IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF ORAL MICROSPHERES OF ANTIHYPERTENSIVE DRUGS BY DOUBLE EMULSION SOLVENT EVAPORATION METHOD

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ABSTRACT

Hypertension is chronic medical condition in which Blood pressure is increase therefore oral microspheres containing antihypertensive drugs is prepared by double emulsion solvent evaporation method by employing ethyl cellulose, Carbopol, and HPMC as a polymers. The prepared formulation was suitability characterized by FTIR, percent yield, swelling index, drug content, optical microscopy and In vitro drug release, studied reveted that particle spherical in shape, percentage yield and In vitro drug release shown promising results as a safest and most effective. Oral microspheres were prepared and suitably characterized for simultaneously deliver of two drugs. This double emulsion solvent evaporation method used for better therapeutic outcome in the hypertension disease.

Keyword:- : Oral microspheres of antihypertensive drug and evaluation parameter

INTRODUCTION

Chronic heart disease known as hypertension causes an increase in the systemic artery blood pressure. Systolic and diastolic blood pressure measurements are involved. At or below 120/80 mmHg, blood pressure is considered normal. Anything exceeding 140/90 mmHg is considered to be high blood pressure. The microspheres are the solid spherical particles ranging in size from 1 to1000µm. They consist of proteins or synthetic polymers & they are spherical free flowing particles, which are

biodegradable in nature. There are 2 types of microspheres as: 1) Microcapsules. 2) Micrometrics. 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 microparticles. To overcome some of the problems of conventional Drugs and enhance the therapeutic efficacy of a given drug they are designed. Control Release is transported through microspheres. Microspheres are employed for a localised effect and to sustain the release of drugs.[1,2]

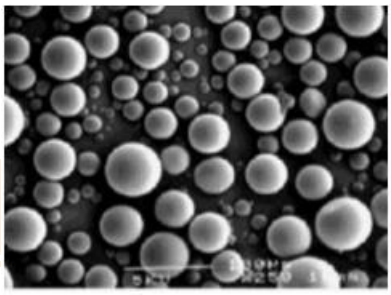

Fig. No. 01: Microspheres

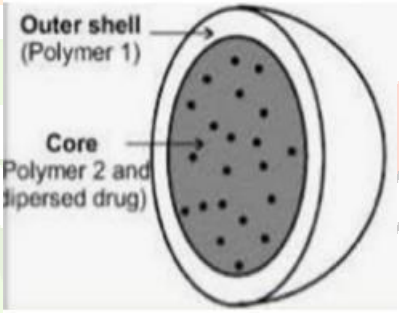

Fig.No. 02: Microspheres Cross Section

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.), it is suitable chemical for oral controlled release. Various physicochemical characteristics and in vitro release rates from these microspheres were then examined.[3] . The intake dose is delivered in several tiny different for multiarticulate particles, which hold and discharge a part of the dosage; therefore, the breakdown of a specific subunit does not affect the whole dosage failure. [4] Microparticles used in skin applications required to benefit the release of the medication into the skin ensure that now the drug remains localized at the application site and does not enter the systemic circulation unnecessarily.[5] They act as a reservoir which releases an active ingredient over a longer period of time to maintain effective concentration of drug products in the skin while decreasing undesired side effects. [6] Consequently, cycles of over- and under-medication are

reduced. It is particularly important for lowering antibiotic resistance while treating infectious disorders. In addition to improving product safety, these distribution methods can facilitate vehicle integration. [7,8]

ADVANTAGES

1) The Oral microspheres have the ability to bind & release the high concentration of thedrug.
2) They may be injected into the body because of their reduced size and spherical form.
3) The controlled variability in the drug release & breakdown is made possible by the microsphere form.
4) The microspheres have a consistent and lasting healing effect. The microspheres reduce the dosing frequency & thereby improve the patientcompliance.
5) The better utilization of drug will improve the bioavailability & reduce the incidenceor intensity of the adverse effects.
6) They have Improved protein & peptide drug delivery system.
7) Simple method of preparation. It enhance biological half-life.

DISDVANTAGES

1) The controlled release formulations generally contain the higher drug load & thus any lossof the integrity of the release characteristics of the dosage form may lead to the potential toxicity.
2) From the variety of factors like food & the rate of transit through the gut the release rate ofthe controlled release dosage form may vary.
3) This type of dose form shouldn't be eaten or crushed.
4) From one dose to another there is differences in the release rate

MATERIAS AND METHODS

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

Double Emulsion Solvent Evaporation Method

Microspheres were prepared by a solvent evaporation method. The solvent system ethanol/liquid paraffin was used. Agglomeration of microspheres was prevented by adding 2.5% (w/v) of Span80. Microspheres polymers were chosen to produce microspheres are carbopol 934P, HPMC and ethyl cellulose which was used for producing sustained release action dissolved as a powder in ethanol. Amlodipine and Valsartan in ethanol were prepared separately and added to the dispersion of polymers. The

homogeneous final dispersion was poured slowly with stirring (2000 rpm) into 50 ml of liquid paraffin. The obtained emulsion was stirred at 40°C for 3h. The suspension of microspheres in liquid paraffin was filtered, microspheres were washed by Diethyl ether and dried under vacuum at room temperature. Different batches of microspheres were prepared to study the effect of polymer concentration and stirring speed on particle size, drug loading, in vitro microspheres and drug release etc**.** [9]

Table No.01 Composition of Amlodipine and Valsartan Containing Microspheres

Sr. No.	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
1	Amlodipine	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
2	Valsartan	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
3	Carbopol	200 mg	400 mg	600 mg	800 mg	1000 mg	1200 mg	1400 mg	1600 mg
4	Ethyl cellulose	400 mg	600 mg	800 mg	1000 mg	1200 mg	1400 mg	1600 mg	1800 mg
5	HPMC	400 mg	600 mg	800 mg	1000 mg	1200 mg	1400 mg	1600 mg	1800 mg
6	Ethanol	15 ml	15 ml	15 ml	20 ml	20 ml	20 ml	25 ml	25 ml
7	RPM	2000	2000	2000	2000	2000	2000	2000	2000

EVALUATION OF RESULT MICROSPHERES

Fourier transform infrared spectroscopy studies

Drug and drug-polymer compatibility research identification procedure:

The FTIR spectra of the pure drug, excipient and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm-1). No peaks are observed which interfere with the main drug peaks. The following spectrum and table show IR spectrum for drug and polymer and the wave number of characteristic bands for the same. [15]

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. [16]

It was calculated by following equation;

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

Table No.02 Percentage Yield

Formulation Batches	Percentage Yield
F1	45.39%
F2	67.21%
F3	77.68%
F4	70.19%
F5	77.81%
F6	85.75%
F7	88.29%
F8	91.55%

From above observation batches F1 to F8 it was found to be F8 have higher percentage yield as 91.55 % due to loss of chemicals in solvent evaporation process percentage yield is up to 91.55 %.

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. [17]

The swelling ratio was calculated from the followed expression,

$$\text{Swelling index} = \frac{W_f - W_0}{W_0} \times 100$$

Where, W_f = weight of micro particle observed at every time interval

W_0 = initial weight of microspheres.

Table No.03 Swelling Index

Formulation Batches	Swelling Index
F1	21.95%
F2	17.64%
F3	28.20%
F4	19.04%
F5	11.11%
F6	25.00%
F7	18.48%
F8	29.87%

Fig. No.:03 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

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. [18]

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

The Entrapment Efficiency of all batches were studied.

Table No.04 Drug Entrapment Efficiency of oral microspheres

Formulation Batches	% Percent Drug Entrapment
F1	67.63%
F2	69.81%
F3	71.27%
F4	81.45%
F5	82.18%
F6	74.90%
F7	76.36%
F8	75.54%

The Entrapment Efficiency of microsphere were found in the range between 67.63 to 82.18 % 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 1000 mg its show higher entrapment. but if we increase the concentration polymers decreased the entrapment efficiency.

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. [19]

Table No.05 Drug Content

Formulation Batches	Drug Content % Amlodipine containing microsphere	Drug Content % Valsartan containing microsphere
F1	66.14 %	62.52 %
F2	59.19 %	66.61 %
F3	60.16 %	75.92 %
F4	56.25 %	69.78 %
F5	63.23 %	78.60 %
F6	68.12 %	83.54 %
F7	57.18 %	64.87 %
F8	78.26 %	86.87 %

From the above observation Loading efficiency of drug loaded batches was found to be 62.52 % to 96 %. 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 78.26 % as Amlodipine and 86.87 % of Valsartan. Therefore, we can conclude F8 batch give best result as compare to other batches.

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 361nm and 241nm using UV spectrophotometer. [20]

Table No.06 Percent Drug released of Amlodipine

Formulation code/Time (Hour)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	7.47	8.72	11.21	7.78	9.65	13.08	11.52	7.9
2	25.13	15.99	23.67	17.82	22.81	29	26.41	38.35
3	39.32	28.8	38.56	29.94	39.77	47.35	44.41	65.78
4	54.2	41.95	55.17	43.094	59.15	67.43	65.52	78.64
5	71.86	58.91	74.21	62.82	80.27	87.85	87.33	88.07
6	72.84	59.65	75.65	63.58	80.23	89.56	82.35	89.67
7	79.58	62.56	78.59	64.26	81.57	88.98	82.28	88.87
8	78.96	63.25	78.14	65.98	82.36	89.56	82.14	91.36

% Cumulative drug release of batches F1-F8 is shown in above table. From this in vitro drug release study. The formulation H8 had highest drug release of 91.36 % 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.

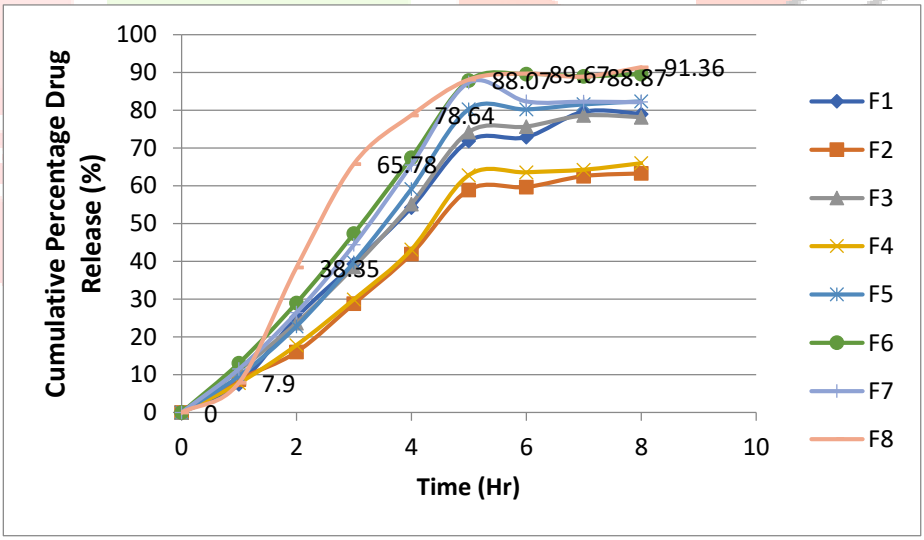

Fig.No.04: In-vitro Dissolution Profile of Amlodipine Microsphere mean Cumulative Percentage Drug Release (%)

From the above observation in vitro drug release graph fig no.4 shows the higher drug release formulation of Amlodipine microsphere is F8 had highest drug release of 91.36% as compare to other batches.

Table No.07 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 I8 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.

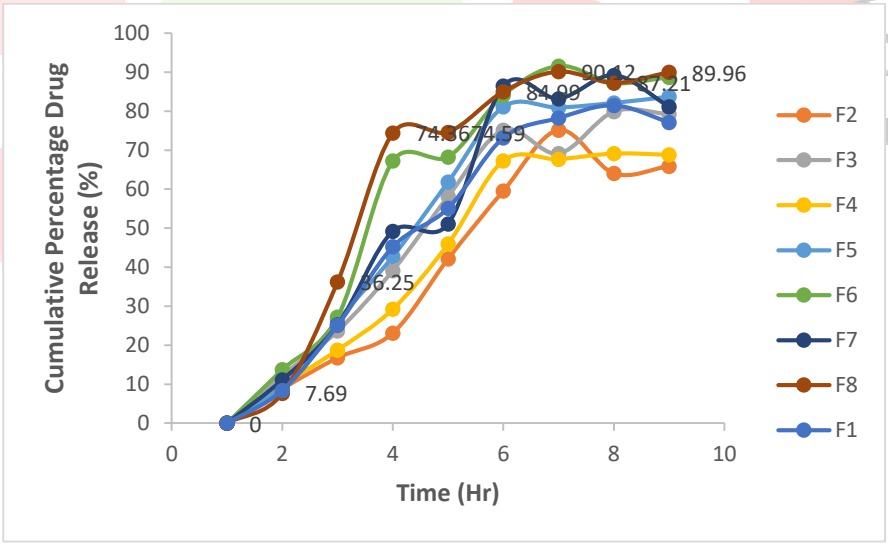

Fig.No.05: In-vitro Dissolution Profile of Valsartan Microsphere mean Cumulative Percentage Drug Release (%)

From the above observation in vitro drug release graph fig no.5 shows the higher drug release formulation of Valsartan microsphere is F8 had highest drug release of 89.96% as compare to other batches. The present study was under taken to evaluate and to design the Antihypertensive microsphere with polymer Carbopol, HPMC, and Ethyl cellulose. The formulation F8 consist of Amlodipine (100mg), Valsartan (100mg), Carbopol (1600mg), Ethyl cellulose (1800mg), HPMC (1800mg) and Ethanol (25

ml). 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.

Optical Microscope

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. [21]

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

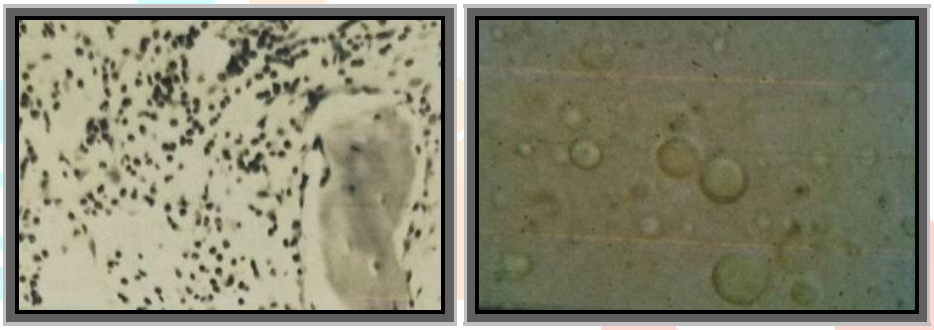

Fig. No.06: Determine of particle Size magnification A:10x, B:45x

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

Table No.08 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, developed by Double Emulsion Solvent Evaporation Method and it was found to be a suitable Two drugs Microsphere of particle size distribution, drug loading capacity and amlodipine and Valsartan Microsphere obtained was White Spherical Crystal are formed. characterized and optimized in following way:

- The size of microsphere confirms by optical microscopy of microsphere ranged 11.12 to 13.97 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 92.64 % 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 Amlodipine and Valsartan. The present study has been satisfactory attempted to formulate microsphere of antihypertensive drugs increase rate of absorption. the amlodipine and valsartan microsphere can retard the drug release in longer period of time and developed % entrapment efficiency was higher than other microsphere. Prior to formulation, preformulation studied carried out in order to establish compatibility between drug and polymers by FTIR Spectroscopy. The result of FTIR study revealed that there is no physical and chemical interaction between drug and polymers. From all parameter studied it can conclude that Carbopol, HPMC and Ethyl cellulose is better for preparation of Antihypertensive microsphere.

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