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FORMULATION AND EVALUATION OF VALSARTAN MICROSPHERES BY IONOTROPIC GELATION TECHNIQUE

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Abstract:

In this present research study, an attempt was made to develop valsartan microspheres and consider the influence of various concentrations of sodium alginate and calcium chloride on particle size, entrapment efficiency, and drug release of the same. These microspheres were prepared by ionotropic gelation technique for oral delivery in the treatment of Hypertension. The formulated microspheres were evaluated regarding entrapment efficiency, percentage yield, drug release and characterization was studied using FTIR and SEM analysis. Among the total 14 formulations, S12 formulation was optimized at 2% of sodium alginate, 10% of calcium chloride with pectin. The in vitro dissolution showed sustained release of Valsartan up to 97.89±5.25 by diffusion mechanism over 12h, which followed the zero order and Higuchi model (R^2 = 0.990, 0.979) respectively, the drug release from microspheres was anomalous Non fickian diffusion. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences. Valsartan alginate microspheres is an effective drug delivery system that offers more predictable and extensive drug release and helps in the treatment of Hypertension.

Key Words: *Valsartan, Microspheres, Hypertension, Cross-linking agent.*

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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]**. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug.to achieve maximum therapeutic efficacy it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period thereby causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion.one such approach is using microspheres as carrier for drug.

Microspheres have potential to deliver drug in a controlled fashion. Microspheres are small spherical particles, with diameters in the micrometer range (1 µm to 1000 µm). **[2]** The microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200 micrometer. Microsphere have been extensively studied for use as drug delivery systems, where they have been shown to protect sensitive macromolecules from enzymatic and acid degradation, and allow controlled release and tissue targeting of the formulated drug. **[3]**

Valsartan is a potent and specific competitive angiotensin II type1 receptor (AT1) antagonist. It is used orally for the treatment of hypertension and has a low bioavailability of 23%, because of its poor absorption in lower gastro intestinal tract. It undergoes little or no hepatic metabolism and its elimination half-life is 6 hrs. Therefore, it is selected as a suitable drug for the design of mucoadhesive microspheres with a view to improve its oral bioavailability and increase its drug release in a sustained manner **[4]**

The aim of the present study is to develop Valsartan loaded microspheres by ionotropic gelation method to obtain an extended retention in the upper GIT, which may result in increased absorption and thereby improved bioavailability. The prepared microspheres were evaluated for particle size, shape, % yield, incorporation efficiency, and *in vitro* release study.

MATERIALS AND METHODS:

Materials:

Valsartan procured from Hetero Drugs Ltd, HYD. Sodium alginate from Pruthvi Chemicals, Mumbai. Calcium chloride from SD Fine ltd, Mumbai, and Ethyl cellulose was purchased from Central Drug House, India. Eudragit RS 100 from Loba chemicals pvt ltd All other chemicals and solvents were of analytical grade.

Methods:

Formulation of Valsartan microspheres:

Table 1: Formulation trials for Valsartan microspheres:

FORMULATION CODE	VALSARTAN(mg)	SODIUM ALGINATE	ETHYL CELLULOSE (mg)	EUDRAGIT RS 100 (mg)	CALCIUM CHLORIDE
S1	80	1 %	100	-	6%
S2	80	1.25 %	200	-	6%
S3	80	1.5 %	300	-	6%
S4	80	1.75 %	400	-	6%
S5	80	2 %	500	-	6%
S6	80	2.5 %	600	-	6%
S7	80	3 %	700	-	6%
S8	80	1 %	-	100	10%
S9	80	1.25 %	-	200	10%
S10	80	1.5 %	-	300	10%
S11	80	1.75 %	-	400	10%
S12	80	2 %	-	500	10%
S13	80	2.5 %	-	600	10%
S14	80	3 %	-	700	10%

Procedure:
Sodium alginate microspheres of Valsartan were prepared by ionotropic gelation technique using different proportion of polymers as shown in table 1. A solution of sodium alginate is prepared, weighed quantity of drug, Ethyl cellulose and Eudragit RS 100 was triturated to form fine powder, and then added to above solution.
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 for 2 hours in a hot air oven and stored in desiccator. **[5]**

Evaluation of Valsartan Microspheres:

Particle size:
Particle size of microspheres was analyzed using laser light diffraction technique. The homogenous aqueous dispersion of microspheres was used for determining the particle size. **[6]**

Angle of repose:
Angle of repose (Θ) of microspheres measures the resistance to particles flow and is calculated according to fixed funnel standing cone method. Where (Θ) is angle of repose, H/D is surface area of the free-standing height of the microspheres heap that is formed on a graph paper after making the microspheres flow from glass funnel. **[7]**

$$\theta = \tan^{-1}(h/r)$$

Bulk density:
Volume of the microspheres in the measuring cylinder was noted as bulk density. **[8]**

Tapped density:
Change in the microspheres volume was observed in mechanical tapping apparatus. **[8]**

Compressibility index:
Also called as Carr's index and is computed according to the reported equation. **[9]**

Hausner'sratio:
Hausner's ratio of microspheres is determined by comparing the tapped density to the fluff density using the reported method. **[10]**

Drug entrapment efficiency and %yield:
To evaluate the amount of the drug inside the microspheres, an indirect method was used. Aliquots from the filtered solutions remaining after removal of the microspheres were assayed spectrophotometrically. The amount of drug entrapped was calculated from the difference between the total amount of drug added and the amount of drug found in the filtered solution. About 100 mg of microspheres were completely dissolved in 500 ml of phosphate buffer solutions (pH 6.8) and stirred for 1h. Then, 2 ml of solution was filtered and the concentration of drug was determined spectrophotometrically at 249nm by UV. **[11]**

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

% yield = [Total weight of microspheres / Total weight of drug and polymer] x 100

In vitro drug release studies:
Release rate of Valsartan from sodium alginate microspheres was carried out using USP type II dissolution apparatus with pH 6.8 buffer of 900ml as dissolution medium. Accurately weighed amount of microspheres from each batch were subjected to dissolution studies in triplicate manner. At appropriate intervals up to 12 h, specific volume of aliquots was withdrawn and analyzed spectrophotometrically. The withdrawn volume was replaced with an equivalent volume of fresh dissolution medium to maintain the volume of dissolution medium constant. The sample solutions were analyzed for the concentration of drug by UV spectrophotometer at 249 nm. The amount of drug released was calculated from the calibration curve of the same dissolution medium. **[12]**

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 microspheres were fitted with various kinetic equations like Zero order as cumulative percentage drug release 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 [13]
The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method, SEM and Differential Scanning Colorimetry

Fourier transform infrared spectroscopy (FTIR)
FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1

Spectrophotometer. The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 cm^{-1} and the resolution was 1 cm^{-1}.

SEM studies

The surface and shape characteristics of pellets were determined by scanning electron microscopy (SEM) (HITACHI, S-3700N). Photographs were taken and recorded at suitable magnification.

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 ^{0}C / 75 % RH for the best formulations for 6 months. The microspheres were characterized for the percentage yield, entrapment efficiency & cumulative % drug released during the stability study period.

RESULTS AND DISSCUSSION:

Formulation of microspheres of Valsartan:

Figure1: **Valsartan microspheres**

Micromeretic parameters:

Microspheres of Valsartan were formulated by ionotropic gelation method (Figure 1), using different polymers like sodium alginate, and calcium chloride in different concentrations. All the formulations were evaluated for their various physical parameters and found to be in limits.

Table 2: Micromeretic properties of Valsartan microspheres

Formulation code	Particle size (µm)	Bulk density(g/cc^3)	Tapped density (g/cc^3)	Angle of repose	Carr's index (%)
S1	59.19±0.10	0.51±0.01	0.65±0.03	21˚.92±0.01	12.29
S2	61.29±0.01	0.50±0.01	0.63±0.02	23 ˚.17±0.02	11.81
S3	60.96±0.01	0.55±0.03	0.64±0.02	22 ˚.98±0.01	11.01
S4	58.29±0.09	0.54±0.02	0.65±0.03	24 ˚.96±0.02	13.56
S5	57.29±0.08	0.53±0.02	0.63±0.02	25 ˚.29±0.03	15.98
S6	62.20±0.02	0.54±0.02	0.64±0.02	23 ˚.18±0.02	14.18
S7	59.27±0.10	0.50±0.01	0.62±0.01	24 ˚.51±0.02	13.26
S8	61.26±0.01	0.52±0.01	0.63±0.02	23 ˚.19±0.02	11.99
S9	60.20±0.01	0.51±0.01	0.61±0.01	22 ˚.21±0.01	12.46
S10	57.19±0.08	0.53±0.02	0.59±0.10	23 ˚.20±0.02	13.96
S11	58.14±0.09	0.52±0.01	0.60±0.01	25 ˚.63±0.03	12.19
S12	**56.12±0.08**	**0.49±0.10**	**0.58±0.09**	**20 ˚.36±0.01**	**10.02**
S13	57.96±0.08	0.54±0.02	0.61±0.01	23 ˚.19±0.02	11.42
S14	60.20±0.01	0.56±0.03	0.62±0.01	24 ˚.96±0.02	11.96

Particle size was measured by using optical microscopy. All the formulations S1 to S14 varied from 56.12±0.08µm to 62.20±0.02µm. The bulk densities of all the formulations S1 to S14 were measured and they are ranged from 0.49±0.10g/cc³ to 0.55±0.03g/cc³. The tapped densities of all the formulations S1 to S14 were measured and they are ranged from 0.58±0.09g/cc³ to 0.65±0.03g/cc³. The compressibility index values were found to be in the range of 10.02 to 15.98 %. These findings indicated that all the batches of formulations exhibited good flow properties. Angle of repose of all the formulations was found satisfactory result. The angle of repose of formulation S12 was found to be 20^0. 36±0.01, it is having good flow property. The percentage yield and entrapment efficiency obtained from the water uptake studies of the formulations is shown in table 2

Table 3: Percentage drug yield and entrapment efficiency of Valsartan microspheres.

Formulation code	Percentage yield (%)	Entrapment efficiency (%)
S1	93.68	90.66
S2	90.18	91.28
S3	92.17	90.69
S4	91.49	92.19
S5	88.61	93.25
S6	92.90	94.64
S7	90.18	89.66
S8	89.66	92.80
S9	93.49	91.24
S10	94.68	90.29
S11	96.17	96.64
S12	**98.92**	**97.18**
S13	94.12	95.19
S14	95.09	94.66

The percentage yield and entrapment efficiency of all the formulations found to be within the limit and shown in Table 3. The formulation S12 shows better percentage yield and entrapment efficiency of 98.92% and 97.18% respectively

***In vitro* drug release studies**

In vitro drug release studies were carried out and the results are depicted in Table 4 & 5 and Figure 2 & 3. The formulation S12 shown highest drug release of 97.89% in 12 hrs.

Table 4: In vitro cumulative % drug release of Valsartan microspheres formulations:

Time (h)	S1	S2	S3	S4	S5	S6	S7
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	18.46±0.99	16.86±0.96	20.89±1.30	15.99±0.95	13.18±0.94	19.92±0.99	17.21±0.97
2	29.14±2.08	26.98±1.36	32.18±2.02	24.38±1.35	26.27±1.35	30.18±2.09	33.18±2.02
4	43.24±2.46	39.08±2.15	44.67±2.50	42.11±2.46	40.19±2.15	46.78±2.51	44.67±2.50
6	58.23±2.96	53.99±2.90	56.99±2.89	50.67±2.83	54.66±2.89	58.20±2.96	55.29±2.89
8	62.14±3.09	60.89±3.05	68.11±3.18	64.94±3.15	66.67±3.16	70.18±3.82	72.30±3.82
10	80.18±4.25	72.18±3.82	75.45±3.80	85.18±4.89	79.18±3.93	82.19±4.28	84.46±4.89
12	90.10±5.01	89.45±4.99	91.45±5.02	93.21±5.06	90.34±5.02	92.66±5.04	93.34±5.06

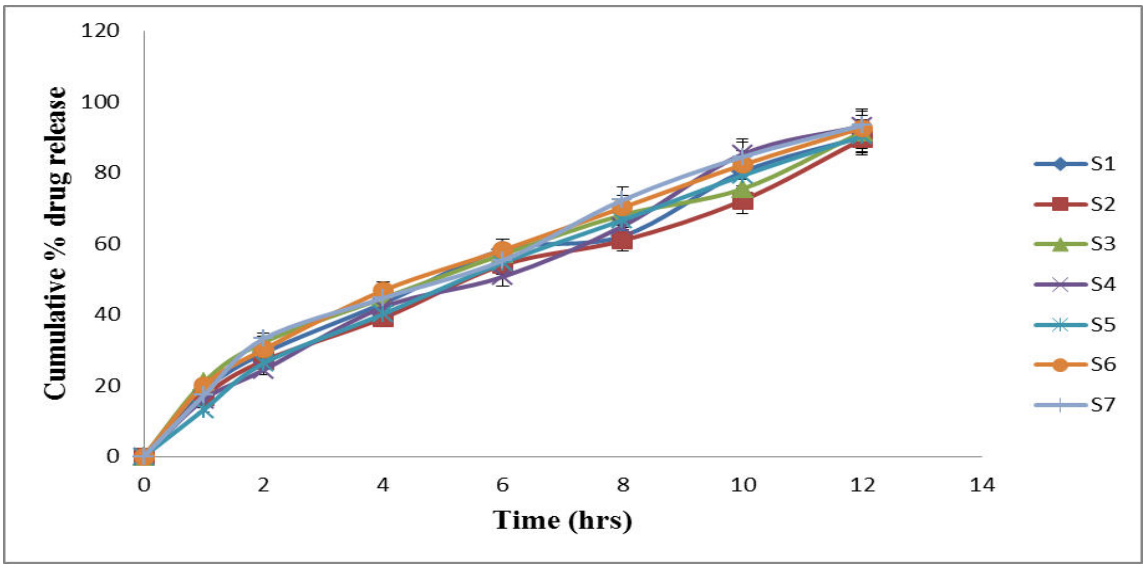

Figure 2: In vitro cumulative % drug release of Valsartan microspheres formulation

Table 5: In vitro cumulative % drug Valsartan microspheres formulation:

Time (h)	S8	S9	S10	S11	S12	S13	S14	Marketed Product
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	21.66±0.94	19.18±0.99	15.18±0.95	22.18±1.32	29.16±1.98	17.89±0.97	14.85±0.93	8.09±0.11
2	28.19±1.89	33.46±2.02	24.66±1.35	31.60±2.09	38.42±2.05	28.14±1.35	27.45±1.35	12.44±1.78
4	46.20±2.49	47.54±2.50	35.18±2.05	46.98±2.50	46.92±2.50	44.76±2.49	40.96±2.46	32.44±2.17
6	58.96±2.99	58.32±2.96	47.67±2.50	55.96±2.89	59.67±2.96	55.37±2.89	52.14±2.81	45.77±2.44
8	68.14±3.58	70.11±3.82	59.80±2.90	69.18±3.19	70.29±3.82	61.98±3.09	62.78±3.10	51.74±3.07
10	81.50±4.05	83.67±4.80	78.66±3.93	79.81±3.93	89.16±4.99	80.14±4.89	82.14±4.90	72.55±3.78
12	90.96±4.89	91.23±5.01	88.98±4.97	90.14±5.01	97.89±5.25	91.45±5.01	89.11±4.44	90.11±5.00

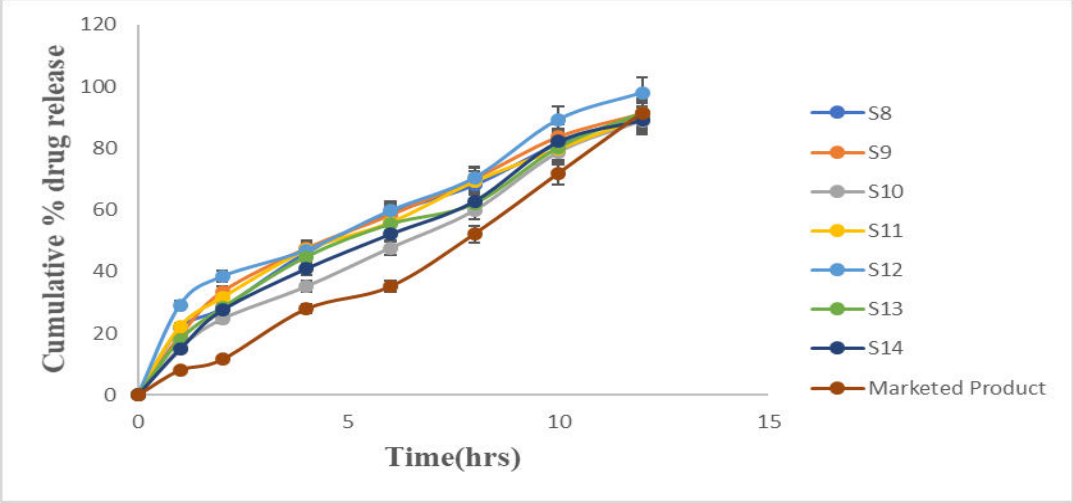

Figure 3: In vitro cumulative % drug Valsartan microspheres formulations

Mathematical modeling of optimized Valsartan microspheres:

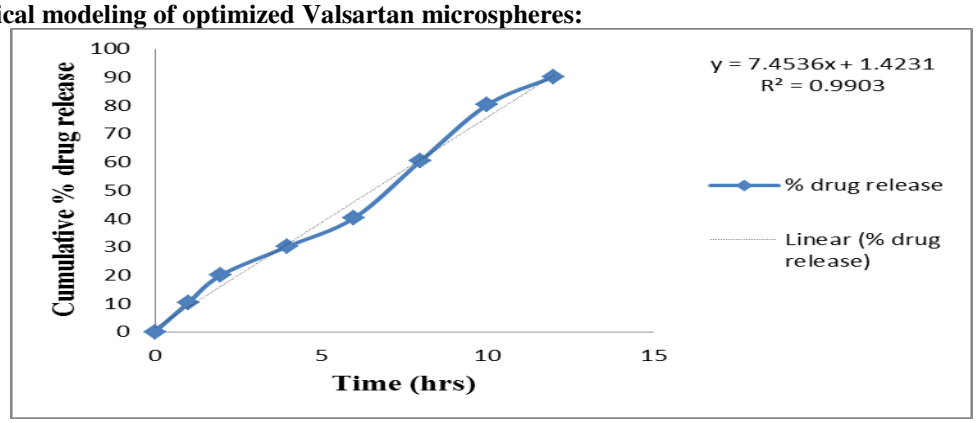

Figure 4: Zero order plot for the optimized formulation of Valsartan micropsheres S12

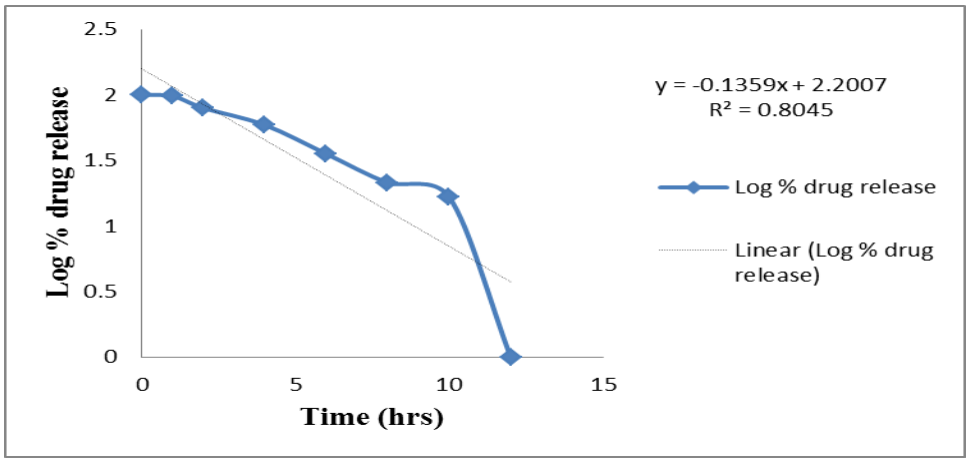

Figure 5: First order plot for the optimized formulation of Valsartan microspheres S12

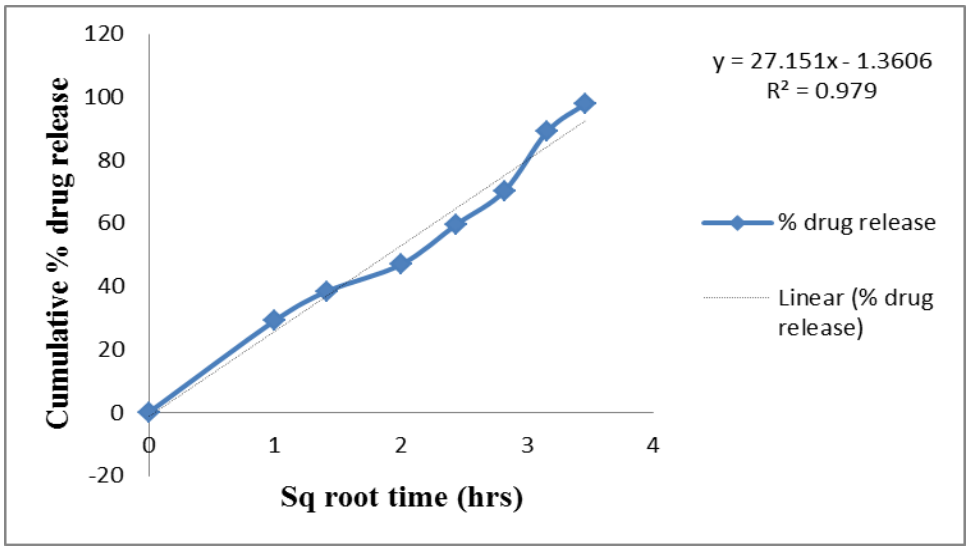

Figure 6: Higuchi plot for the optimized formulation of Valsartan microspheres S12

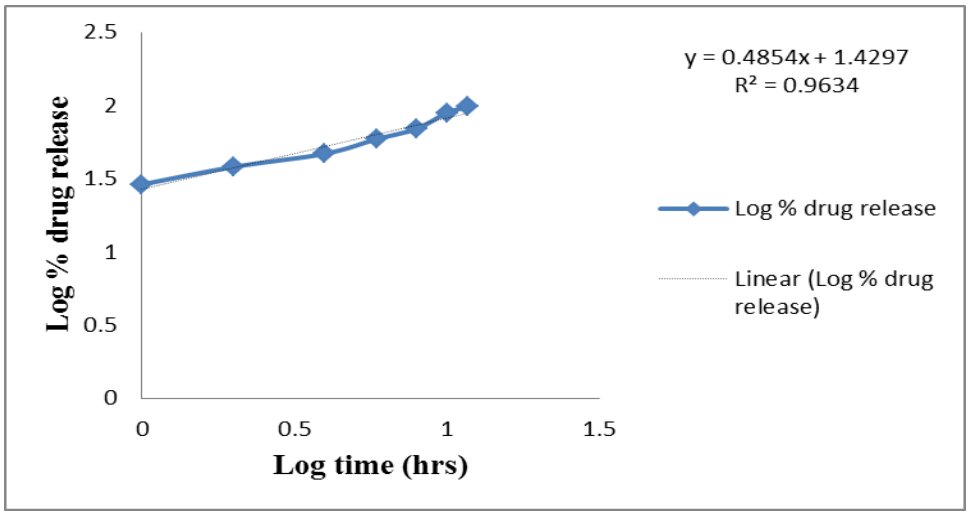

Figure 7: Korsmeyer-peppas plot for the optimimized Valsartan microspheres S12

Release Order Kinetics of Marketed product

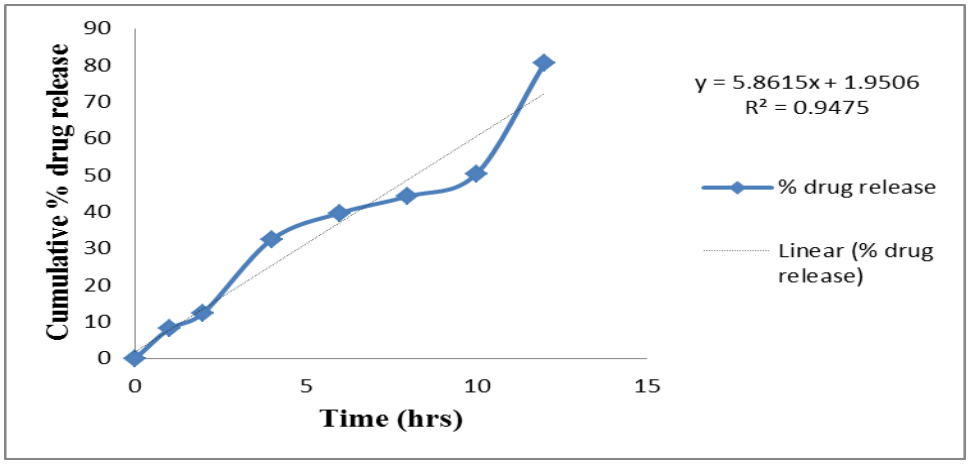

Figure 8: Zero order plot for the Marketed product

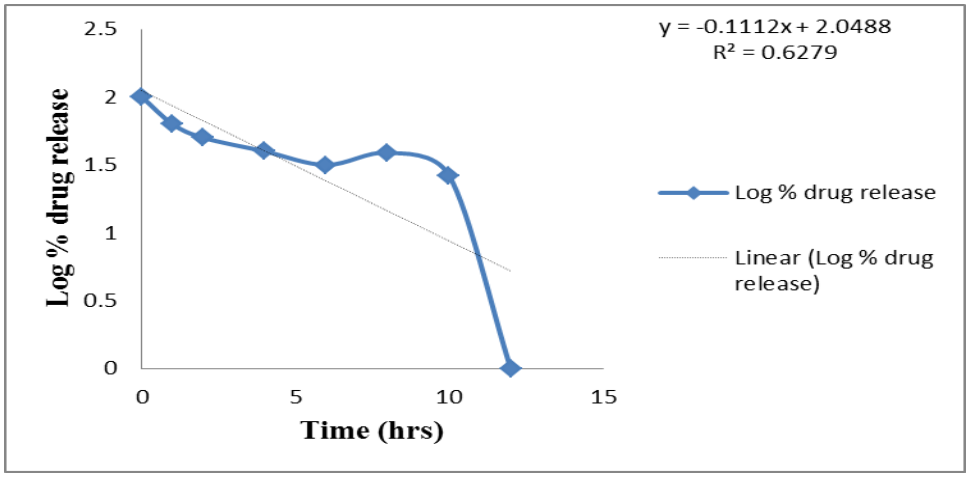

Figure 9: First order plot for the Marketed product

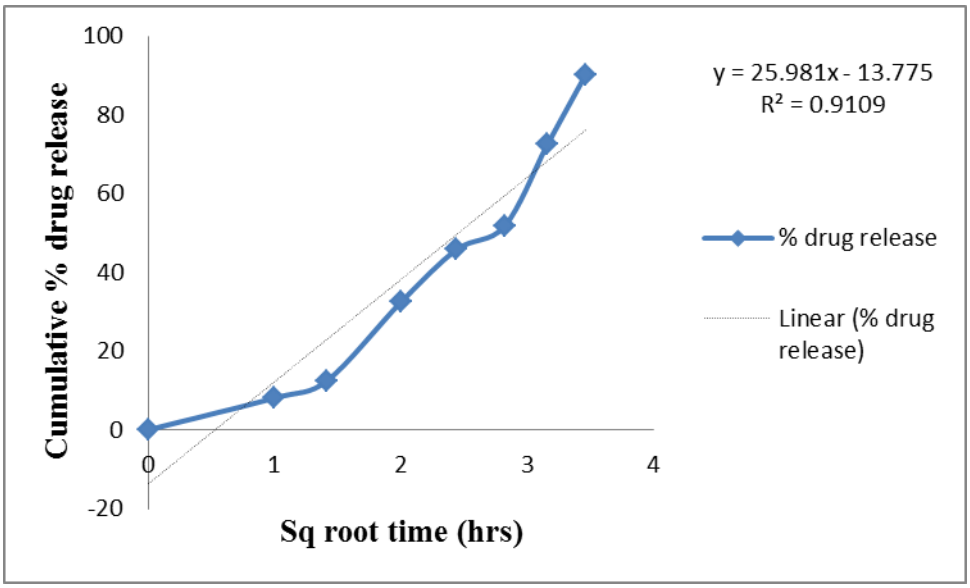

Figure 9: Higuchi plot for the Marketed product

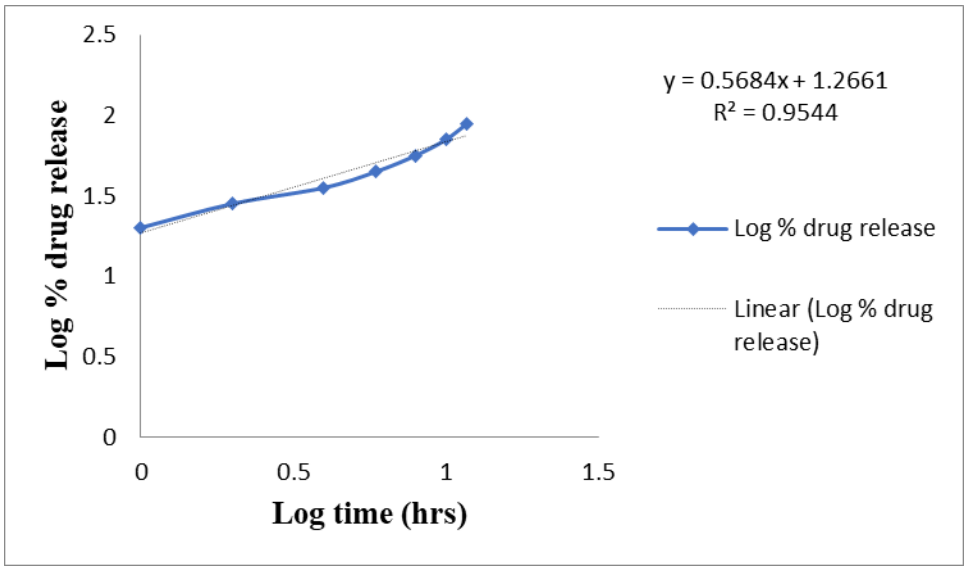

Figure 10: Korsmeyer-peppas plot for the Marketed product

Table 6:Release order kinetics of optimized microspheres (S12)

Formula Code	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
S12	0.990	7.453	0.804	0.135	0.979	27.151	0.963	0.485
Marketed product	0.947	5.861	0.627	0.111	0.910	25.981	0.954	0.568

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.990 indicates that the drug release follows a zero-order mechanism (Figure 4). 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. First order plot was showing in Figure 5. 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 Korsmeyer 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. 0.979 starting that the release from the matrix was through diffusion (Figure 6). Further the n value obtained from the Korsmeyer plots i.e. 0.485 suggest that the drug release from microspheres was anomalous Non fickian diffusion (Figure 7).

Drug excipient compatibility Studies:

FT-IR:

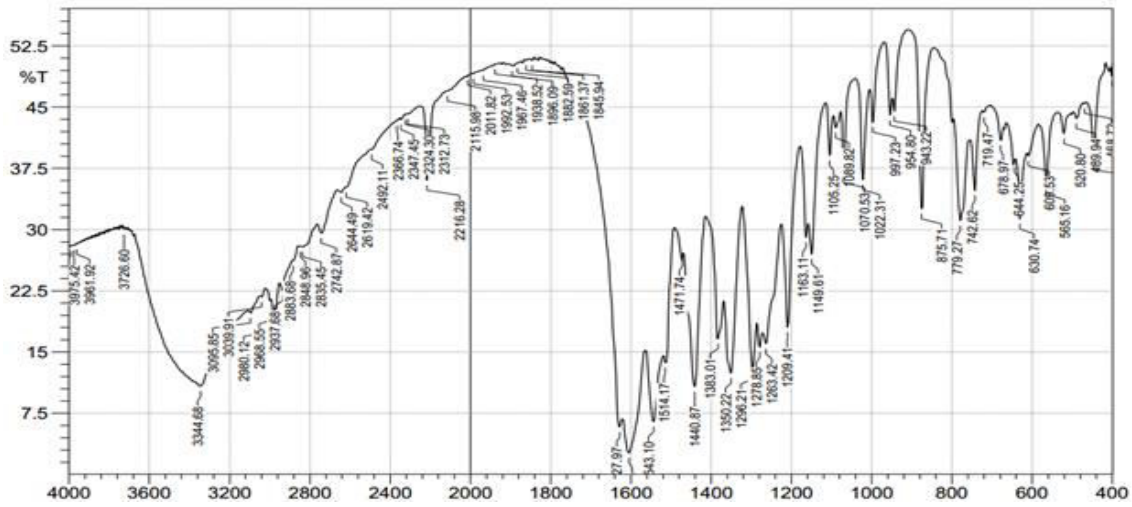

Figure 8: FT-IR spectrum of pure drug Valsartan

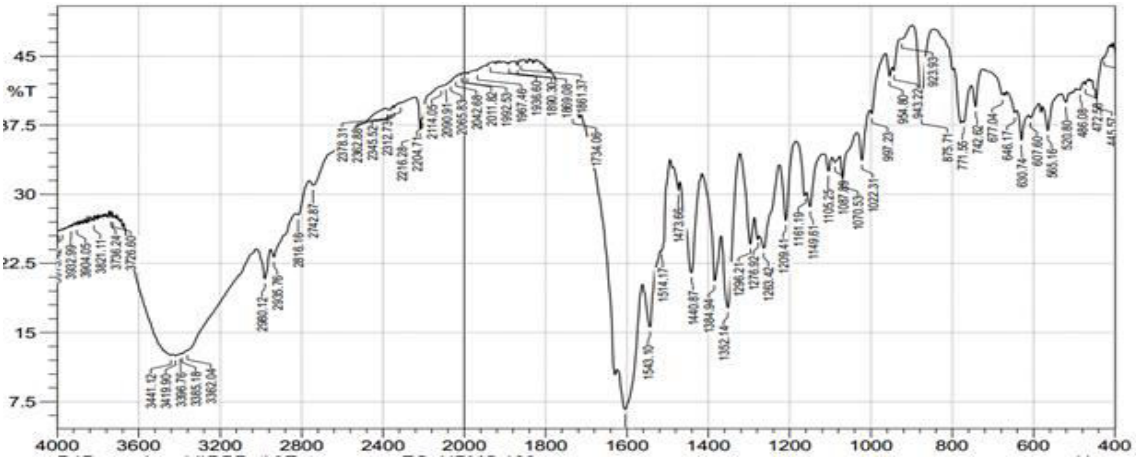

Figure 9: FT-IR spectrum of physical mixture

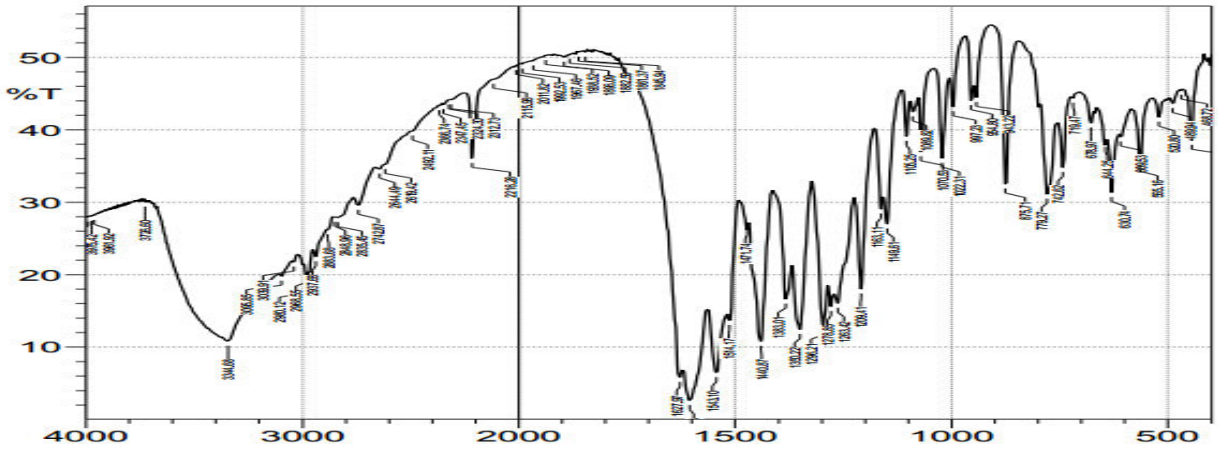

Figure 10: FT-IR spectrum of Valsartan optimized formulation

Overall there was no alteration in peaks of Valsartan pure drug (Figure 8), physical mixture (Figure 9) and optimized formulation (Figure 10), suggesting that there was no interaction between drug & excipients. There are additional peaks appeared or disappeared hence no significant changes in peaks of optimized formulation was observed when compared to pure drug, indicating absence of any interaction.

SEM of Valsartan microspheres

The external and internal morphology of controlled release microspheres were studied by Scanning Electron Microscopy.

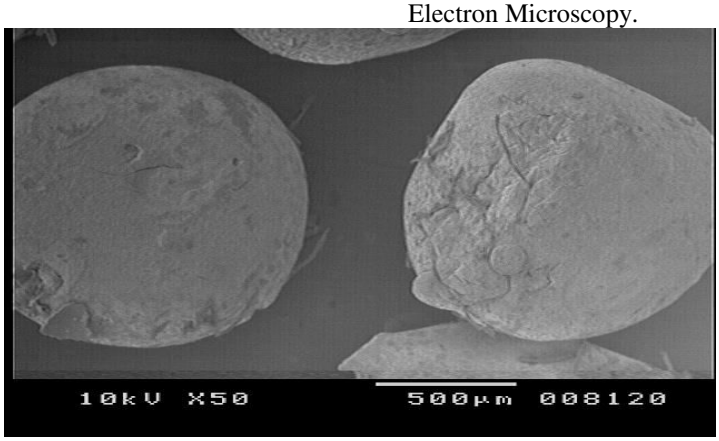

Figure 11: Scanning electron micrographs of Valsartan microspheres

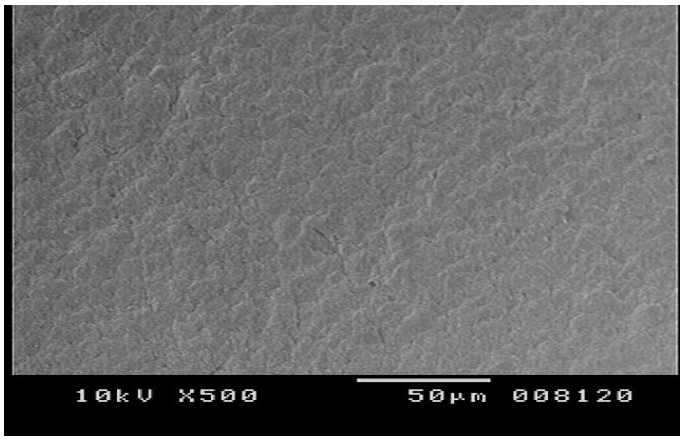

Figure 12: Scanning electron micrographs of Valsartan microspheres

Morphology of the various formulations of Valsartan microspheres prepared was found to be discrete and spherical in shape. The surface of Valsartan microspheres was rough due to higher concentration of drug uniformly dispersed at the molecular level in the sodium alginate matrices. There are no crystals on surface which states that drug is uniformly distributed (Figure 11 & 12).

Stability studies:
Optimized formulation S12 was selected for stability studies based on high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences which depicted in Table 7.

Table 7: Staility studies of optimized microspheres

Retest Time for Optimized formulation	Percentage yield	Entrapment efficiency	*In-vitro* drug release profile (%)
0 days	98.92	97.18	97.89
30 days	96.19	96.45	96.25
60 days	95.34	94.67	95.48
120 days	93.23	93.99	94.23
180 days	92.84	90.24	93.26

SUMMARY AND CONCLUSION:

Valsartan normal microspheres were prepared by both Ethyl cellulose and Eudragit RS 100 of 14 different formulations. The flow properties of all the formulations were found to be within the limits. The microspheres were prepared by ionotropic gelation method using different polymers like sodium alginate, calcium chloride etc. All formulations were evaluated for their various physical parameters and found to be within the limits. Formulation S12 was found to be optimized one based on the different evaluation parameters like percentage yield, entrapment efficiency and dissolution studies. The amount of drug release was found to be 97.89% upto 12h. Valsartan microspheres are an effective drug delivery system that offers more predictable and extensive drug release with enhanced shelf-life in the treatment of Hypertension.

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