20° to 30° (n=3), Bulk and Tapped densities showed good packability of floating microspheres. Carr's index ranges from 5% to 15 %. Hausner's ratio was ranging from 1.037 to 1.143 i.e. all the formulation showed that they had good flow properties. (Table 5)

***In Vitro* Drug Release Study:**

The in vitro performance of Valsartan gastroretentive floating microspheres showed prolonged and controlled release of drug. The drug release of floating microspheres was in the range 84.64% to 95.60%. The result of in vitro dissolution studies shows controlled manner as the polymer concentration increases the drug release from the floating microspheres decreases. The 95.60% drug release in 12 hrs of F7 batch and 84.64% release were found in F3 batch. The in vitro

dissolution data described in Table 6 and 7 and percent cumulative drug release profile was shown in Figure 9.

Determination of Release Kinetics:

The plots of cumulative percentage drug release V/s. time, cumulative percent drug retained V/s. root time, log cumulative percent drug retained V/s. time and log cumulative percent drug release V/s. log time were drown and represented graphically as shown in figure respectively. The slopes and the regression coefficient of determinations (r^2) were listed in table 8. The coefficient of determination indicates that the release data best fitted with zero order kinetics. Higuchi equation explains the diffusion controlled release mechanism (figure 10, 11, 12, 13)

Selection of optimized batch:

Formulation F6 shows all evaluation parameters were found in a standard range. Hence, the formulation batch F6 is optimized batch. In batch F6 used Ethyl cellulose 150 mg, HPMC K15M 100 mg and HPMC K15M 50 mg. Particle size of F6 is 191.17 ± 1.98, percentage yield 92.19%, drug entrapment 94.12 ± 0.04% and drug release 89.64% in 12 hrs in dissolution study. So F6 is selected as optimized batch from nine batches of floating microspheres of Valsartan.

Stability study of optimized formulation:

The stability studies of optimum formulation F6 revealed that no significant changes in the physical parameters when stored at temperature and humidity conditions of 40^0C/ 75% RH and at room temperature. No significant changes physical morphology and %cumulative drug release after 12 hours was observed over a period of two month, as shown in Table 9

Conclusion

In present work, gastroretentive floating microspheres of valsartan were prepared successfully by non aqueous solvent diffusion method using different concentration and combination of polymers like HPMC K15M, HPMC K100M and ethyl cellulose. Preformulation studies like melting point, solubility and analysis of were complied with standards. The FTIR spectra revealed that, there was no interaction between valsartan and polymers. All the polymers used were compatible with the pure drug. The percent yield of all floating microspheres formulation was more than 60% suggesting that the methods used for formulation was effective. The average particle size of microspheres was in the range of 157.21-348.35µm. From the results it can be conclude that there was a proper distribution of valsartan in the floating microspheres. The percent buoyancy was more than 70% after 12 hours indicated satisfactory performance of prolonged formulations. The coefficient of determination indicates that the release data was best fitted with zero order kinetics. From the study it is evident that promising controlled release floating microspheres of valsartan may be developed by Non aqueous solvent diffusion techniques by using polymers like HPMC K100M, HPMC K15M and Ethyl Cellulose.

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Table 1. Composition of Floating Microspheres of Valsartan.

Batch. No	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (mg)	400	400	400	400	400	400	400	400	400
HPMC K100M (mg)	50	50	50	100	100	100	150	150	150
Ethyl Cellulose (mg)	100	100	100	100	100	100	100	100	100
HPMC K15M (mg)	150	100	50	150	100	50	150	100	50
Liquid paraffin (ml)	200	200	200	200	200	200	200	200	200
Solvent ratio	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)	(1:1)
Isopropyl alcohol	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.

Table 2. Preliminary study of drug.

Identification Test	Observation Result	Reported Standard
Appearance	Amorphous powder	Amorphous powder
Color	White	White
Odor	Odorless	Odorless
Melting point	116-117^{0}C	116-118°C

Table 3. Concentration Vs Absorbance for linearity study for Valsartan in 0.1 N HCL.

Sr. No	Concentration of Valsartan (ppm)	Absorbance (nm)
1.	2	0.220
2.	4	0.446
3.	6	0.655
4.	8	0.858
5.	10	1.099

Table 4. Evaluation of floating microspheres of Valsartan.

Sr. No	Batch No	Percentage yield (%)	Average particle size (µm)	Buoyancy percentage (%)	Drug entrapment (%)
1	F1	71.54	234.21±1.2	87.12±1.32	79.4±0.01
2	F2	89.21	264.13±2.01	75.24±0.95	86.2±0.03
3	F3	76.75	310.91±2.45	64.15±0.15	81.01±0.28
4	F4	84.15	345.59±3.14	59.34±1.02	81.50±0.05
5	F5	85.45	271.60±1.65	80.94±1.35	80.15±0.07
6	F6	92.19	191.17±1.98	81.24±0.35	94.12±0.04
7	F7	80.15	301.61±2.15	64.35±0.68	89.12±0.09
8	F8	81.25	324.15±2.94	69.20±1.02	83.25±0.14
9	F9	79.95	274.21±1.69	78.12±1.65	78.20±0.07

Mean ± SD, n=3

Table 5. Micromeritic Property of Floating Microspheres of Valsartan.

Sr. No	Batch No	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index (%)	Angle of repose (degree)
1	F1	0.294±0.010	0.365±0.010	1.13±0.09	10.28±0.9	23.5±0.04
2	F2	0.321±0.012	0.414±0.020	1.16±0.04	11.66±0.8	25.5±0.06
3	F3	0.309±0.008	0.424±0.014	1.16±0.08	9.47±0.06	28.6±0.03
4	F4	0.354±0.014	0.435±0.012	1.15±0.02	10.71±0.05	25.6±0.07
5	F5	0.212±0.015	0.333±0.030	1.20±0.01	10.65±0.61	27.1±0.01
6	F6	0.289±0.032	0.357±0.010	1.12±0.11	9.03±0.01	22.5±0.02
7	F7	0.321±0.019	0.416±0.017	1.24±0.22	14.5 ±0.08	28.4±0.06
8	F8	0.358±0.021	0.440±0.014	1.16±0.03	11.48±0.02	26.4±0.01
9	F9	0.279±0.001	0.351±0.040	1.18±0.02	10.64±0.07	24.3±0.19

Mean ± SD, n=3

Table 6. Cumulative drug release (%) (F1 to F4).

Time (hrs)	Cumulative Drug release (%)			
	F1	F2	F3	F4
0	0	0	0	0
0.5	1.1566±1.18	0.9024±1.64	0.9874±1.97	2.1551±1.24
1	3.1914±0.25	4.1545±1.25	4.4119±2.45	5.1414±1.59
2	11.5864±1.68	20.0164±1.79	7.4167±2.37	8.9124±2.64
3	24.0925±0.38	34.7548±0.49	22.4764±1.14	12.0464±2.14
4	38.5049±2.95	49.2157±0.74	32.4045±1.02	39.6424±2.36
5	47.0814±2.94	56.4864±0.19	42.9009±2.15	46.9535±1.47
6	54.7901±1.94	59.3548±2.63	51.0712±1.67	57.0554±1.63
7	59.0610±0.25	64.5484±2.12	55.5491±1.43	61.0646±0.36
8	67.2831±2.49	69.4815±2.58	59.6848±2.91	67.7802±1.03
9	74.8219±1.45	75.6401±1.23	64.8537±2.67	72.7530±2.05
10	80.9857±1.35	79.4502±0.14	71.4946±1.49	79.3615±2.15
11	86.2331±2.45	86.1213±2.14	77.8712±2.81	88.6424±1.62
12	92.8930±2.20	91.2527±1.25	84.9695±1.78	93.6497±1.02

Mean ± SD, n=3

Table 7. Cumulative drug release (%) (F5 to F9).

Time (hrs)	Cumulative Drug release (%)				
	F5	F6	F7	F8	F9
0	0	0	0	0	0
0.5	1.1454±2.05	3.1415±1.02	2.1291±0.32	1.3564±0.36	1.3737±1.25
1	2.0846±2.03	6.0254±0.25	7.2517±1.25	3.6449±0.21	4.8782±1.35
2	7.87671±2.15	9.0246±1.98	13.8973±2.01	17.7261±1.02	8.5991±1.94
3	23.1617±1.94	21.2462±1.35	31.2854±1.36	31.4248±2.36	23.1446±1.05
4	36.7479±1.04	33.6725±0.25	41.3535±2.01	40.6972±2.15	33.2676±0.35
5	46.1494±1.35	41.0158±2.35	52.3657±2.36	58.156±2.15	42.3582±0.12
6	52.9742±0.15	51.0759±2.08	67.4579±2.15	62.1434±1.06	51.2991±2.15
7	61.0726±1.06	58.1595±1.54	71.5764±2.98	67.9519±1.02	58.1518±2.34
8	68.9064±2.05	63.1575±1.99	78.9041±1.02	75.4805±1.35	64.4927±2.15
9	74.0749±2.15	68.4753±1.02	86.6519±1.64	82.9510±2.01	69.5443±1.78
10	79.3595±2.36	73.9931±2.15	84.9093±1.26	86.4534±2.4	77.1864±0.64
11	84.2853±1.02	81.0617±2.65	89.1852±0.20	89.1591±2.35	86.6595±1.25
12	91.7402±0.35	89.6479±2.15	95.6048±0.65	93.9642±2.14	90.2318±0.35

Mean ± SD, n=3

Table 8. Values of correlation coefficient for all formulations.

Formulation code	Zero-order kinetic	First - order kinetic	Higuchi Model	Kosermeyer Peppas kinetic
	Regression coefficient (r^2)	Regression coefficient (r^2)	Regression coefficient (r^2)	Regression coefficient (r^2)
F1	0.980	0.956	0.940	0.937
F2	0.947	0.899	0.964	0.968
F3	0.982	0.957	0.945	0.965
F4	0.972	0.945	0.920	0.918
F5	0.980	0.942	0.938	0.952
F6	0.989	0.973	0.981	0.982
F7	0.957	0.965	0.936	0.953
F8	0.961	0.925	0.957	0.971
F9	0.990	0.972	0.950	0.937

Table 9. Accelerated stability study of optimized formulation F6.

Accelerated Stability (40^0C±2^0C/75±5% RH)	Physical changes	Cumulative Drug release (%)
Initial	No change	89.64
30 days	No change	85.79
60 days	No change	84.25

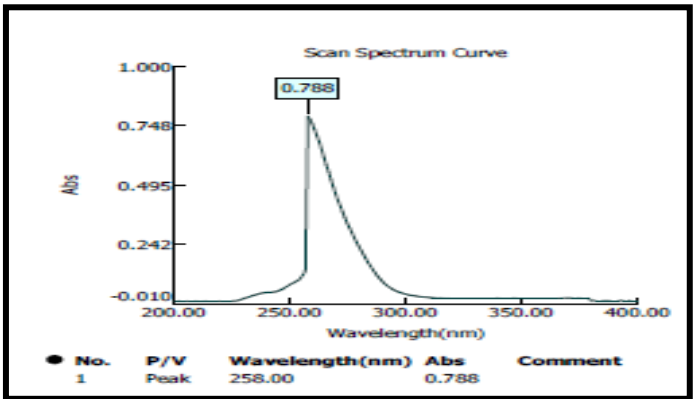

Figure 1: UV spectrum of Valsartan in 0.1N HCL.

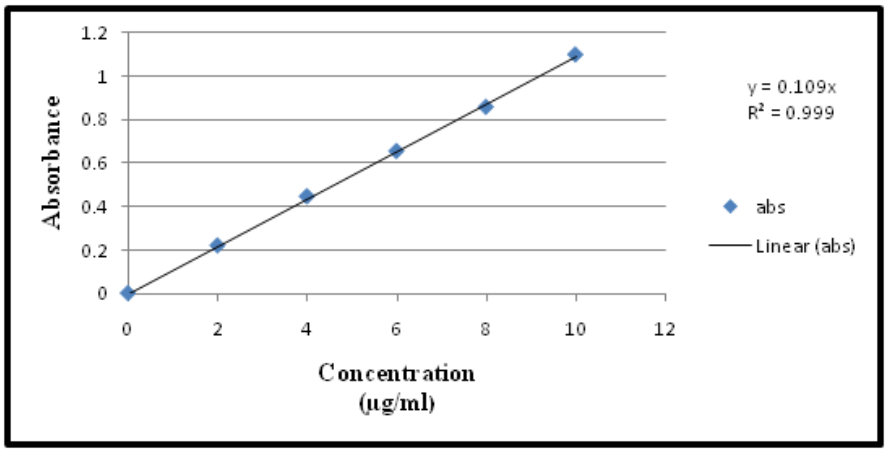

Figure 2: Calibration curve of Valsartan in 0.1N HCL.

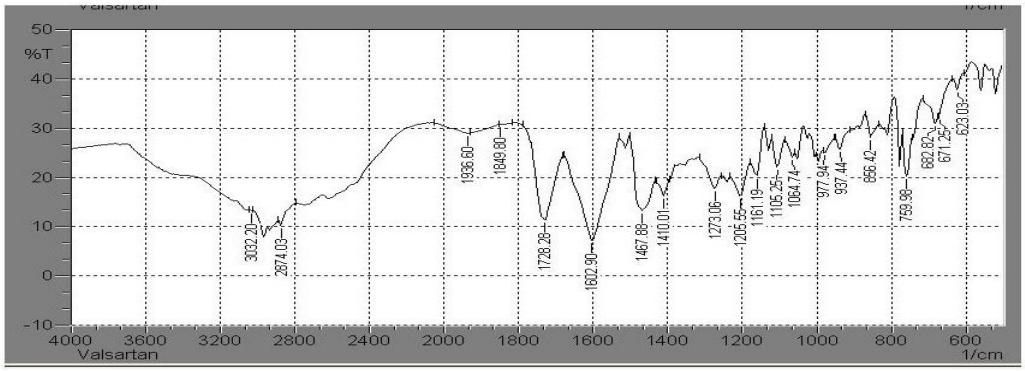

Figure 3: IR spectra of Valsartan.

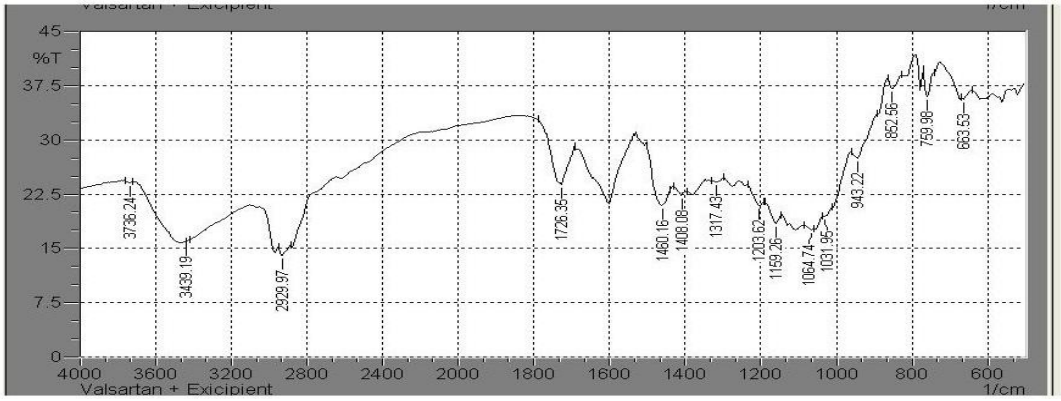

Figure 4: IR spectra of Valsartan and all excipients.

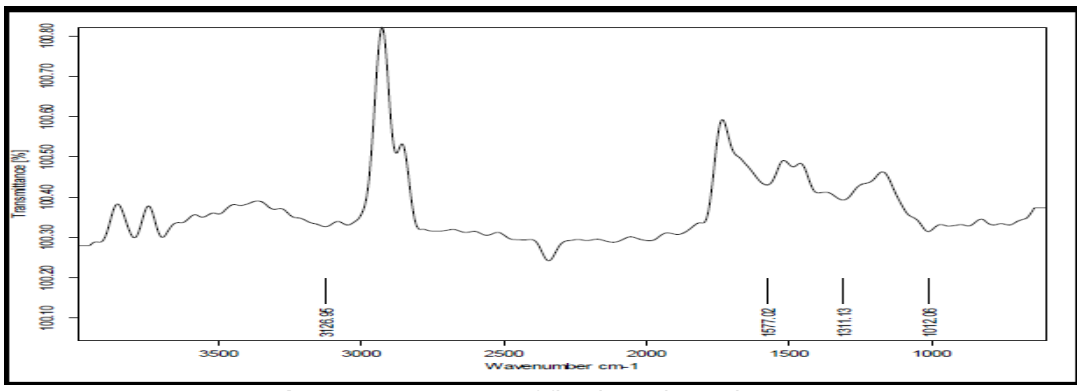

Figure 5: IR spectra of floating microspheres.

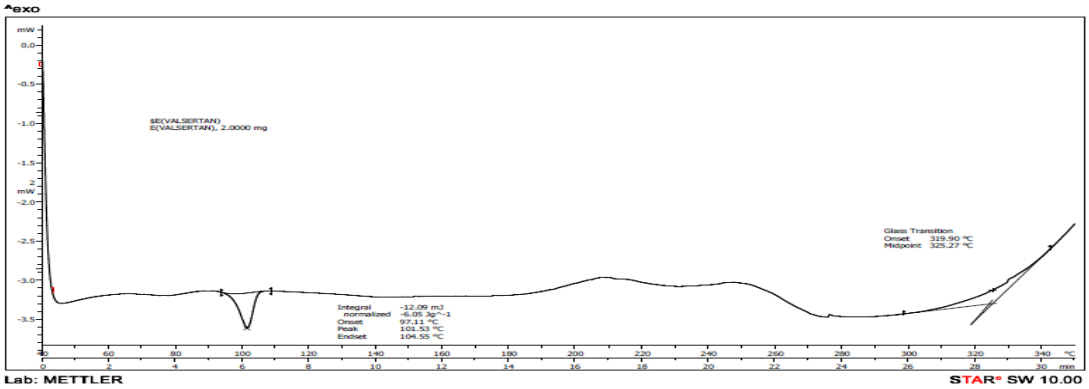

Figure 6: DSC spectra of Valsartan.

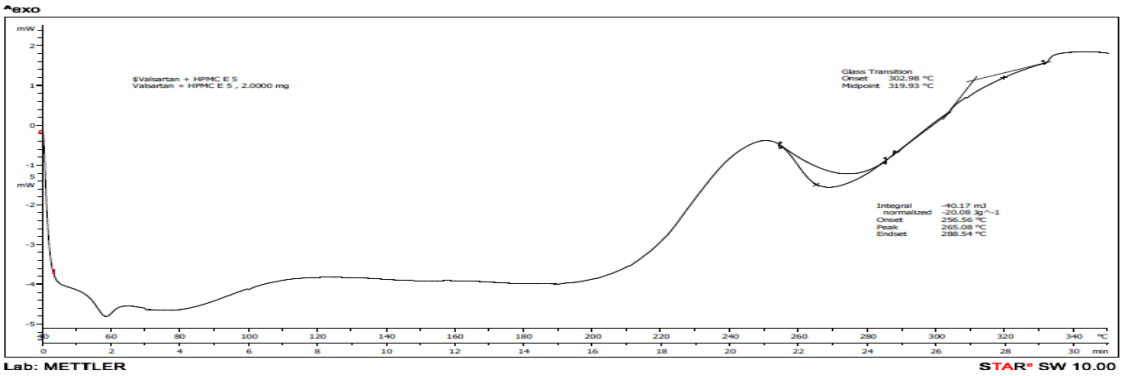

Figure 7: DSC of the Drug + All Excipients.

Figure 8: Image showing floating microspheres of Valsartan formulation.

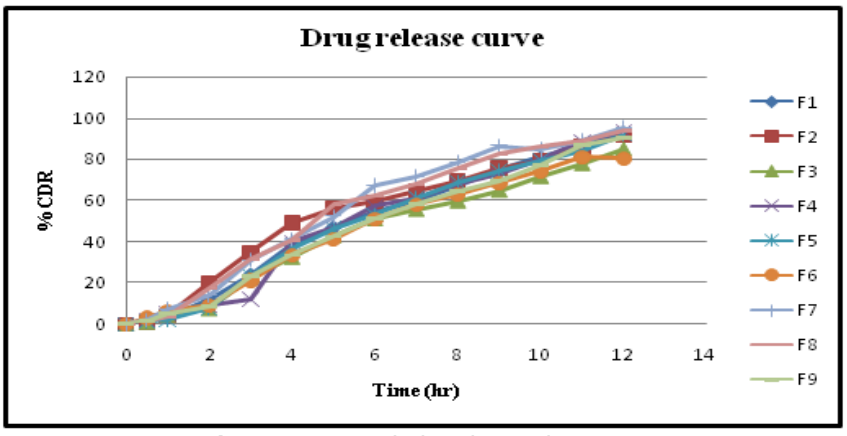

Figure 9: Cumulative drug release%.

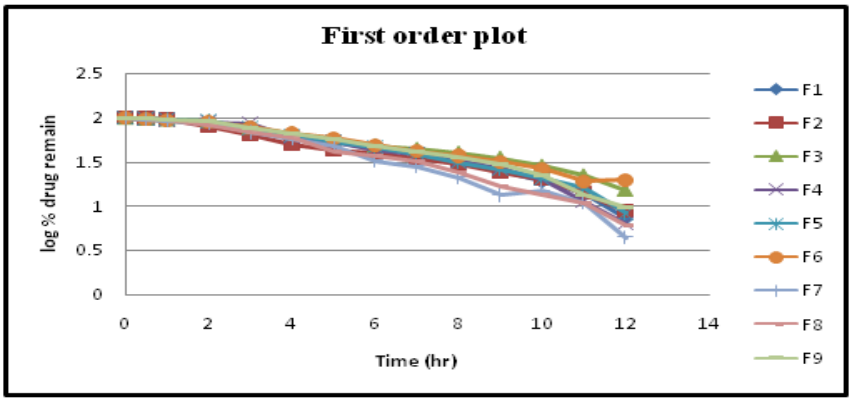

Figure 10: First order release kinetics profile plot (F1 to F9).

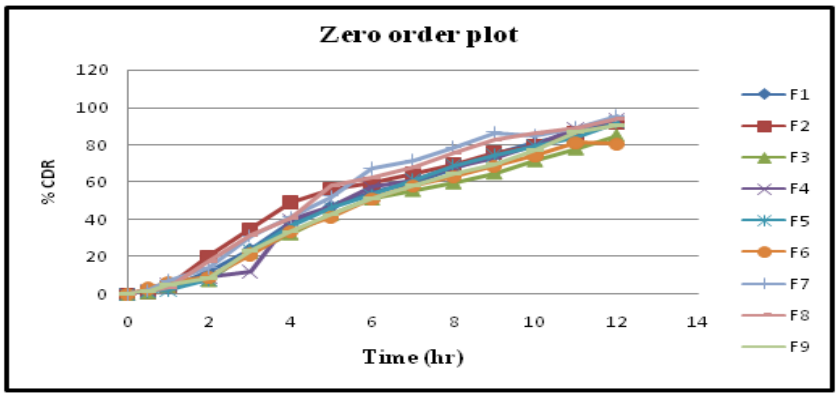

Figure 11: zero order release kinetics profile plot (F1 to F9).

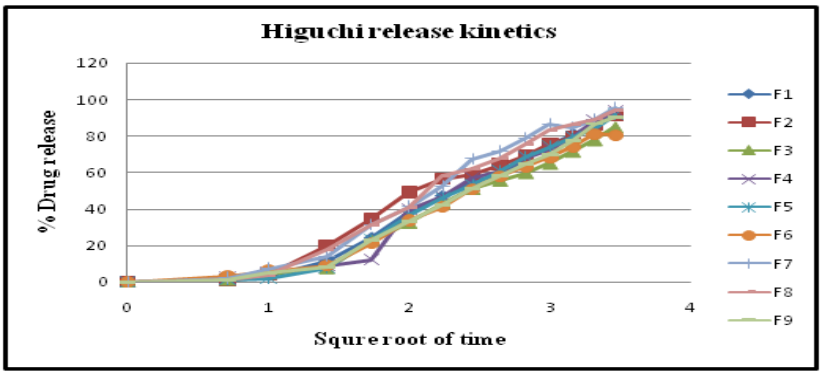

Figure 12: Higuchi release kinetics profile (F7 to F9).

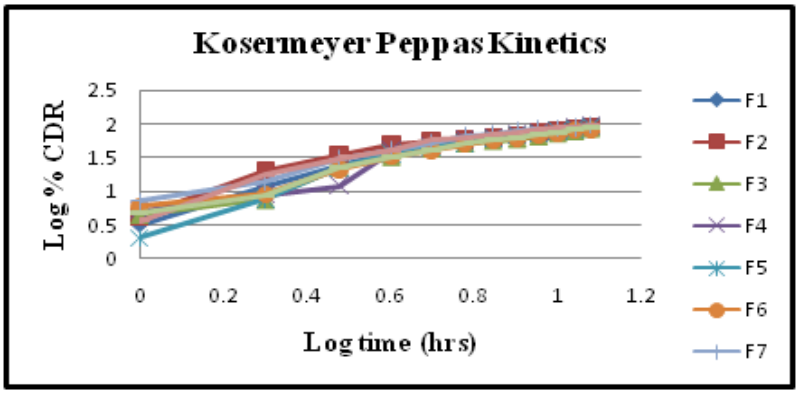

Figure 13: Kosermeyer Peppas release kinetics profile (F7 to F9).

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