CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND EVALUATION OF LINAGLIPTIN MICROSPHERES BY USING DIFFERENT POLYMERS

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Abstract:

In the present work, Microspheres of Linagliptin using PLGA, Ethyl cellulose and HPMC K4M as polymers were formulated to deliver Linagliptin via oral route. The results of this investigation indicate that solvent evaporation method can be successfully employed to fabricate Linagliptin microspheres. In this work an effort was made to formulate microsphere of Linagliptin by using different polymers. Prepared formulations are evaluated for bulk density, tapped density, precent mucoadhesion, Percent compressibility, hausners ration, percentage yield, size and interaction study by Differential scanning calorimeter and in vitro drug release. Formulation which passed all the evaluation parameters was considered as best formulation of Linagliptin. The present study conclusively that Linagliptin microsphere could be prepared successfully and formulation F5 was shows satisfactory result.

Keywords: *Linagliptin, PLGA, Ethyl cellulose and HPMC K4M and Microspheres.*

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Please cite this article in Mohd. Rizwan Hussain et al, ***Formulation And Evaluation Of Linagliptin Microspheres By Using Different Polymers****, Indo Am. J. P. Sci, 2023; 10 (11).*

INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of Oral route drug administration is by far the most preferable route for taking medications. However, their short circulating half life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of medication to achieve therapeutic effect. Rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamics profile is to release the drug in a controlled manner and site specific manner. Microspheres are small spherical particles, with diameters 1 µm to 1000 µm. They are spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature. There are two types of microspheres; microcapsules and micromatrices, which are described as, Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall. and micromatrices in which entrapped substance is dispersed throughout the matrix. Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Microsphere play an important role to improve bioavailability of conventional drugs and minimizing side effects. Ideal characteristics of microspheres:

Ideal characteristics of microspheres:

- ✓ The ability to incorporate reasonably high concentrations of the drug.
- ✓ Stability of the preparation after synthesis with clinically acceptable shelf life.
- ✓ Controlled particle size and dispersability in aqueous vehicles for injection.
- ✓ Release of active reagent with a good control over a wide time scale.
- ✓ Biocompatibility with a controllable biodegradability.
- ✓ Susceptibility to chemical modification.

Advantages of microspheres:

1. Particle size reduction for enhancing solubility of the poorly soluble drug.
2. provide constant and prolonged therapeutic effect.
3. provide constant drug concentration in blood there by increasing patent compliance,
4. Decrease dose and toxicity.
5. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.
6. Reduce the dosing frequency and thereby improve the patient compliance
7. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
8. Microsphere morphology allows a controllable variability in degradation and drug release.
9. Convert liquid to solid form & to mask the bitter taste
10. Protects the GIT from irritant effects of the drug.
11. Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
12. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Limitation:

Some of the disadvantages were found to be as follows
1. The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.

Application Of Microspheres In Pharmaceutical Industry:

1. Ophthalmic Drug Delivery:

Microspheres developed using polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles.
Eg. Chitosan, Alginate, Gelatin.

2. Oral drug delivery:

The ability of microspheres containing polymer to form films permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make microspheres more

suitable for oral drug delivery applications. Eg. Chitosan, Gelatin.

3. Gene delivery:
Microspheres could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. Eg. Chitosan, Gelatin, viral vectors, cationic liposomes, polycation complexes.

4. Nasal drug delivery:
Polymer based drug delivery systems, such as microspheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Eg. Starch, Dextran, Albumin, Chitosan+Gelatin.

5. Intratumoral and local drug delivery:
In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, polymer films are fabricated. Mixture of drug has promising potential for use in controlled delivery in the oral cavity. Eg. Gelatin, PLGA, Chitosan and PCL.

6. Buccal drug delivery:
Polymer is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. Chitosan, Sodium alginate.

7. Gastrointestinal drug delivery:
Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug . eg. Eudragit, Ethyl cellulose+Carbopol BSA, Gelatin.

8. Transdermal drug delivery:
Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Eg. Chitosan, Alginate, PLGA.

9. Colonic drug delivery:
Polymer has been used for the specific delivery of insulin to the colon. Eg. Chitosan.

10. Vaginal drug delivery:
Polymer, modified by the introduction of thioglycolic

MATERIALS AND METHODS:

Linagliptin Procured from Hetero Pharma limited Hyd, provided by SURA LABS, Dilsukhnagar, Hyderabad, PLGA from Merk specialiities Pvt Limited, Mumbai, Ethyl cellulose from M/S Micro labs limited, Hosur. India, HPMC K4M from Coloron Asia Private Limited; Goa, Dichloro methane (mL) from Qualikems Fine Chem Pvt., Ltd, Methanol (mL) from Merk specialiities Pvt Limited,Mumbai, Sodium lauryl sulphate (mg) from Merk specialiities Pvt Limited,Mumbai.

PREPARATION OF 0.1N HCl (pH 1.2):
Take 8.5 ml of HCl in a 1000ml volumetric flask and make up the volume with distilled water

Preparation of Standard Calibration Curve of Linagliptin:

- ✓ 10 mg of Linagliptin was accurately weighed and dissolved in 10ml of methanol (Stock Solution – I) to get a concentration of 1000 µg/ml.
- ✓ From the stock solution- I, 1ml of aliquots was taken and suitably diluted with 0.1N HCl (Stock Solution-II) to get concentrations of 100µg/ml.
- ✓ From the stock solution- II, aliquots were taken and suitably diluted with 0.1N HCl (pH 1.2) to get concentrations in the range of 2 to 10µg/ml. The absorbance of these samples were analyzed by using UV-Visible Spectrophotometer at 295nm against reference solution 0.1N HCl (pH 1.2). The procedure repeated to pH 6.8 phosphate buffer and pH 7.4 phosphate buffer.

METHOD OF PREPARATION
SOLVENT EVAPORATION METHOD:
Linagliptin microspheres were prepared using PLGA, Ethyl cellulose and HPMC K4M and distilled water as continuous phase by solvent evaporation technique. Initially dichloromethane (DCM) and methanol was mixed uniformly at room temperature, then PLGA, Ethyl cellulose and HPMC K4M in various proportions was dissolved in the above solution. To this mixture, a drug solution corresponding was added and mixed thoroughly and injected drop wise in to the continuous phase consisting of 100mL of 0.2% (w/v) SLS (sodium lauryl sulphate) at 250 rpm. The microspheres obtained was washed for 2-3 times with distilled water and dried at room temperature. Different concentrations and ratios of polymers used in the formulation of microspheres are mentioned in Table.

CHARACTERIZATION OF MICROSPHERES:

INGREDIENTS (MG)	FORMULATIONS								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Linagliptin	5	5	5	5	5	5	5	5	5
PLGA	25	50	75	-	-	-	-	-	-
Ethyl cellulose	-	-	-	25	50	75	-	-	-
HPMC K4M	-	-	-	-	-	-	25	50	75
Dichloromethane (mL)	20	20	20	20	20	20	20	20	20
Methanol (mL)	30	30	30	30	30	30	30	30	30
Sodium lauryl sulphate (mg)	20	20	20	20	20	20	20	20	20

Micromeritic properties

The microspheres were characterized by their micromeritic properties such as Particle size, Bulk density, Tapped density, Compressibility index, Hausners ratio and Angle of repose.

Bulk density

In this method floating microspheres are transferred to a measuring cylinder and is tapped manually till a constant volume is obtained. This volume is bulk volume and it includes true volume of the powder and the void space among the microspheres.

$$\text{Bulk density} = \frac{\text{Mass of microspheres}}{\text{Bulk volume}}$$

Tapped density

In this method floating microspheres were transferred to a measuring cylinder & tapped for 100 times. After tapping volume of microspheres was visually examined. The ratio of mass of microspheres to volume of microspheres after tapping gives tapped density floating microspheres.

Percent Compressibility index was determined by using the formula,

Carr's Index = (tapped density – bulk density) x 100 / tapped density

Hausners ratio

Hausners ratio of microspheres was determined by comparing tapped density to bulk density using the equation

Hausner ratio = tapped density / bulk density

Angle of repose

Angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method4. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed microspheres were allowed to pass through the funnel freely on to the surface. The height and radius of the powder cone was measured and angle of repose was calculated using the following equation.

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

Here,

θ - Angle of repose

h - Height of granules above the flat surface

r - Radius of the circle formed by the granule heap.

Percentage yield

The percentage of production yield was calculated from the weight of dried microsphe-res recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical mass (Microspheres)}}{\text{Theoretical mass (Polymer + Drug)}} \times 100$$

Drug entrapment efficiency:

Weighed amount of microspheres (100 mg) with phosphate buffer pH 7.4 (10 ml) was added in a vial. The solution was stirred vigorously for 24 hours with mechanical stirrer. Supernatent was collected by centrifugation and drug content in supernatent was determined by using UV spectrophotometer at wavelength 295nm. The amount of drug entrapped in the microspheres was calculated by the following formula,

$$\% \text{ Drug Entrapment Efficiency} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Swelling study:

Swelling ratio of different dried microspheres were determined gravimetrically in simulated gastric fluid pH 1.2 .The microspheres were removed periodically from the solution, blotted to remove excess surface liquid and weighed on balance. Swelling ratio (% w/v) was determined from the following relationship:

$$(Wt - W0)$$

$$\text{Swelling ratio} = \frac{\text{Wt}}{\text{W0}} \times 100$$

Where W0 & Wt are initial weight and Final weight of microspheres respectively

***In vitro* drug release study:**

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5^0C, 50 rpm) using the USP type – I rotating basket method in simulated gastric fluid pH 1.2 (900ml) for 2 hours then replace the media with pH 6.8 phosphate buffer for 3 hours, then replace the media with pH 7.4 Phosphate buffer. A quantity of accurately weighed microspheres equivalent to 100mg Linagliptin each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 295nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed simulated gastric fluid pH 1.2 maintaining sink conditions throughout the experiment.

***In Vitro* drug release kinetics**

The release data obtained was fitted into various mathematical models. The parameters 'n' and time component 'k',the release rate constant and 'R', the regression coefficient were determined by Korsmeyer-Peppas equation to understand the release mechanism. To examine the release mechanism of Linagliptin from the microspheres, the release data was fitted into Peppa's equation,

$Mt / M\infty = Ktn$

Where, $Mt / M\infty$ is the fractional release of drug, 't' denotes the release time, 'K' represents a constant incorporating structural and geometrical characteristics of the device, 'n' is the diffusional exponent and characterize the type of release mechanism during the release process.

Table 7.2 : *In-Vitro* drug release kinetics

If n < 0.5, the polymer relaxation does not affect the molecular transport, hence diffus-ion is Fickian.

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport or non-Fickian	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

If n > 0.5, the solid transport will be non-fickian and will be relaxation controlled.

Other equations to study the drug release kinetics from dosage forms

a. Zero Order

% R = kt

This model represents an ideal release in order to achieve prolonged pharmacological action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as Matrix tablets containing low soluble drugs.

b. First Order

Log (fraction unreleased) = kt/2.303

The model is applicable to hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

c. Matrix (Higuchi Matrix)

% R = kt 0.5

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

d. Peppas Korsmeyer Equation

% R = kt n

log % R = logk + nlogt

This model is widely used when release mechanism is well known or when more than one type of release phenomenon could be involved. The 'n' values could be used to characterize different release mechanisms as.

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Agilent spectrophotometer and the IR spectrum was recorded from 4000 cm-1 to 500

cm-1. The resultant spectrum was compared for any spectrum changes.

SEM (Scanning Electron Microscope) studies:
The surface morphology of the layered sample was examined by using SEM(JEOL Ltd.,Japan). The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stubs were coated with a thin layer (300A) of gold by employing POLARON - E 3000 sputter coater. The samples were examined by SEM with direct data capture of the images on to a computer.

RESULT AND DISCUSSION:

Determination of λ_{max}

A solution of 10µg/ml of Linagliptin was scanned in the range of 200 to 400nm. The drug exhibited a λ_{max} at 295 nm in simulated gastric fluid pH 1.2 and pH 7.4 phosphate buffer respectively.

Table : Calibration curve data for Linagliptin in simulated gastric fluid pH 1.2

Concentration (µg /ml)	Absorbance
0	0
5	0.178
10	0.358
15	0.525
20	0.676
25	0.849

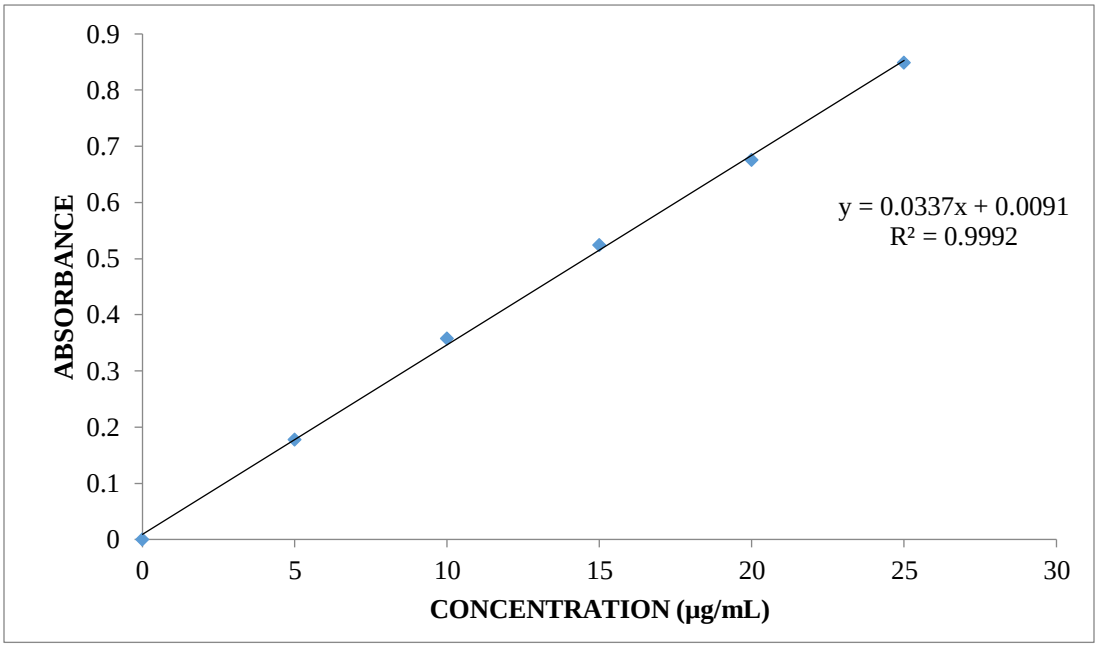

Figure : Standard graph Of Linagliptin in simulated gastric fluid pH 1.2

Table : Calibration curve data for Linagliptin in pH 7.4 phosphate buffer

Concentration (µg /ml)	Absorbance
0	0
5	0.175
10	0.305
15	0.428
20	0.561
25	0.697

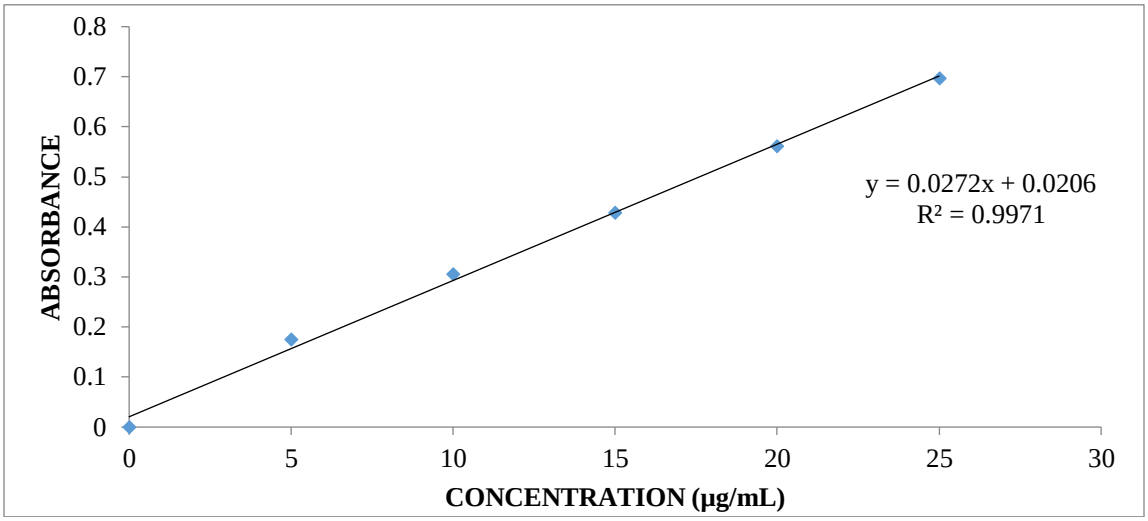

Figure : Standard graph Of Linagliptin in pH 7.4 phosphate bufferEvaluation:

Table: Micromeritic property of microspheres of Linagliptin

Formulation code	Mean partical size	Bulk density ((gm./cm^3))	Tapped density (gm./cm^3)	Hauseners ratio	Carr's index	Angle of repose
F1	412.14	0.434 ± 0.2	0.476 ± 0.3	1.095	8.695	23.2 ± 0.2
F2	421.95	0.277 ± 0.2	0.312 ± 0.2	1.133	11.11	25.2 ± 0.1
F3	458.41	0.588 ± 0.3	0.666 ± 0.4	1.333	11.76	27.1 ± 0.1
F4	410.15	0.521 ± 0.3	0.631 ± 0.3	1.121	17.39	24.4 ± 0.4
F5	420.96	0.625 ± 0.1	0.833 ± 0.1	1.333	25.00	28.3 ± 0.4
F6	441.65	0.476 ± 0.3	0.526 ± 0.2	1.105	9.52	25.1 ± 0.1
F7	425.14	0.416 ± 0.2	0.476 ± 0.3	1.142	12.50	26.7 ± 0.4
F8	432.69	0.384 ± 0.4	0.434 ± 0.3	1.130	11.53	26.0 ± 0.3
F9	461.54	0.555 ± 0.1	0.714 ± 0.1	1.285	22.22	26.6 ± 0.2

Table: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% yield	Drug Content (mg)	% Drug entrapment efficiency
1	F1	89.31	96.14	86.14
2	F2	91.12	98.65	90.91
3	F3	96.08	99.76	91.72
4	F4	90.74	98.14	95.58
5	F5	96.91	96.52	98.45
6	F6	98.24	100.04	93.87
7	F7	96.39	97.24	88.72
8	F8	98.52	98.53	92.51
9	F9	98.47	99.21	99.82

***IN VITRO* MUCOADHESION TEST**

As the polymer to drug ratio increased, microspheres containing PLGA exhibited % mucoadhesion ranging from 61 to 70%, microspheres containing Ethyl cellulose exhibited % mucoadhesion ranging from 75 to 95% and microspheres containing HPMC K4M exhibited % mucoadhesion ranging from 78 to 93%. The results of in-vitro mucoadhesion test are compiled in Table 8.6. Effect of polymer proportion on % mucoadhesion is depicted in Figures 8.6 to 8.8 and comparative depiction of % mucoadhesion is depicted in Fig. 8.6.Table 8.6: Percentage mucoadhesion of the prepared microspheres..

Table: *In Vitro* Mucoadhesion Test of all Formulations

S.NO.	FORMULATION CODE	No. OF MICROSPHERES		PERCENTAGE MUCOADHESION
		INITIAL	FINAL	
1	F1	20	15.48	61
2	F2	20	11.85	58
3	F3	20	15.14	70
4	F4	20	17.96	93
5	F5	20	20.71	95
6	F6	20	16.17	75
7	F7	20	16.80	93
8	F8	20	11.58	86
9	F9	20	17.21	78

Table : *In-vitro* drug release data of Linagliptin microspheres

TIME (H)	Cumulative percentage of drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	21.89	16.87	16.18	17.82	13.91	15.67	18.90	20.15	26.39
2	28.96	25.50	27.92	24.31	18.68	21.75	23.36	27.96	35.52
3	35.75	31.89	36.27	34.93	24.90	26.90	30.21	32.82	42.80
4	48.18	45.23	49.96	47.72	36.53	33.83	38.89	37.56	59.93
5	55.09	52.19	58.19	53.15	47.95	40.76	47.23	41.29	65.28
6	62.10	60.97	65.76	64.91	52.18	47.92	50.15	48.75	70.23
7	78.67	68.57	72.51	68.75	63.87	53.76	56.82	56.51	78.06
8	85.79	74.21	78.93	73.81	68.56	62.81	64.97	60.18	82.16
9	90.14	78.92	82.74	82.94	78.97	70.47	68.56	74.32	87.47
10	97.58	87.28	87.94	97.14	84.28	78.38	72.10	78.69	98.14
11		98.12	90.75		91.84	84.10	79.64	86.82	
12			97.35		99.88	91.17	84.78	90.53	

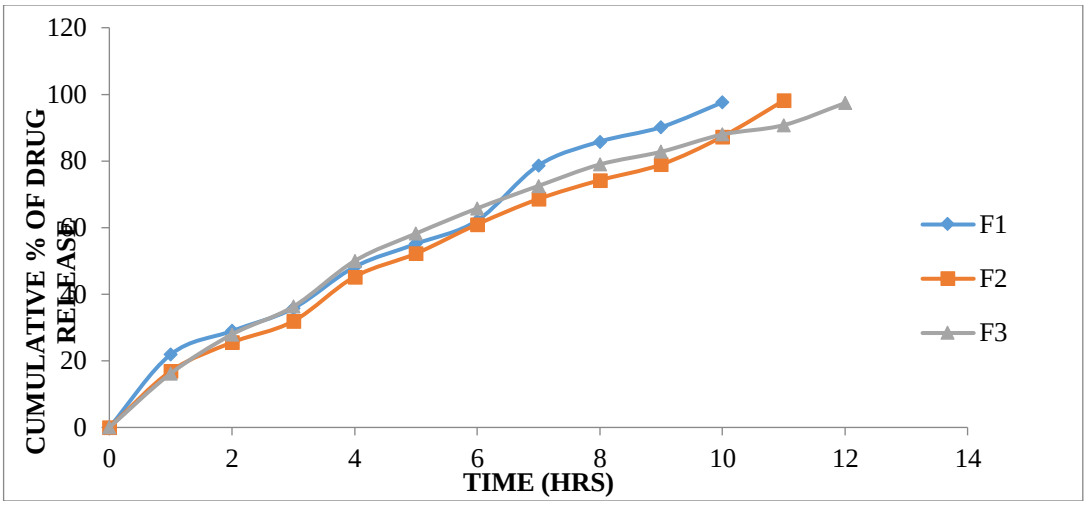

Figure : *In-Vitro* drug release profile of Linagliptin microspheres containing PLGA

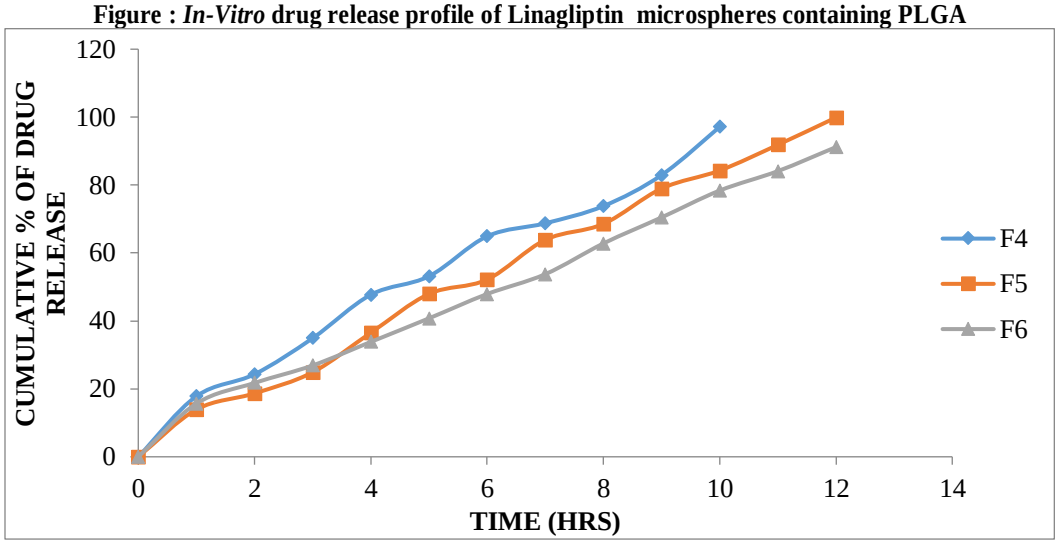

Figure: *In-Vitro* drug release profile of Linagliptin microspheres containing Ethyl cellulose

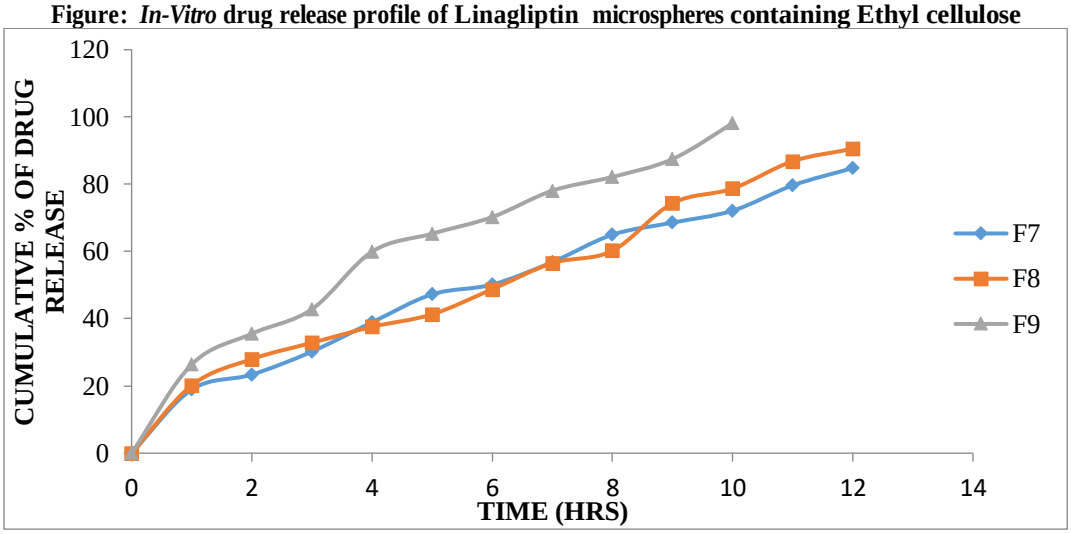

Figure: *In-Vitro* drug release profile of Linagliptin microspheres containing HPMC K4M

Table: Release kinetics studies of the optimized formulation (E5)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
13.91	1	1.000	1.143	0.000	1.935	13.910	0.0719	-0.857	86.09	4.642	4.416	0.226
18.68	2	1.414	1.271	0.301	1.910	9.340	0.0535	-0.729	81.32	4.642	4.332	0.309
24.9	3	1.732	1.396	0.477	1.876	8.300	0.0402	-0.604	75.1	4.642	4.219	0.423
36.53	4	2.000	1.563	0.602	1.803	9.133	0.0274	-0.437	63.47	4.642	3.989	0.653
47.95	5	2.236	1.681	0.699	1.716	9.590	0.0209	-0.319	52.05	4.642	3.734	0.908
52.18	6	2.449	1.718	0.778	1.680	8.697	0.0192	-0.282	47.82	4.642	3.630	1.012
63.87	7	2.646	1.805	0.845	1.558	9.124	0.0157	-0.195	36.13	4.642	3.306	1.336
68.56	8	2.828	1.836	0.903	1.497	8.570	0.0146	-0.164	31.44	4.642	3.156	1.485
78.97	9	3.000	1.897	0.954	1.323	8.774	0.0127	-0.103	21.03	4.642	2.760	1.881
84.28	10	3.162	1.926	1.000	1.196	8.428	0.0119	-0.074	15.72	4.642	2.505	2.137
91.84	11	3.317	1.963	1.041	0.912	8.349	0.0109	-0.037	8.16	4.642	2.013	2.628
99.88	12	3.464	1.999	1.079	-0.921	8.323	0.0100	-0.001	0.12	4.642	0.493	4.148

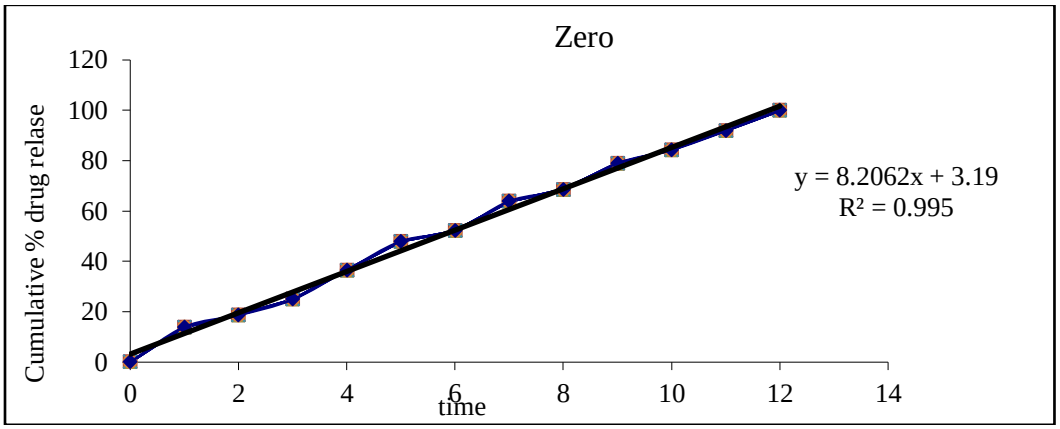

Figure: Graph of zero order release kinetics of optimized formula

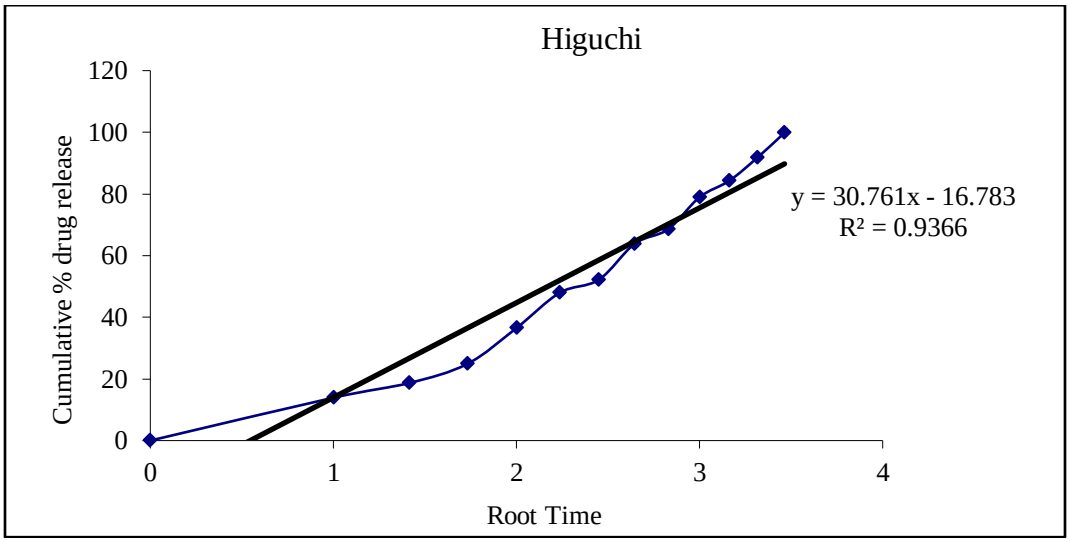

Figure: Graph of Higuchi release kinetics of optimized formula

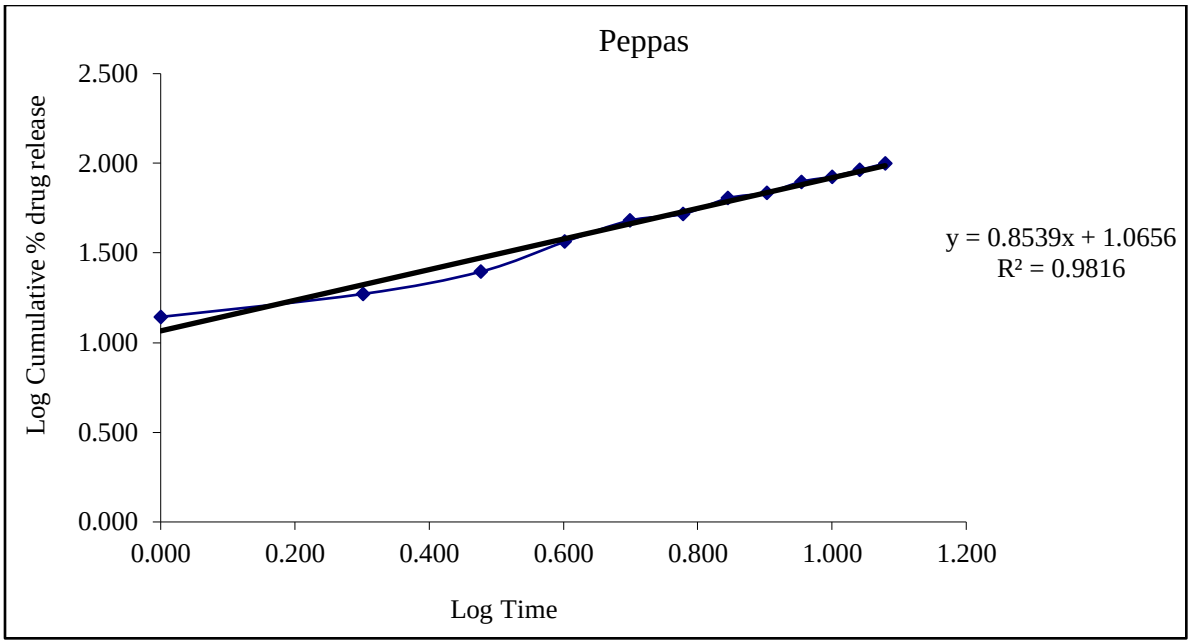

Figure: Graph of Peppas drug release kinetics of optimized formula

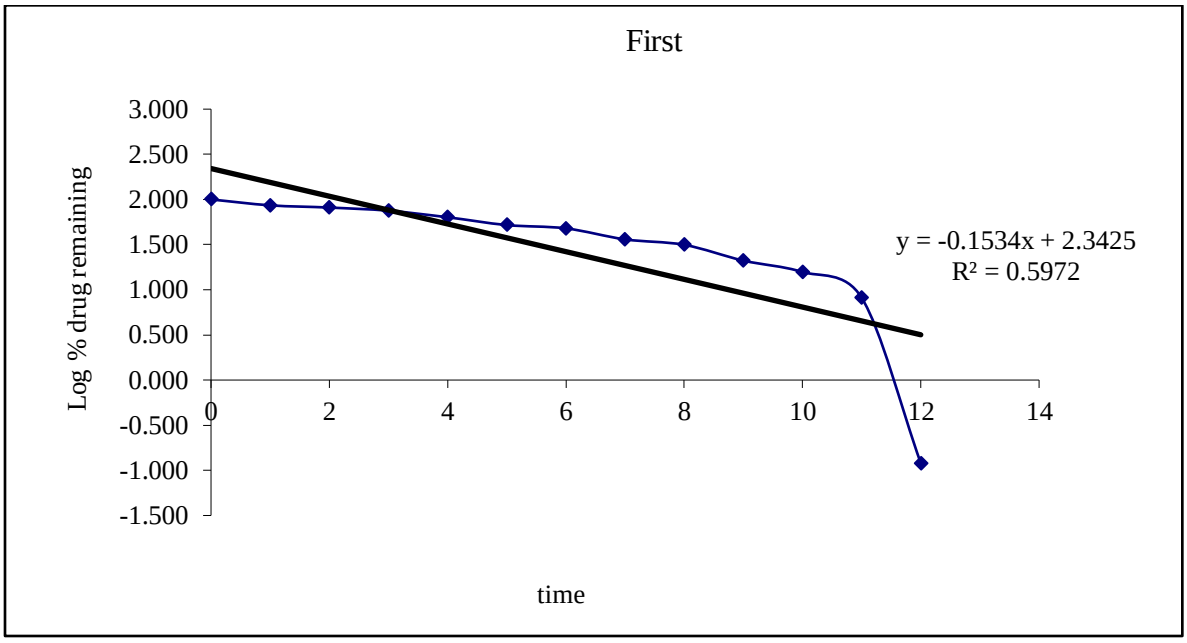

Figure: Graph of first order release kinetics of optimized formula

Optimised formulation F5 was kept for release kinetic studies. From the above graphs it was evident that the formulation F5 was followed zero order release kinetics.

COMPATIBILITY STUDIES

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish any possible interaction of Drug with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug.

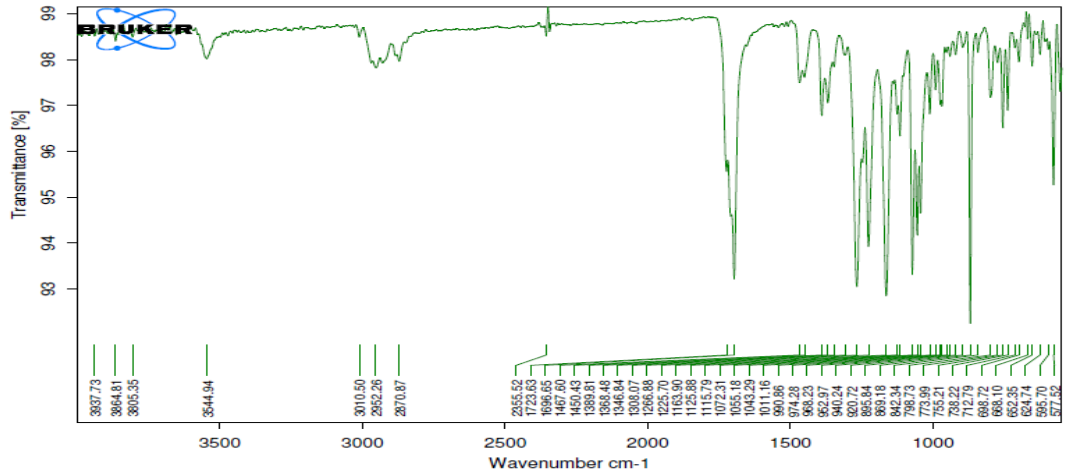

Figure: FT-IR spectra of Pure drug

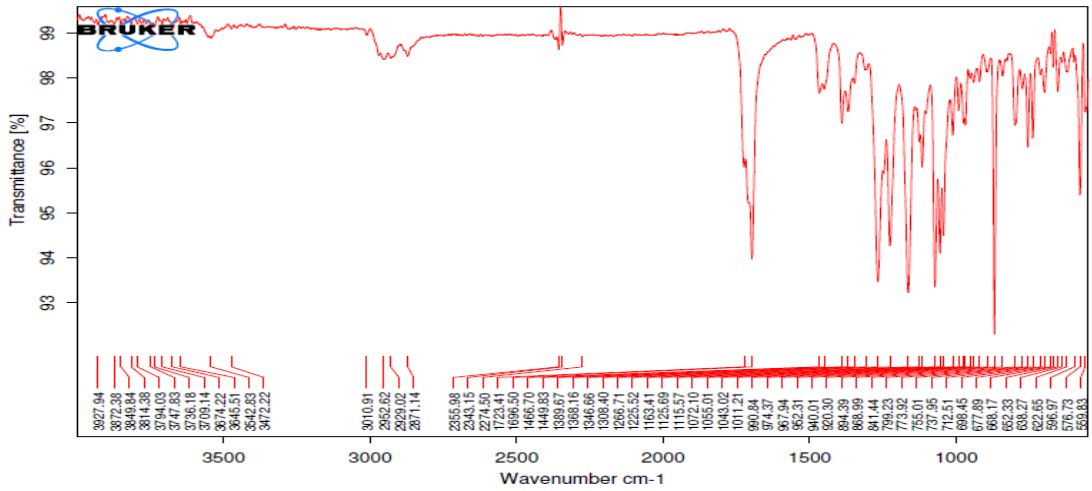

Figure : FT-IR spectra of Optimised formulation

SEM :

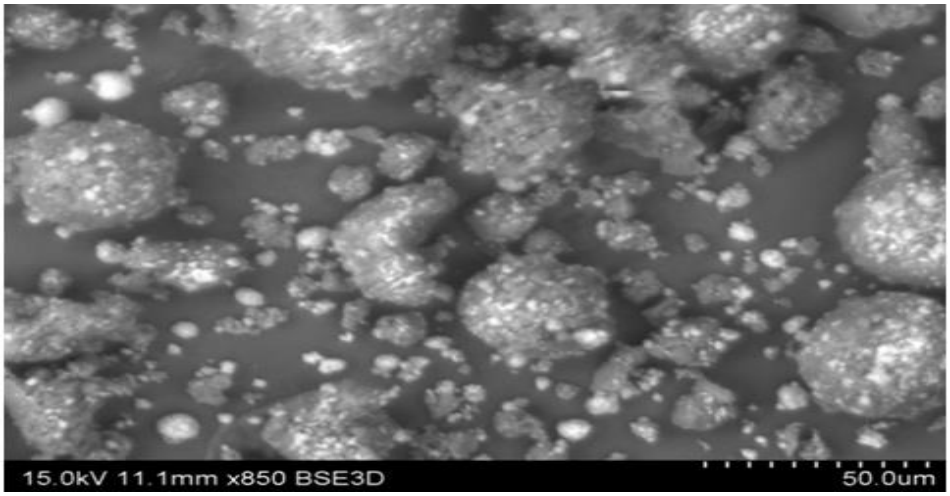

Figure : SEM of Optimised formulation

CONCLUSION:

Microspheres are prepared with PLGA, Ethyl cellulose and HPMC K4M successfully by the solvent evaporation technique. Microspheres of Linagliptin showed excellent mucoadhesivity, % yield, Drug Content, % Drug entrapment efficiency and prolonged drug release up to 12 hours. Microspheres of different size and drug content could be obtained by varying the formulation variables. Thus the prepared microspheres may prove to be potential candidates for oral delivery devices. Formulation Batch F5 showed best appropriate balance between mucoadhesivity and drug release rate, which can be considered as a best fit for microspheres. The polymer ratio (Ethyl cellulose) of 1:2 were selected as best formulation, The formulated system showed sustained release up to 12 h and the system is potentially useful to overcome poor bioavailability problems associated with Linagliptin . Analysis of drug release mechanism showed that the drug release from the formulations the best fit model was found to be zero order release kinetics. Hence it can be concluded that Linagliptin loaded Ethyl cellulose Microsphere may be useful to achieve sustained drug release profile suitable for oral administration.

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