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RESEARCH ARTICLE
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FORMULATION AND EVALUATION OF ORAL MICROSPHERES CONTAINING ANTIHYPERTENSIVE DRUGS BY EMULSION SOLVENT EVAPORATION METHOD

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Abstract:
Hypertension is a serious heart condition in which the blood pressure in the arteries throughout the body is high. Blood pressure involves two measurements, systolic and diastolic. Normal blood pressure is equal to or less than 120/80 mmHg. High blood pressure is above 140/90 mmHg. The microspheres are thus spherical solid particles with a size between 1 and 1000 µm.Using synthetic protein or polymer carbomer, ethyl cellulose, HPMC, ethanol, liquid paraffin, Span 80, etc. As raw materials, microspheres containing antihypertensive drugs were prepared by the emulsified solvent evaporation method.

Introduction:
The microcapsules are those in which the entrapped substance is distinctly surrounded by the distinct capsule wall & micrometrics in which the entrapped substance is dispersing throughout the microsphere's matrix. The solid biodegradable microspheres which incorporated the drug dispersed or dissolved through the particle matrix, for the controlled release of the drug they have the potential. They are made up of waxy, polymeric or other protective materials that are modified natural products & biodegradable synthetic polymers. The oral microspheres are also called as micro particles. To overcome some of the problems of conventional Drugs and enhance the therapeutic efficacy of a given drug they are designed. Microspheres are carriers for Control Release. Microspheres are used to sustain the release of drug and for localized effect .[1,2]

Hypertension is one of the primary risk factors for heart disease and stroke, the leading causes of death due to its high prevalence all around the globe. Approximately 7.5 million deaths worldwide occur due to hypertension and predicted to be increased to 1.56 billion adults with high blood pressure in 2025.Those are highly specific angiotensin 2 type receptor antagonist with antihypertensive activity. The drug is readily absorbed from the GI tract, the absolute bioavailability of certain drugs is estimated to be 60 to 70 % Tmax ranges below 5 to 6 hours.

The following oral microspheres administration. It has significant first pass metabolism hence its bio availability increases 80- 85%. Since the drug has low elimination half-life (i.e., 5-6 hrs.) [3]

Microspheres are small spherical particles with diameter in the micrometer range typically 1µm-1000µm. Microspheres are also called as microparticles. Mucoadhesive microspheres form an important part of novel drug delivery system. The short residence time of the microspheres at the site of absorption can be overcome by coupling bioadhesion characters to the microspheres and developing bioadhesive microspheres[4]

The novel design of oral controlled drug delivery system should be primarily aimed at achieving more predictable and increased bioavailability of drugs. 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, its elimination half life is 6hrs. Therefore, it is selected as a suitable drug for the design of microspheres with a view to improve its oral bioavailability and increase its drug release in a sustained manner. [5]

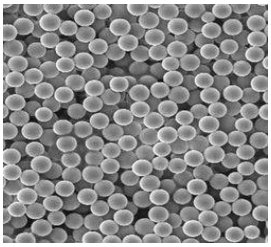

Fig. No. 01: Microspheres

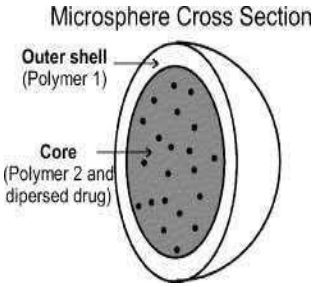

Fig. No. 02: Microspheres Cross Section

Advatantages:

1. Microspheres, due to high surface area and low particle size significantly increase the absorption rate and bio-availability.
2. Microspheres can support the controlled release of a drug to specific target sites.
3. Oral microspheres have the ability to bind & release the high concentration of the drug.
4. Simple method of preparation. It enhance biological half-life.
5. Microspheres and microcapsules aid in prolonging drug release and targeting the therapeutic or a particular site.

MATERIAL AND METHODS:

Materials:

A gift sample of Valsartan was obtained Ajanta pharmaceuticals PVT. LTD. Chitegaon . Carbopol, ethyl cellulose, HPMC, Span80, diethyl ether, liquid paraffin, Dihydrogen phosphate, sodium hydroxide research lab thermo chem laboratories Nagpur and S.D. fine chemicals, Mumbai

Preparation of Mucoadhesive Microspheres by Emulsion Solvent Evaporation method:
Valsartan microspheres are prepared by Emulsion Solvent Evaporation technique using polymers Carbopol and HPMC and ethyl cellulose individually. The following are the steps for the preparation of microspheres. In this method first the accurately weighed polymer is added to 50ml of ethanol and homogenized by continuous stirring at 500-600 rpm. To this accurately weighed amount of drug was added and stirring is continued until a homogenous dispersion is formed. Separately, 50ml of liquid paraffin containing 1ml Span80 was placed on a mechanical stirrer and homogenised. The above formed polymer-drug dispersion (aqueous phase) was added slowly to liquid paraffin in a thin-stream over 3-5 minutes. This emulsion was stirred at 2000 rpm and heated to 80^0 C for 2-3 hrs. Constant heating upto 75-80^0 C should be maintained with the help of hot plate. The aqueous phase evaporates leaving the microspheres dispersed in oil phase.

The formed microspheres were separated by decantation and washed 2-3 times with 100ml aliquots of n-hexane to remove traces of oil. Then the microspheres were dried at 40^0C for 1.30 hour in a hot air oven.[6]

Table No.01 Composition of Valsartan Containing Microspheres

Sr. No.	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
1	Valsartan	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
2	Carbopol	100 mg	200 mg	300 mg	400 mg	500 mg	600 mg	700 mg	800 mg
3	Ethyl cellulose	200 mg	300 mg	400 mg	500 mg	600 mg	700 mg	800 mg	900 mg
4	HPMC	300 mg	400 mg	500 mg	600 mg	700 mg	800 mg	900 mg	1000 mg
5	Ethanol	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml
6	Liquid paraffin	49 ml	49 ml	49 ml	49 ml	49 ml	49 ml	49 ml	49 ml
7	Span 80	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml

Evaluation Parameter of Microspheres
Percentage Yield
To prepared oral microsphere of all batches accurately weight. The measured weight of prepared microspheres was divided by total amount of all excipient and drug used in preparation of oral microspheres, which give the total percentage yield of total microspheres. [7]

It was calculated by following equation;

$$\% \text{ yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipient and drug}} \times 100$$

Swelling Index
The swelling indexes of the formulated microspheres were performed phosphate buffer pH 6.8 at 37.5 ± 0.5°C for 8 hours. Drug loaded microspheres were equilibrated in different test tubes and at every one-hour interval; microspheres were withdrawn filtered transferred into a small beaker and the weighed. [8]

The swelling ratio was calculated from the followed expression,

$$\text{Swelling index} = \frac{Wf - W0}{W0} \times 100$$

Drug Entrapment Efficiency

Entrapment efficiency of oral microspores was evaluated by deriving percent drug entrapment. the drug content of drug loaded oral microsphere was determine by dispersing 10 mg of oral microspheres in 10 ml ethanol followed by agitation with of magnetic stirrer for about 30 min to extract the drug and dissolved completely. after filtration though paper the 1 ml of filtrate is pipette out and diluted up to 10 ml volumetric flask. Drug concentration in ethanol phase was recorded by taking absorbance of this solution. The drug concentration was calculated. Thus, the total drug entrapped in total yield of microspheres from the procedure was calculated. It is express in percentage it is called as % drug entrapment. the amount of drug loaded and entrapped in oral microsphere was calculated by following formula. [9]

$$\% \text{ Drug Entrapment} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug loaded expected}} \times 100$$

Drug Content

Drug content study the drug content of microsphere was determined by spectrophotometrically at 361 nm and 241 (Model No. 1700 PC- Shimadzu, Japan). Each determination was made in triplicate. 32-35 Drug content were calculated by using following formula Drug Content = Conc. × dilution factor × volume/1000. [10]

In-Vitro Dissolution Study

Drug release from the microsphere was performed using the rotating basket method as specified in USPXXIV. In-vitro release profile was examined in Phosphate buffer pH 6.8 from 1- 8 hours. Microspheres equivalent to 100 mg of drug were placed in the basket and the medium was maintained at 37°C and was kept at a rotation of 750 rpm. An aliquot of 5 ml were withdrawn periodically at intervals of one hour and same volume of fresh medium was replaced. The concentration of drug released at time intervals was determined by measuring the absorbance at 241nm using UV spectrophotometer. [11]

Optical Microscopy

The particle size determination of hollow microspheres was resolved with an optical microscopic technique using polarized light and calibrated ocular micrometer was to measure the mean particle size**.** [12]

RESULT AND DISCUSSION

Pre formulation Studies

Standard Calibration curve of Valsartan

The standard calibration curve of drug phosphate buffer ph 6.8 depicted as a figure .the data of absorbance was shown in table No.04 the data had correlation with coefficient of 0.998 the equation of regression line depicted as equation Calibration curve of Valsartan with 6.8 pH phosphate buffer at 241 nm.

Table No.12 Calibration curve of Valsartan

Sample No	Concentration (µg/ml)	Absorbance at 241 nm
1	0	0
2	10	0.297
3	20	0.559
4	30	0.788
5	40	1.096
6	50	1.339

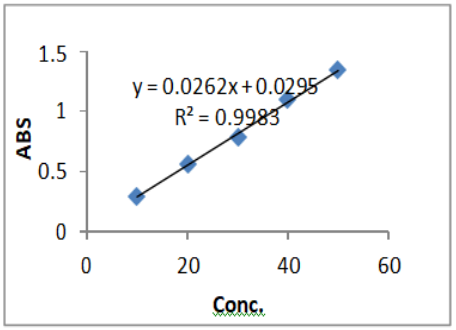

Fig. No.: 16 Calibration curve of Valsartan with 6.8 pH buffer at 241 nm

From the standard curve, it was observed that the drug obeys Beer's law in concentration range of 10-50 µg/ml in 6.8 pH phosphate buffer. Drug show good linearity with regression of coefficient and equation for this line obtained was found to be (y = 0.026x +0.029) which used for calculation of amount of drug .

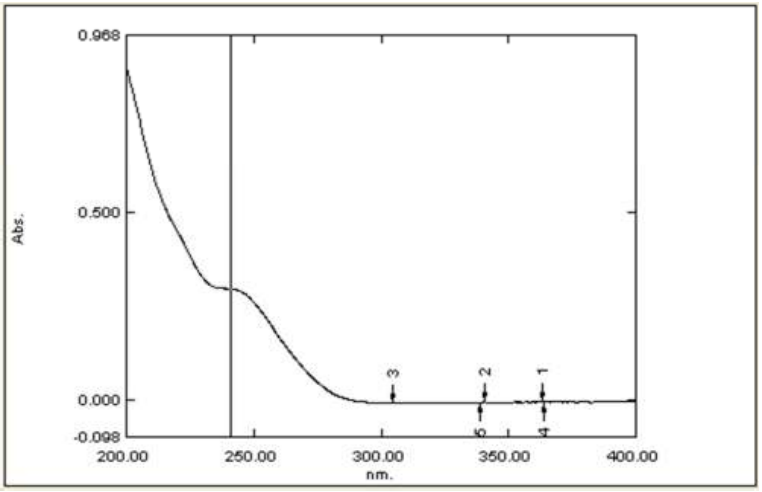

Fig. No.: 17 Absorbance of Valsartan with 6.8 pH buffer at 241 nm

FTIR Study

The IR Spectrum preview pictures are as follows:

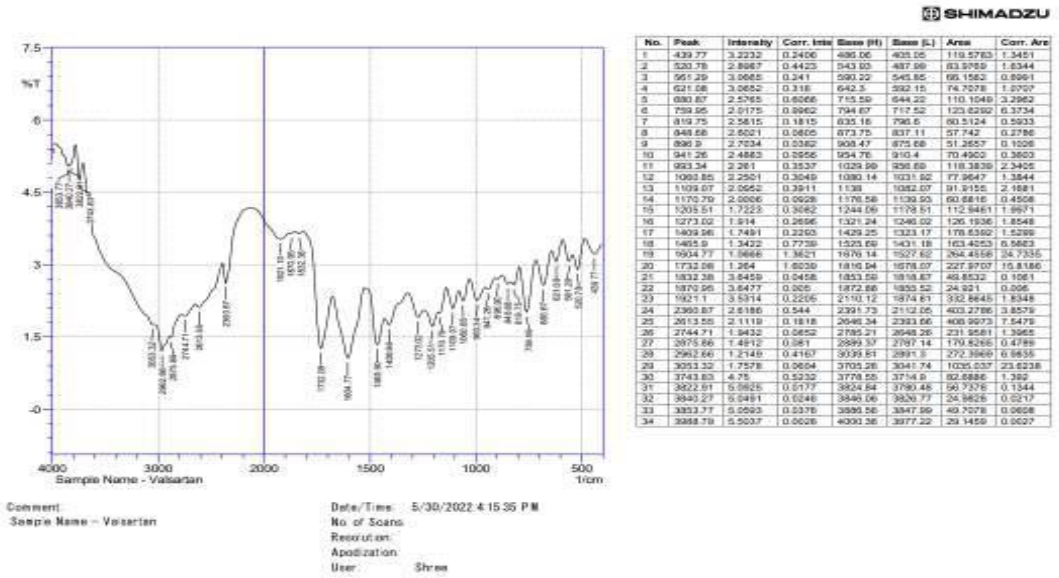

Table No. 14 Identification Functional Group of Valsartan

Sr.No.	Wave number (cm-1)	Functional groups present
1	3035.96	0H stretching
2	2873.94	CH stretching
3	1734.01	C=O stretch, acid
4	1602	C=O stretch, amide
5	1570	N-N bending

From above observation it was conclude which is functional group present in graph similar with Valsartan.

The possible interaction between the drug and polymer was studied by FTIR spectroscopy. There was no consideration change in position of characteristic absorption band and bond of various functional groups present in drug. This observation clearly suggest that the Valsartan shows no prominent change in characteristics even in its physical mixture. The result of FTIR spectra indicate the interaction between drug and polymers. It shows that

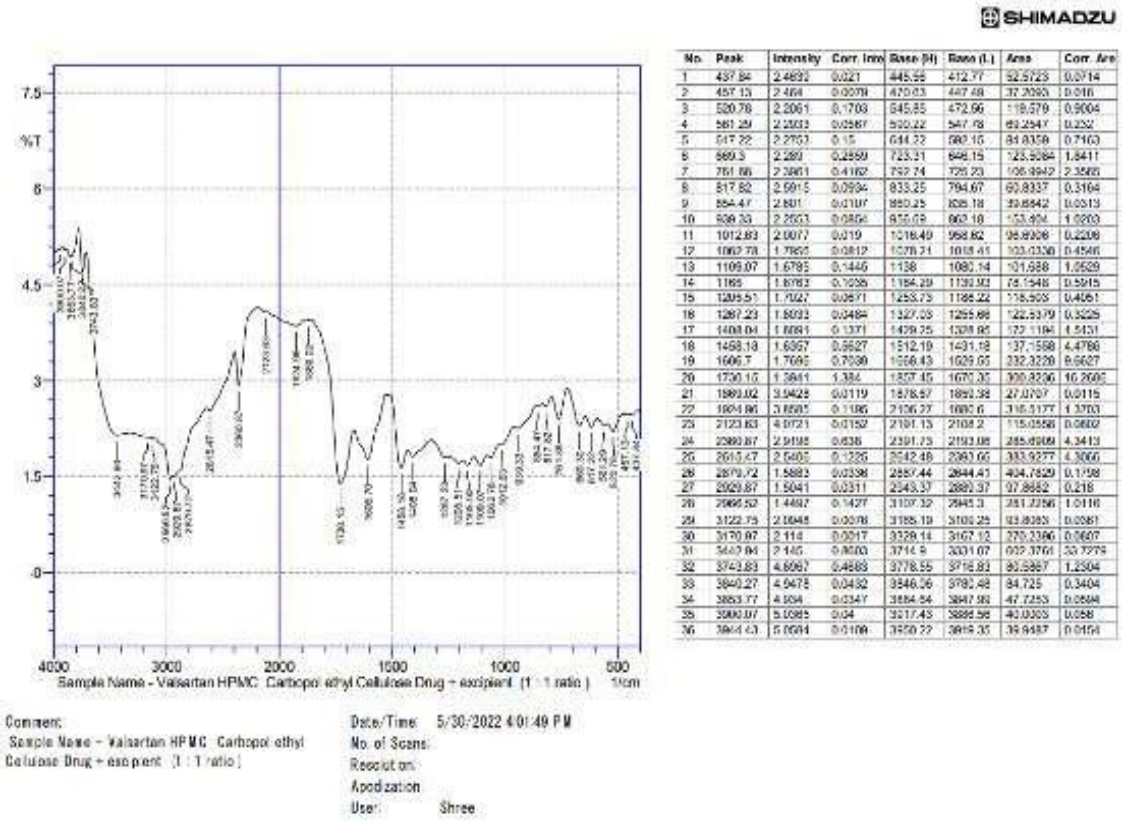

Fig No.: 21 FTIR spectra of Valsartan with Polymers

Valsartan confirmed was compatible with Carbopol, Hydroxypropyl methylcellulose and Ethyl cellulose.

Physicochemical

Sr. No.	No. Characteristics	Result
1	Color	White
2	Order	Order less

The physical appearance of sample of valsartan is carried out as per I.P. it shows that white in colour, Order less amorphous powder.

Solubility study

Table No.16 Solubility study

Sr. No.	Solvent	Solubility
1.	Water	Soluble
2.	Methanol	Freely Soluble
3.	Ethanol	Freely Soluble
4.	2-propanol	Sparingly Soluble
5.	Phosphate buffer 6.8 pH	Soluble
6.	DMSO	Soluble
7.	Chloroform	Soluble

This determination is carried out in accordance with the experimental requirement as well as literature standard.

Melting point

Melting point values of Valsartan sample was found to be 116 ºC, 115 ºC and 114 ºC . The reported melting point Average for Valsartan 115ºC. Hence, experimental values are in good agreement with official values.

Evaluation of Microspheres

Percentage Yield

Table No.23 Percentage Yield

Formulation Batches	Percentage Yield
F1	42.39%
F2	65.21%
F3	76.23%
F4	70.19%
F5	75.81%
F6	82.57%
F7	86.92%
F8	90.84%

From above observation batches F1 to F8 it was found to be F8 have higher percentage yield as 90.84 % due to loss of chemicals in solvent evaporation process percentage yield is up to 90.84 %.

Swelling Index

Table No.24 Swelling Index

Formulation Batches	Swelling Index
F1	18.65%
F2	15.67%
F3	26.24%
F4	17.25%
F5	10.11%
F6	23.10%
F7	19.48%
F8	28.78%

Fig. No.:22 Bar graph of % swelling index

From above observation of bar graph represent all batches of F1 to F8 have swelling index but higher swelling index is batch F8. therefore, it was concluded F8 is good formulation as compare to other baches.

Drug Entrapment Efficiency

The Entrapment Efficiency of all batches were studied.

Table No.25 Drug Entrapment Efficiency of oral microspheres

Formulation Batches	% Percent Drug Entrapment
F1	65.35%
F2	66.58%
F3	70.14%
F4	80.85%
F5	80.15%
F6	82.90%
F7	82.34%
F8	83.46%

The Entrapment Efficiency of microsphere were found in the range between 65.35 to 83.46 % as the concentration of polymer increase, entrapment efficiency increases both are higher and lower stirring rate. Increase polymer concentration entrapment efficiency also increase. as F4 batch contain polymers carbapol 800 mg, HPMC 1000 mg and Ethyl cellulose 900 mg its show higher entrapment. but if we increase the concentration polymers decreased the entrapment efficiency.

Drug Content

Table No.26 Drug Content

Formulation Batches	Drug Content % Valsartan containing microsphere
F1	61.22 %
F2	66.61 %
F3	75.92 %
F4	69.78 %
F5	78.60 %
F6	83.54 %
F7	64.87 %
F8	85.52 %

From the above observation Loading efficiency of drug loaded batches was found to be 61.22 % to 85.52 %. The drug loading efficiency of all formulations were shown in table No.24 which indicates that the highest drug content was found to be F8 as 85.52% of Valsartan. Therefore, we can conclude F8 batch give best result as compare to other batches.

In-Vitro Dissolution Study

Table No.28 Percent Drug released of Valsartan

Formulation code/Time (Hour)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	8.44	8.85	12.27	9.74	9.74	13.72	11.14	7.69
2	25.13	16.76	23.64	18.77	26.38	27.22	25.23	36.25
3	45.23	23.12	39.14	29.25	42.78	67.25	49.23	74.36
4	55.12	42.14	58.12	45.98	61.87	68.26	51.12	74.59
5	73.17	59.56	75.14	67.28	81.14	84.12	86.47	84.99
6	78.24	75.14	69.12	67.69	80.97	91.57	83.22	90.12
7	81.47	64.02	79.87	69.12	82.14	87.25	89.21	87.21
8	77.14	65.87	79.21	68.81	83.76	88.71	81.14	89.96

% Cumulative drug release of batches F1-F8 is shown in above table. From this in vitro drug release study. The formulation F8 had highest drug release of 89.96 % as compared to other batches. The present study was under taken to evaluate and to design the antihypertensive microsphere with polymers carbopol, HPMC and ethyl cellulose. All the batches were evaluated for physical parameters and also for the in vitro evaluation studies. therefore, it was concluded F8 batch gives better % drug release.

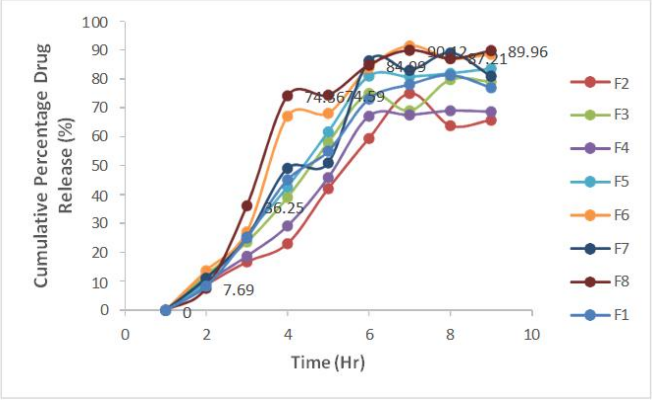

Fig.No.24: In-vitro Dissolution Profile of Valsartan Microsphere mean Cumulative Percentage Drug Release (%)

Optical Particles Analysis

The mean particle size of microsphere ranged from 11 to 13.15 µm, indicating narrow size distribution. such particle size narrow considers favourable for microspheres administration. It has been suggested that 4 µm is sufficient particle size for oral microspheres, it was noted that increasing concentration of polymers slightly increase the particle size of microspheres

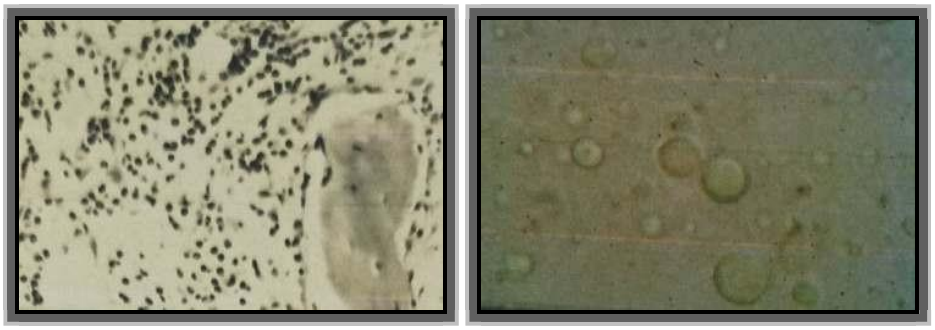

Fig. No.26: Determine of particle Size magnification A:10x, B:45x

From the above observation of particle size of batches was nearby same of avenge batch F8 have a spherical shape microsphere.

Table No.31 Average Particle Size

Formulation of Batches	Average Particle Size in µm	Shape
F1	11.15	Irregular
F2	12.14	Irregular
F3	14.22	Irregular
F4	12.98	Irregular
F5	12.00	Irregular
F6	13.41	Spherical
F7	13.97	Spherical
F8	11.12	Spherical

SUMMARY AND CONCLUSION

Oral microsphere was formulated as Antihypertensive Microsphere prepared by using polymer Carbopol, HPMC and ethyl cellulose, Ethanol, Liquid paraffin & Span 80. developed by Emulsion Solvent Evaporation method and it was found to be a suitable drugs Microsphere of particle size distribution, drug loading capacity Valsartan Microsphere obtained was White Spherical Crystal are formed. characterized and optimized in following way :

Preformulation studies were performed for oral Antihypertensive Microsphere such as colour of Microsphere melting point and solubility and preformulation studies were found to be good.

Chemical study using FTIR spectroscopy revelled no interaction between the drug and excipient. i.e. no compatibility with polymers Carbapol, HPMC and ethyl cellulose, ethanol , liquid paraffin .
The size of microsphere confirms by optical microscopy of microsphere ranged 11.00 to 13.15 um. and particle size mainly depends on stirring rate, hence as stirring rate increase particle size decreased irrespective of concentration of microsphere.

Evaluation of microsphere carried out by various test as production yield, Swelling Index, drug entrapment efficacy, Drug Content and Vitro Dissolution Studies performed for all formulation the formulation F8 has higher cumulative drug release of 89.96 % as compare to other formulation.

Conclusion

From this study it was conclude that double emulsion solvent evaporation technique is suitable for preparation of antihypertensive microsphere of Valsartan. The present study has been satisfactory attempted to formulate microsphere of antihypertensive drugs increase rate of absorption. the valsartan microsphere can retard the drug release in longer period of time and developed % entrapment efficiency was higher than other microsphere the particle size analysis revealed that all formulation gave particle size in range of um to 60 um. From all parameter studied it can conclude that Carbopol, HPMC and ethyl cellulose is better for preparation of antihypertensive microsphere.

Future Scope

Pharmacology and toxicology study.
In-vivo and in-vitro correlation study.
Pharmaceutical companies prefer to development of oral microspheres form due to both patient compliance and safety. (Especially Hypertensive patient)
This technology is a good tool for product life cycle management for increasing patient life of existing product.

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