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Design and Characterization of Pitavastatin Loaded Nanosponges

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ABSTRACT
By targeting cells and tissues to elicit the desired pharmacological activity, nanotechnology-mediated drug delivery has been shown to improve treatment efficacy, bioavailability, reduce toxicity, and improve patient compliance. The study's major goal was to create pitavastatin-loaded nanosponges and test them. Emulsion solvent diffusion method was used to make pitavastatin-loaded nanosponges from several polymers (Ethyl cellulose, Polyvinyl alcohol,β -cyclodextrin, Pluronic F68, Hydroxy Propyl β- cyclodextrin). The FTIR test is used as a preliminary test, and it shows that the medicine and polymers have no interaction. The particle size, PDI, zeta potential, SEM, entrapment efficiency, and in vitro drug release of nanosponges were then assessed. The particle size ranged from 295.5 to 578.8 nm, PDI ranged from 0.189 to 0.465, zeta potential from -17.3 to -35.96 mV and entrapment efficiency was ranged from 78.38 to 95.77 %. The cumulative percentage release from all nanosponges varied from 66.86 to 96.60% after 12 hours depending upon the drug and polymers ratio and F5 formulation showed highest drug release i.e., 96.60%. The release kinetic studies showed that the release first order diffusion controlled and the n value(0.6017) from the Korsmeyer-Peppa's model indicated the release mechanism was Non-fickian type.

Keywords: pitavastatin, Nanosponges, FTIR, in-vitro drug release.

I. INTRODUCTION

[1]Nanosponges are microscopic particles with a few nm size cavities that can encapsulate a wide range of compounds. These particles can carry both lipophilic and hydrophilic substances, boosting the solubility of molecules which are poorly water soluble. Early trials suggest that this method is up to five times more successful at delivering medicines for breast cancer than conventional approaches, according to research undertaken in this sector.

[2]The nanosponge is about the size of a virus and has a naturally degradable polyester 'backbone' (scaffold structure). They 'cross link' polyester segments to construct a spherical shape with numerous pockets (or cavities) in which pharmaceuticals can be contained. Because the polyester is biodegradable, the medicine can be released on a predetermined schedule when it breaks down in the body.

[3,4]Pitavastatin, a highly lipophilic drug is frequently used as a blood cholesterol-lowering agent. It is a prodrug and after oral administration, the inactive parent lactone is hydrolyzed to the corresponding hydroxyacid form. Pitavastatin belongs to BCS class II, has a napthalien ring and a lactone ring, where the lactone ring binds to the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase enzyme and inhibits the formation of cholesterol. Pitavastatin shows low oral bioavailability (< 5%) because of least absorption and rapid metabolism in the liver.

Advantages of Nanosponges:

(1) Being amphiphilic in nature, nanosponges can carry both hydrophobic and hydrophilic molecules.

(2) The superior properties of nanosponges have been attributed to 'tunability', that is the ability to control the structure of particles and control the nature and size of aperture.

(3)[5]Nanosponges have the ability to produce predictable/controlled drug release.

(4)Nanosponges can be tagged with specific linkers to target diseased cells hence achieving greater efficacy while reducing side-effects, decreasing dose and dosing frequency and in turn increasing patient compliance.

(5)Nanosponges can significantly reduce the irritation of drugs without reducing their efficacy.

(6) [6]Biodegradable in nature and easy scale up for commercial production .

Applications of Nanosponges :

(1)[7,8]Nanosponges are being used for Solubility Enhancement because presence of crosslinking agent and cavities in the nanosponge structure helps interaction with active molecules. The hydrophilic hydroxyl groups on the external surface remain exposed to the environment, while the

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hydrophobic functionality of the complex hides in the interior cavity of the cyclodextrin the net effect is that a water-soluble complex is formed.

(2) [9]In drug delivery due to its spherical shape and nanometric in size making them ideal in preparing various dosage forms like topical, parenteral, aerosol, tablets and capsules. It is found that highest solubility and in vitro drug release is observed in inclusion complex.

(3) During protein delivery**,** nanosponges helps in maintenance of the native protein structure both during the formulation process and upon the long term storage. The nanosponges were found to be stable at 300°C and high protein complexation capacity was also observed.

(4)[10]Nanosponge formulations were developed as oxygen delivery systems for topical application which were having the ability to store and to release oxygen slowly over time.

II. MATERIALS AND METHODS:

Pitavastatin was purchased from Balaji drugs, Bangalore, Ethyl Cellulose and Poly Vinyl Alcohol from Research lab fine chem industries, β-cyclodextrin and Hp-β- cyclodextrin from Gattefose, Hyderabad, Pluronic F68 from HI Media laboratories Pvt ltd, Bengaluru Dichloromethane from SD Fine Chem, Bangalore. All the reagents were analytical grade.

Determination of λ max of Pitavastatin in methanol

Accurately weighed quantity of 10 mg of Pitavastatin was taken in 10 ml volumetric flask and it was dissolved in methanol and made up to 10 ml using methanol. From the above stock solution, 10 µg/ml solution was prepared and scanned between 200-400 nm by keeping methanol as blank. The absorption maxima of 245nm for Pitavastatin was obtained and used for further studies.

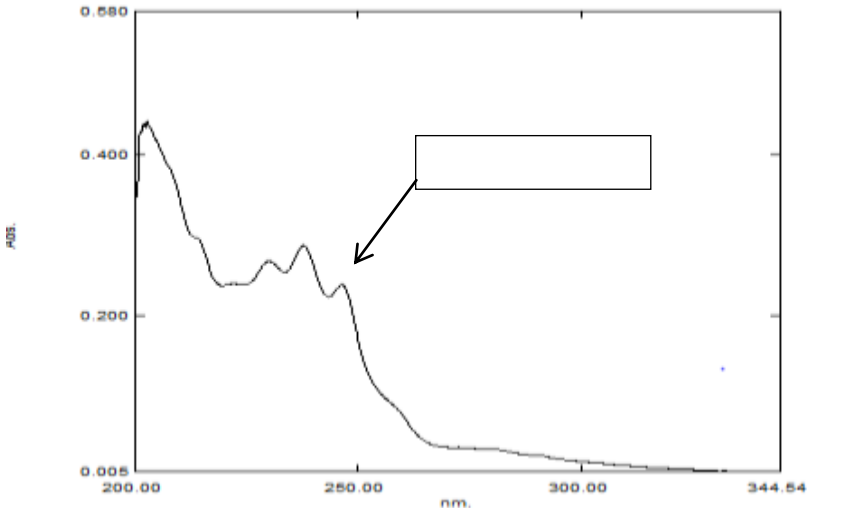

Figure no.1: Determination of λ max of Pitavastatin in methanol.

Determination of λ max of Pitavastatin in phosphate buffer of pH 6.8

Accurately weighed quantity of 10 mg of Pitavastatin was taken in 10 ml volumetric flask and it was dissolved in methanol and made up to 10 ml using phosphate buffer of pH 6.8.From the above stock solution, 10µg/ml solution was prepared and scanned between 200-400nm by keeping phosphate buffer as blank. The absorption maxima of 245nm for Pitavastatin was obtained and used for further studies.

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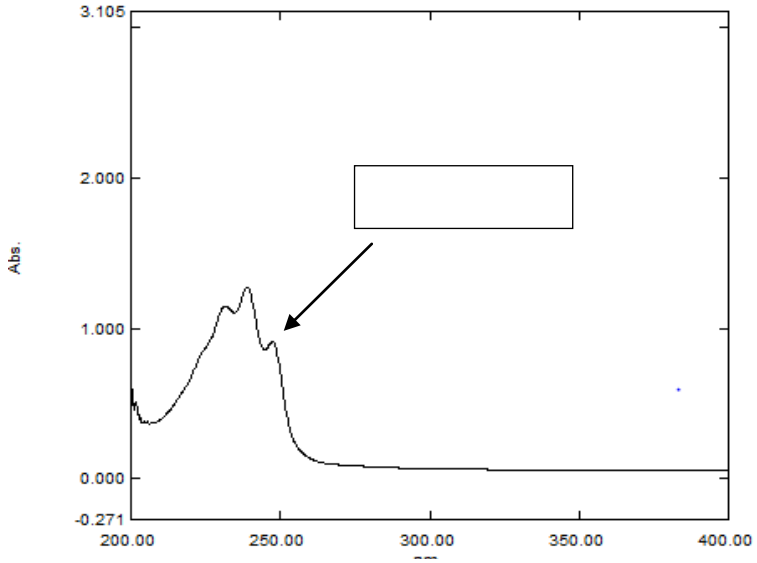
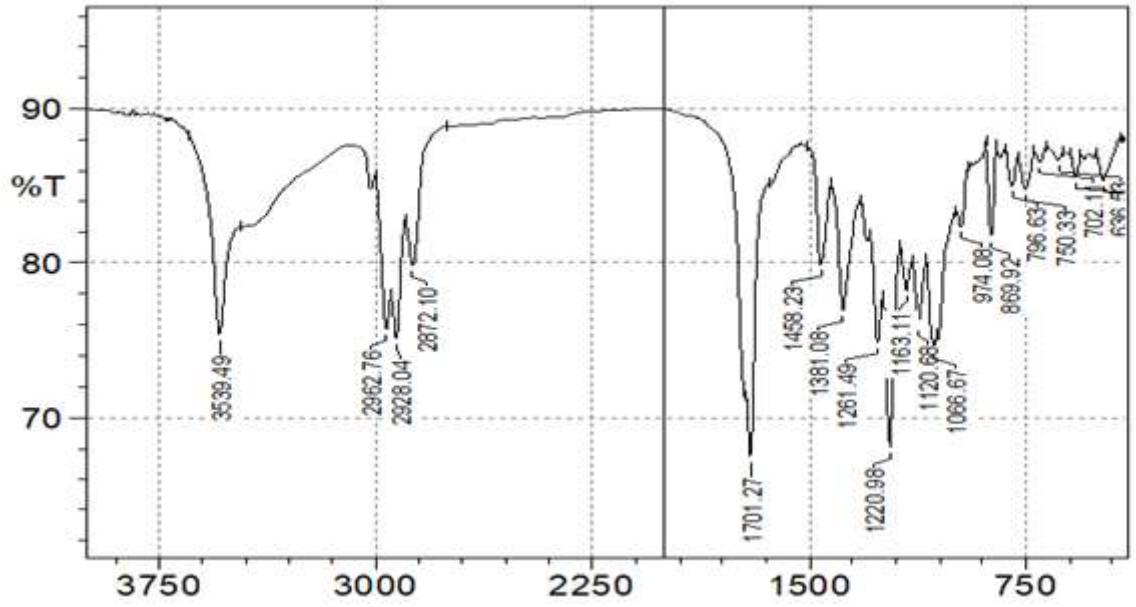


Figure no. 2: Determination of λ max of Pitavastatin in phosphate buffer pH 6.8

Fourier-transform infrared spectroscopy (FT-IR)

Drug-polymer interactions were studied by FTIR spectroscopy. Pure drug and excipients were subjected to FT-IR studies. Also, physical mixtures were subjected and the spectra recorded by scanning in the wavelength of 400-4000 cm^{-1} in a FT-IR spectrophotometer. The samples analysed by FT-IR include



1. Pure drug (Pitavastatin)

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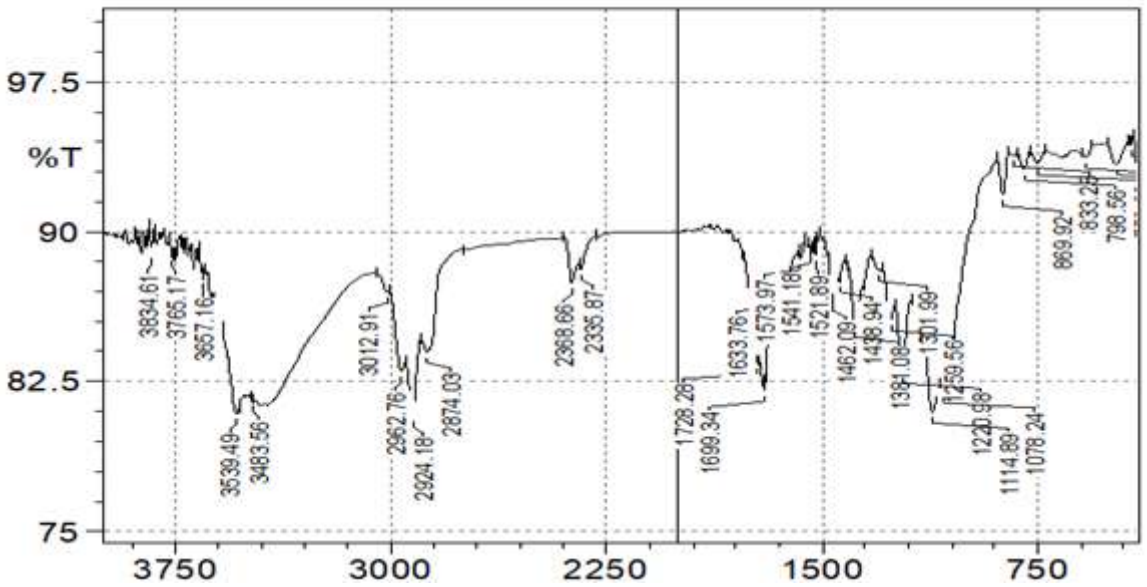
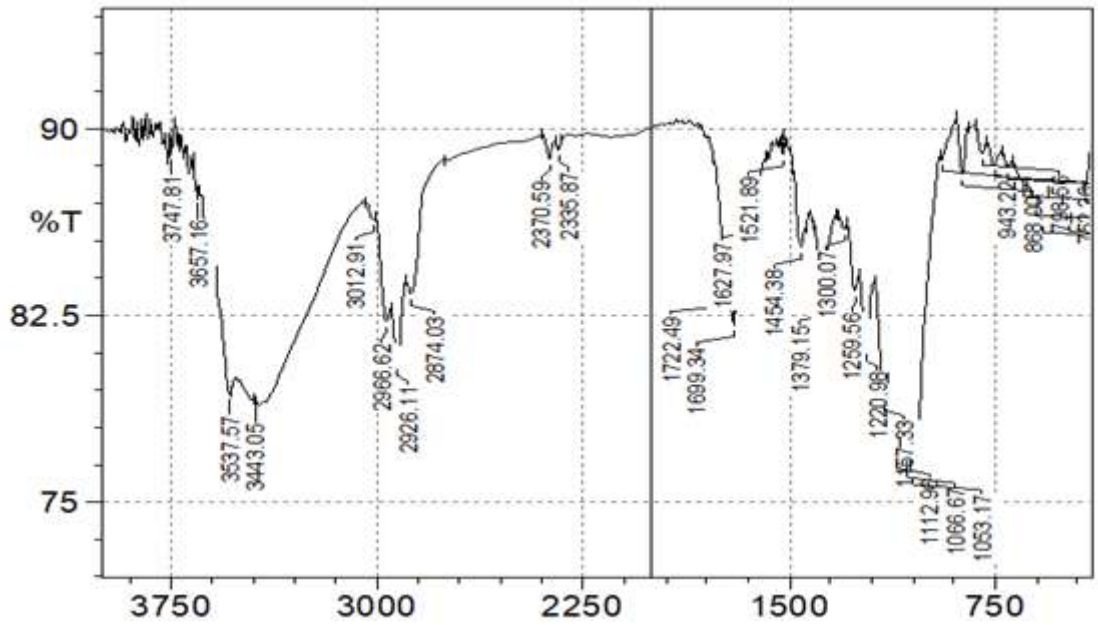


2. Physical mixture of drug + Ethyl Cellulose + Poly Vinyl Alcohol



3. Physical mixture of drug + Ethyl Cellulose + β –Cyclodextrin

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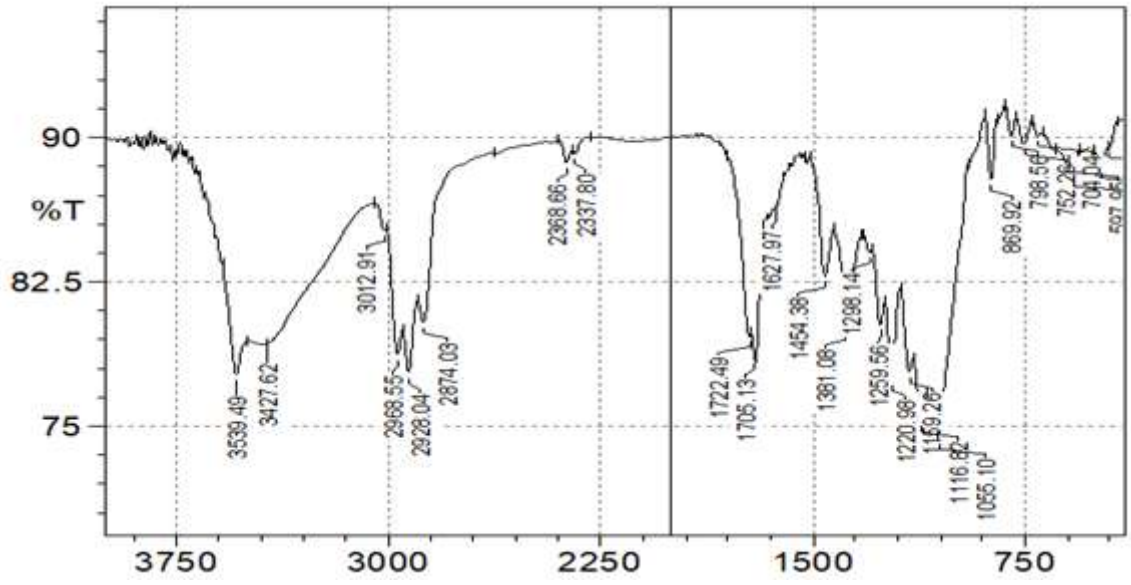
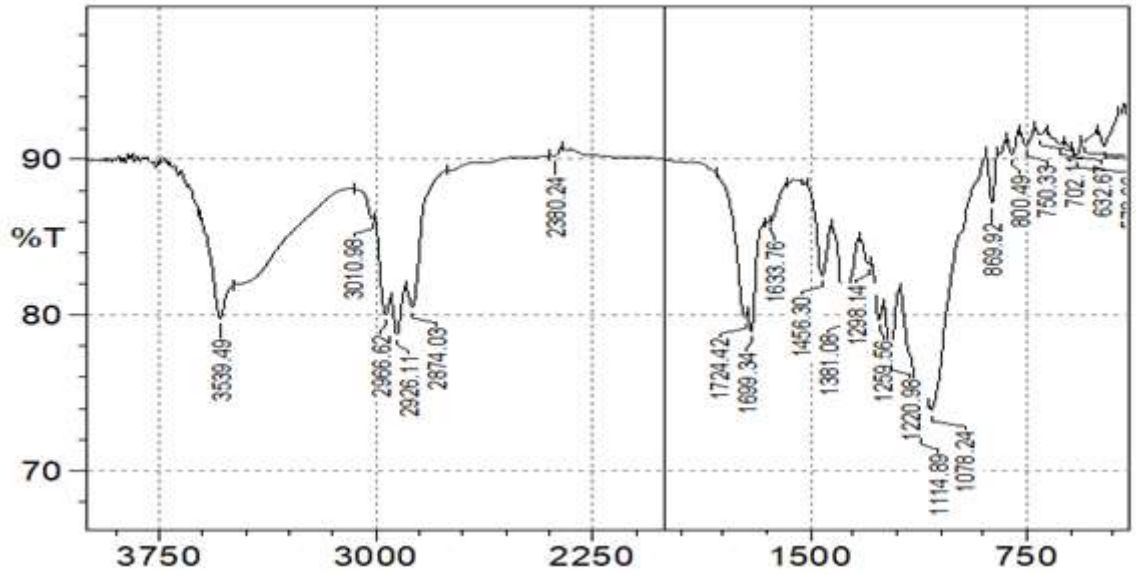


4. Physical mixture of drug + Ethyl Cellulose+ Pluronic F68



5. Physical mixture of drug + Ethyl Cellulose+ Hp - β - Cyclodextrin

Preparation of calibration curve in methanol

Accurately weighed quantity of 100 mg of Pitavastatin was taken in 100 ml volumetric flask and it was dissolved in methanol (Stock Solution I 1000µg/ml). From Stock Solution I, 5ml was taken and transferred to 50 ml volumetric flask and volume was made up to 50 ml methanol (Stock Solution II 100 µg/ml). From Stock solution 2, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, and 1.4 ml was taken and transferred to 10 ml volumetric flasks and volume was made up to 10 ml using methanol. 2, 4, 6, 8, 10,12 and 14 µg/ml solutions respectively. The aliquots were analysed at 245 nm. The plot of concentration v/s absorbance was plotted.

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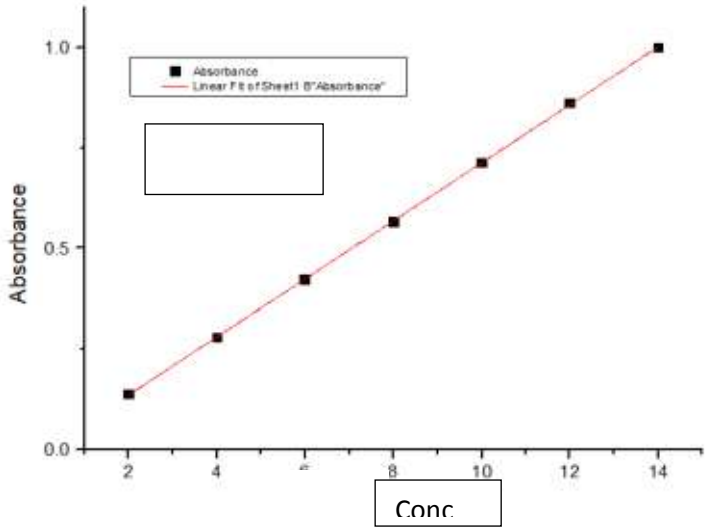

Figure no.3: The Standard graph of Pitavastatin using Methanol

Preparation of calibration curve in Phosphate buffer pH 6.8

Accurately weighed quantity of 100 mg of Pitavastatin was taken in 100 ml volumetric flask and it was dissolved in methanol and volume was made upto 100ml using phosphate buffer 6.8 (Stock Solution I 1000µg/ ml). From Stock Solution I, 5ml was taken and transferred to 50 ml volumetric flask and volume was made up to 50 ml methanol (Stock Solution II 100 µg/ml). From Stock solution I, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2 and 1.4 ml was taken and transferred to 10 ml volumetric flasks and volume was made up to 10 ml using phosphate buffer 6.8. 2, 4, 6, 8, 10, 12 and 14 µg/ml solutions respectively. The aliquots were analysed at 245 nm. The plot of concentration v/s absorbance was plotted.

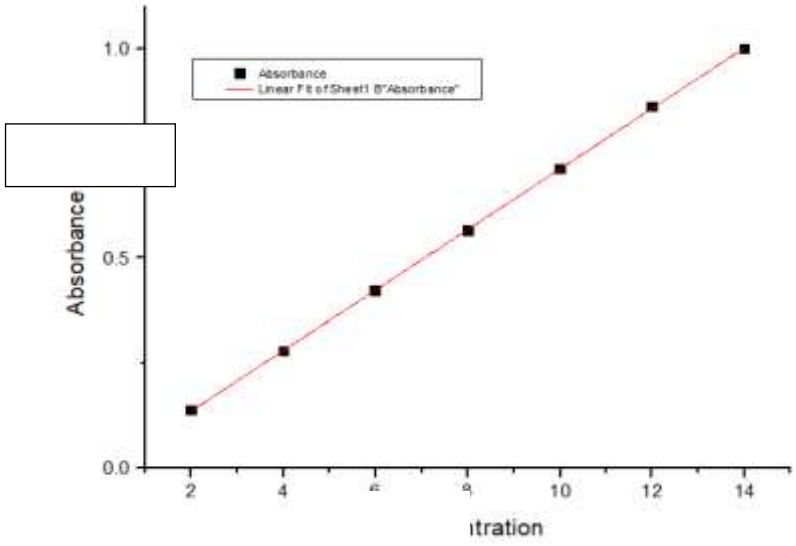

Figure no.4: The Standard graph of Pitavastatin using phosphate buffer of pH 6.8

Preparation of Pitavastatin loaded Nanosponges using Emulsion Solvent Diffusion method.

[11]Nanosponges using different proportions of ethyl cellulose, polyvinyl alcohol, β-cyclodextrin, Pluronic F68 and HP-β cyclodextrin were prepared by Emulsion solvent diffusion method. Disperse phase consisting of drug (100mg) and requisite quantity of ethyl cellulose dissolved in 10 ml solvent(dichloromethane) was slowly added to a definite amount of polymer in100ml of

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aqueous continuous phase. The reaction mixture was stirred at 1000 rpm for three hours on a magnetic stirrer. The nanosponges formed were collected by filtration through whatmann filter paper and dried in oven at 50°C for 2 hours. The dried nanosponges were stored in vacuum desiccator to ensure the removal of residual solvent.

Table No 1: Composition of different formulation of Pitavastatin loaded nanosponges.

Formulation Code	Drug (mg)	EC (mg)	PVA (mg)	β - CD (mg)	PL F68 (mg)	HP- β-CD (mg)	Dist. H_2O (ml)
F1	100	100	100	-	-	-	100
F2	100	100	200	-	-	-	100
F3	100	100	-	100	-	-	100
F4	100	100	-	200	-	-	100
F5	100	100	-	-	100	-	100
F6	100	100	-	-	200	-	100
F7	100	100	-	-	-	100	100
F8	100	100	-	-	-	200	100

DRUG- Pitavastatin;EC = Ethyl Cellulose; PVA= Poly Vinyl Alcohol;β - CD = β - Cyclodextrin; PL F68 = Pluronic F68 (Poloxamer F68); HP-β -CD = Hydroxy Propyl β- cyclodextrin;Dist. H_2O = Distilled Water.

EVALUATION OF NANOSPONGES

Particle size analysis

The particle size was determined by dynamic light scattering, using a Malvern system, with vertically polarized light supplied by an argon-ion laser (Cyonics) operated at 40 mW. Experiments were performed at a temperature of 25.0 ± 0.1ºC at a measuring angle of 90º to the incident beam. The technique of laser diffraction is based around the principle that particles passing through a laser beam will scatter light at an angle that is directly related to their size. As the particle size decreases, the observed scattering angle increases logarithmically. The observed scattering intensity is also dependent on particle sizes and diminishes, to a good approximation, in relation to the particle's cross-sectional area. Large particles therefore scatter light at narrow angles with high intensity, whereas small particles scatter at wider angles but with low intensity.

Zeta potential

Zeta potential analysis was performed to estimate the stability of the Nanosponges. Zeta potential is a measure of effect of electrostatic charges. This is the basic force that causes the repulsion between adjacent particles. Net results are attraction or repulsion depends upon the magnitude of both forces. The thumb rule describes the relation between zeta potential determination responses of the Nanosponges.

Polydispersity index

[12,13]In light scattering, the term polydispersity and % polydispersity is derived from the Polydispersity Index, a parameter calculated from a Cumulants analysis of the DLS-measured intensity autocorrelation function. In the Cumulants analysis, a single particle size mode is assumed and a single exponential fit is applied to the auto correlation function and the polydispersity describes the width of the assumed Gaussian distribution. The Polydispersity Index is dimensionless and scaled such that values smaller than 0.05 are rarely seen other than with highly mono disperses standards. Values greater than 0.7 indicate that the sample has a very broad size distribution and is probably not suitable for the dynamic light scattering (DLS) technique. The various size distribution algorithms work with data that falls between these two extremes. Particle size, zeta potential and Polydispersity index were determined by the same instrument i.e. Malvern zeta sizer.

Scanning electron microscopy

[14]For the evaluation of the surface morphology of nanosponges, the sample was analyzed in a scanning electron microscope after

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preparing the sample by lightly sprinkling on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum. The stub containing the coated sample was placed in a scanning electron microscope. The samples were then randomly scanned and photomicrographs were taken at the acceleration voltage of 20 kV. From the resulting image, average particle size was determined.

Drug Content

[15]An accurately weighed amount of 20 mg of pitavastatinnanosponges were added to 20 ml methanol and placed in a thermo-shaker operated at 100 rpm at 25ºC for 45 minutes, followed by vortexing for 10 minutes. The solution was filtered through a 45 µm membrane filter, and the drug was determined spectrophotometrically at λmax 237nm, on the basis of the previously constructed standard curve. The drug content of the formulated nanosponges was calculated on the basis of the following equation.

$$\%\ \textbf{Drug content} = \frac{\textbf{Practical amount of the drug obtained}}{\textbf{Theroretical amount of drug added}}\ \textbf{X 100}$$

Percentage Drug entrapment efficiency (%DEE)

[16]50 mg from the prepared drug loaded nanosponges by emulsion solvent diffusion method using suitable polymer were suspended in 50 ml of methanol and were subjected for ultracentrifugation for 40 minutes. The percentage of incorporated Pitavastatin was determined spectrophotometrically at 237nm. After centrifugation of the aqueous suspension, amount of free drug was detected in the supernatant and the amount of incorporated drug was determined as a result of the initial drug minus the free drug. The drug Entrapment efficiency (EE) of lovastatin nanosponges was determined using the formula:

$$\textbf{\% of drug entrapment} = \frac{\textbf{Total drug content– Drug weight in aqueous phase}}{\textbf{Total drug content}}\ \textbf{x100}$$

In vitro Drug Release Study

[17]In vitro drug release studies were carried out in Franz diffusion cell. 2 ml of Nanosponges dispersion was used for diffusion study. Nanoponges containing drug were placed in donor compartment while the receiver compartment consists of 22 ml of diffusion medium Phosphate buffer pH 6.8 maintained at 37 °C temperature in Franz diffusion cell. The rpm of the magnetic bead was maintained at 50 rpm. 2 ml of the sample was withdrawn at predetermined intervals. The samples were analysed for the drug content by UV spectrophotometer at 238 nm. Equal volume of the diffusion medium was replaced in the vessel after each withdrawal to maintain sink condition. From the data obtained the percentage drug release was calculated and plotted against function of time to study the pattern of drug release.

Kinetic Modelling of Drug Dissolution Profiles:

[18]The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows**:**

Zero order kinetic model – Cumulative % drug released versus T.

First order kinetic model – Log cumulative percent drug remaining versus T.

Higuchi's model – Cumulative percent drug released versus square root of T.

Korsmeyer equation/Peppa's model–Log cumulative percent drug released versus log T.

III. RESULTS AND DISCUSSION

Drugs-polymer interaction study by FT-IR spectrophotometer

An FT-IR spectroscopy study has been carried out separately to check the compatibility between the drug (Pitavastatin) and the polymers (EC, PVA, β – CD, PL- F68 and HP-β -CD) used for the preparation of Nanosponges. The FT-IR was performed for drug and physical mixture of drug and polymers. The spectra obtained from FT-IR spectroscopy study at wave number from 4000 to 400 cm^{-1} are shown below.

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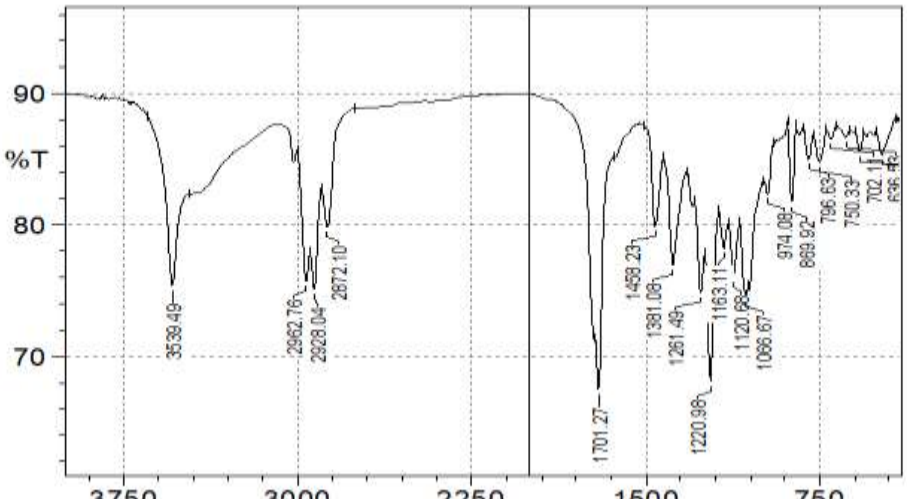

Figure no. 5: The FTIR spectrum of pure Pitavastatin

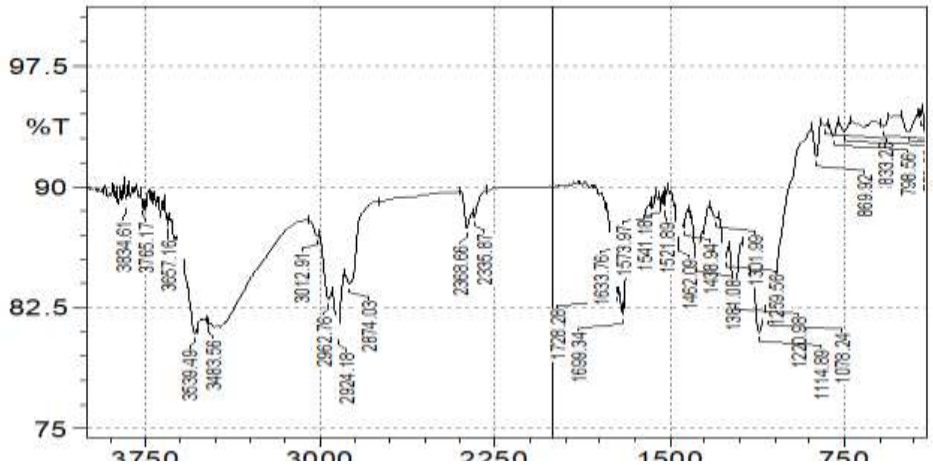

Figure no.6: The FTIR spectrum of physical mixture of Pitavastatin, EC and PVA

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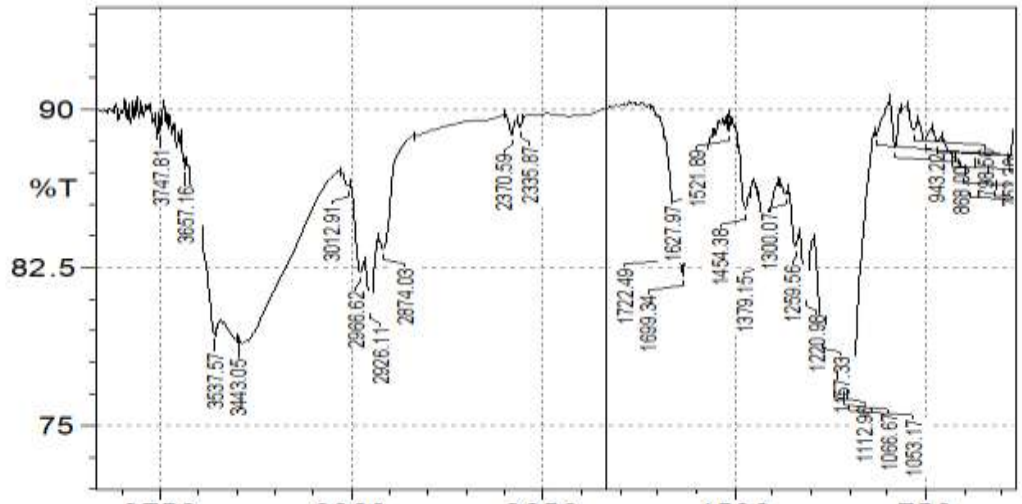

Figure no. 7: The FTIR spectrum of physical mixture of Pitavastatin, EC and β - CD

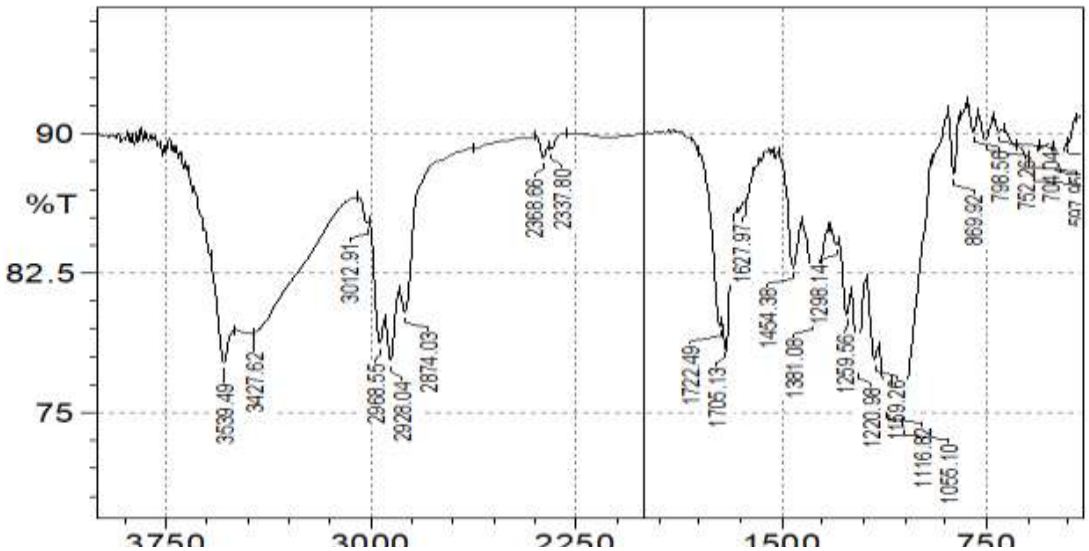

Figure no.8: The FTIR spectrum of physical mixture of Pitavastatin, EC and Pluronic F68

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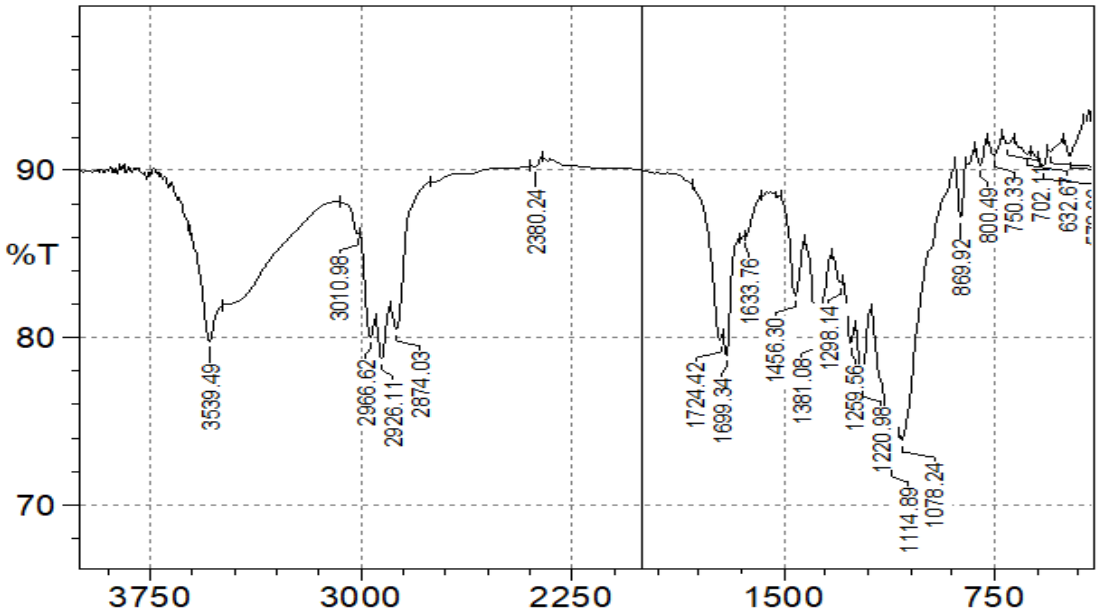

Figure no.09: The FTIR spectrum of physical mixture of Pitavastatin, EC and HP-β - CD

FTIR Interpretation

Perusal to the above FTIR spectra, the characteristic peaks of Pitavastatin of pure spectrum was retained in the FTIR spectra of physical mixture of drug with Ethyl Cellulose, PVA, β – CD,PL-F68 and HP-β -CD. Therefore, there was no drug polymer interaction is found. Hence, these polymers were used for the preparation of Nanosponges.

Characterization of Nanosponges.

Pitavastatin loaded nanosponges were prepared by Emulsion solvent diffusion method. The Nanosponges were evaluated for particle size, zeta potential and polydispersity index and the results were reported as follows.

Particle size,Zeta potential and PDI

The particle size ranged from 295.5 to 578.8d. nm, PDI ranged from0.189 to 0.465 and zeta potential from -17.3 to -35.96 mV.

Table No. 2: The particle size, PDI and zeta potential of Pitavastatin loaded nanosponges prepared with PVA, β – Cyclodextrin, Pluronic F68 and HP-β-cyclodextrin.

Formulation Code	Particle size (d. nm)	PDI	Zeta potential (mV)
F1	326.5	0.384	-17.30
F2	295.5	0.286	-19.40
F3	422.7	0.349	-20.40
F4	532.3	0.465	-18.70
F5	496.6	0.426	-35.96

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F6	561.2	0.398	-15.54
F7	578.8	0.250	-25.62
F8	429.8	0.435	-23.70

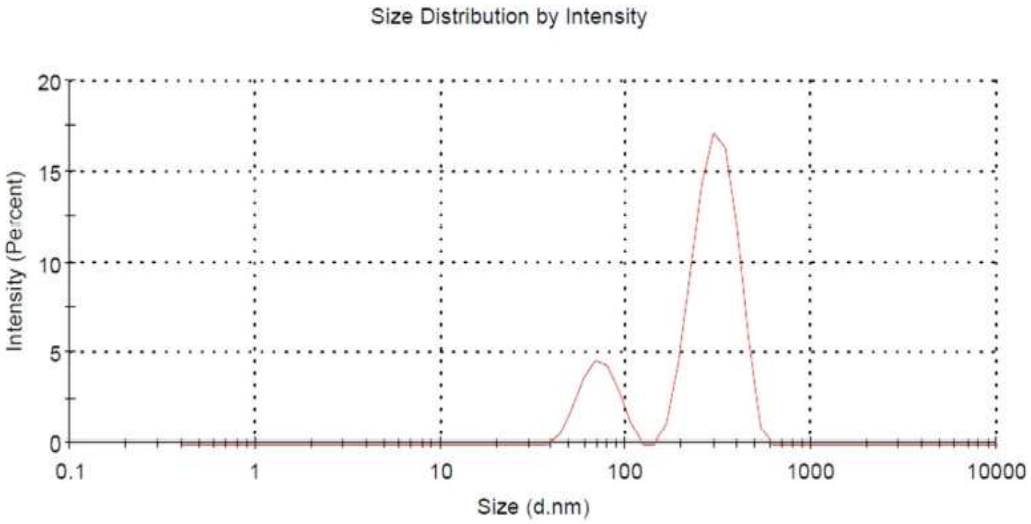

Figure no. 10: Size Distribution Profile of optimized formulation F5.

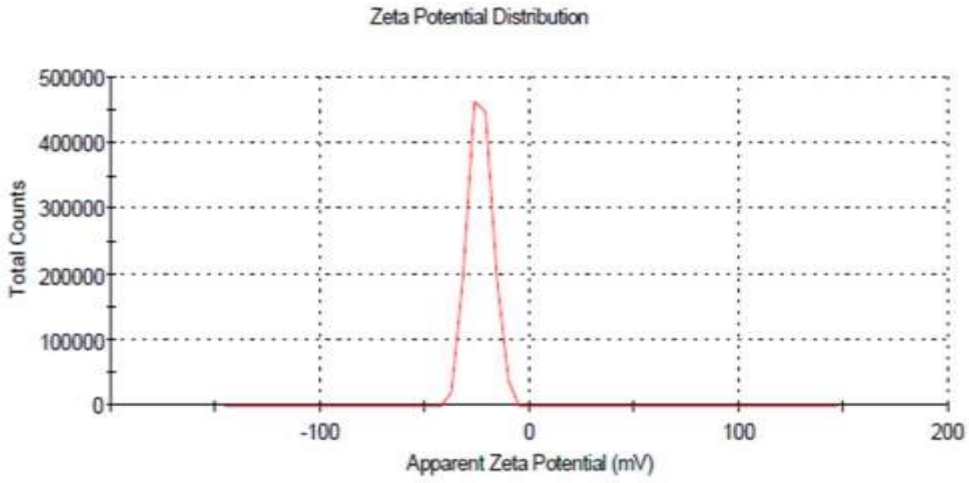

Figure no. 11: Zeta potential profile of optimized formulation F5.

Scanning Electron Microscopy

SEM analysis of the formulated Pivastatinnanosponges were performed to evaluate the surface morphology of nanosponges. The SEM images of optimized formulation F5 is shown in below.

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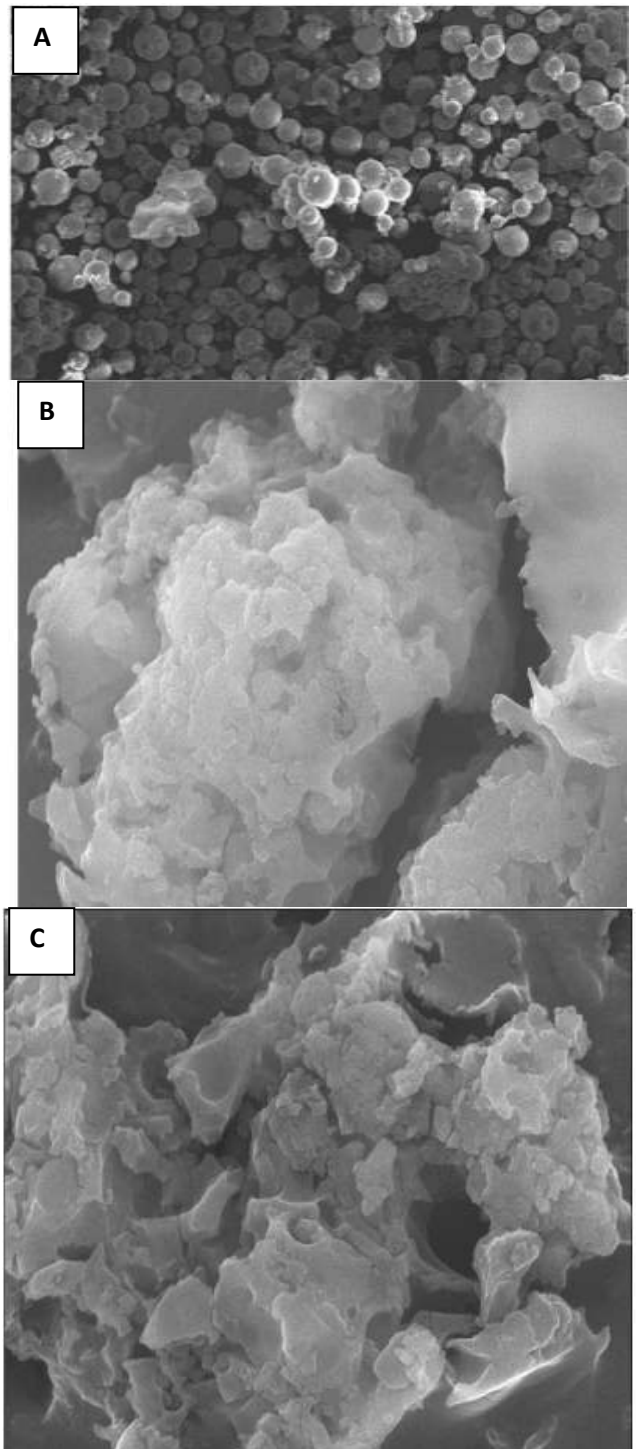

Figure no.12: SEM images of optimized formulation F5 (A) 100X (B) 10,000X (C) 20,000X.

Drug content and Entrapment efficiency

The drug content of formulations was carried out by extraction with methanol as mentioned in the methodology section. Formulations (20 mg) were extracted Pitavastatin using 20 ml of methanol. The drug content results were ranged between 79.47 to 96.82% and drug entrapment efficiency results were ranged between 78.38 to 95.77%.

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Table No. 3: Data of drug content and entrapment efficiency of Pitavastatin loaded nanosponges prepared with EC, PVA, β – Cyclodextrin, Pluronic F68 and HP-β-cyclodextrin.

Formulation Code	Drug Content %	Entrapment efficiency (%)
F1	84.53	80.12
F2	88.32	78.38
F3	79.47	80.77
F4	92.25	89.35
F5	96.82	94.23
F6	87.04	90.16
F7	92.15	95.77
F8	89.21	86.32

Release studies

The drug releases from the Nanosponges were studied by Franz diffusion method. The in vitro release profiles of Pitavastatin from Pitavastatinnanosponges are shown in Table No.4The cumulative percentage release of Pitavastatin from different Pitavastatinnanosponges varied from 72.16 to 96.60% depending upon the drug polymer ratio.

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Table No.4: Table showing percentage drug released from different formulations (F1-F8) during 12 hours.

Time (Hours)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	12.03	12.15	12.57	12.87	14.4	11.94	12.03	11.02
1	19.56	17.76	18.36	18.37	21.68	15.39	12.20	11.70
2	36.17	39.16	36.19	32.57	37.4	27.12	18.73	15.03
3	45.67	45.08	42.07	42.05	55.30	44.31	27.13	18.79
4	50.12	49.23	43.20	43.88	60.41	49.36	29.13	23.48
5	61.20	61.50	57.83	52.65	64.13	57.51	50.16	30.33
6	61.77	62.07	61.66	58.13	72.34	64.55	59.09	45.55
8	67.36	68.24	64.64	62.94	78.45	68.64	63.92	57.62
10	74.17	75.06	70.36	65.00	85.53	72.46	69.76	64.23
12	80.74	81.07	78.09	72.89	96.60	78.59	74.82	66.86

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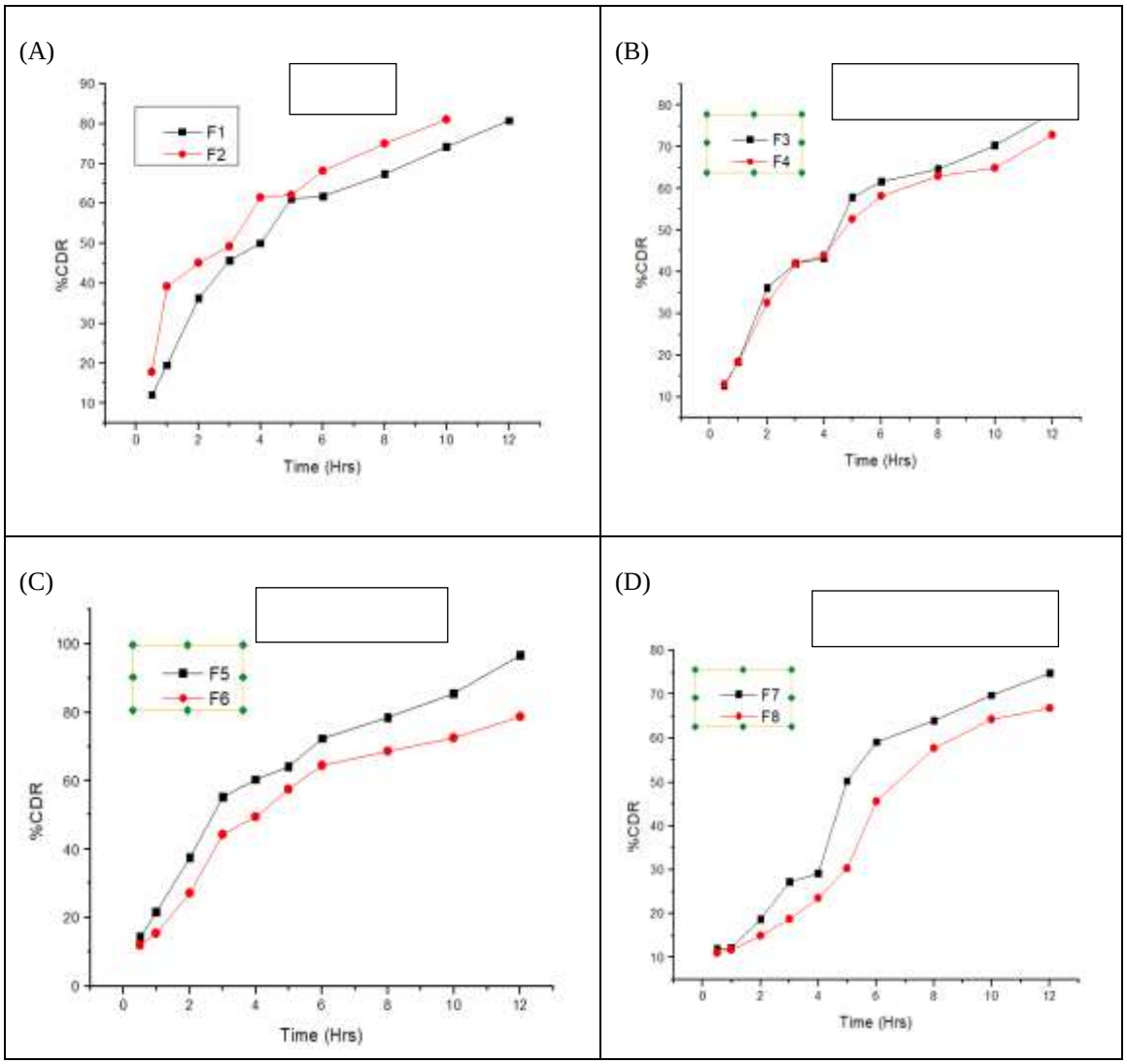

Figure no. 13: The comparison of percentage cumulative drug release profile of Pitavastatin loaded Nanosponges. (A) F1-F3 (B) F4-F6 (C) F7-F9 (d) F10-F12**.**

Release kinetics

Data obtained from Invitro release studies were fitted to various kinetic equations such as zero order, first order, Higuchi model and Korsmeyer-Peppa's model. A model processing of the Invitro release for F5 were shown in **Table No.5** and **6.** For remaining formulation, a similar procedure was followed.

Table no.5: The regression values of kinetic models of different formulations.

Formulation Code	**Regression Factor**	**Korsmeyer-Peppa's**

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	Zero order	First order	Higuchi model	R^2	n value
F1	0.8498	0.9736	0.967	0.9706	0.6202
F2	0.8416	0.9702	0.9587	0.9584	0.6282
F3	0.8695	0.9715	0.9675	0.9715	0.6014
F4	0.841	0.8988	0.9358	0.9684	0.594
F5	0.8855	0.9846	0.9740	0.9727	0.6017
F6	0.7598	0.8658	0.9013	0.9466	0.6915
F7	0.9015	0.9514	0.9245	0.9179	0.6572
F8	0.8763	0.8889	0.8389	0.8076	0.5985

Table no.6: Processing of release data of formulation F5 into different kinetic models.

Time (Hours)	Log time	SQRT	%CDR	Log %CDR	%CRR	Log % CRR
0.5	-0.3010	0.7071	14.40	1.1583	85.60	1.9324
1	0 .000	1.000	21.68	1.3360	78.32	1.8938
2	0.3010	1.4142	37.40	1.5728	62.60	1.7965
3	0.4771	1.7320	55.30	1.7427	44.70	1.6503
4	0.6020	2.0000	60.41	1.7811	39.59	1.5975
5	0.6989	2.2360	64.13	1.8070	35.87	1.5547
6	0.7781	2.4494	72.34	1.8593	27.66	1.4418
8	0.9030	2.8284	78.45	1.8945	21.55	1.3334
10	1.0000	3.1622	85.53	1.9321	14.47	1.1604
12	1.0791	3.4641	96.60	1.9849	3.40	0.5314

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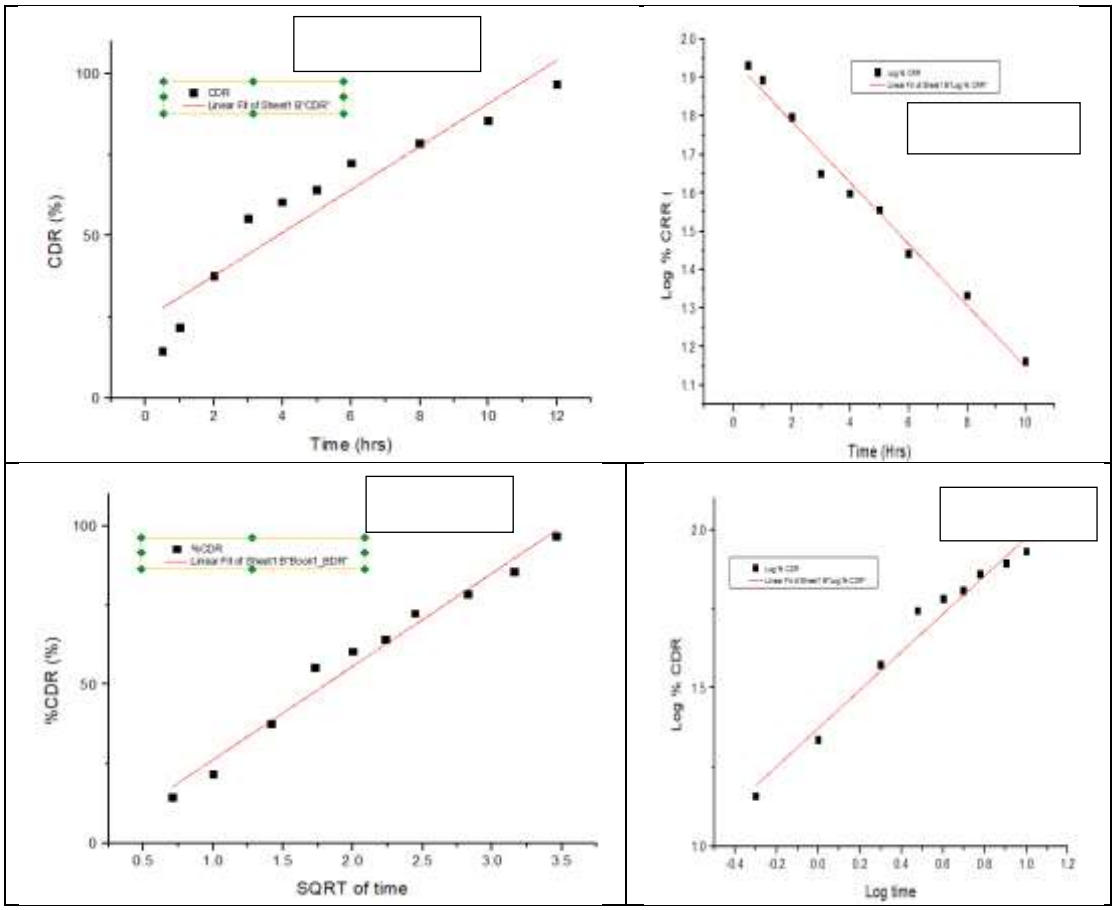

Figure no.14: The Zero order, First order, Higuchi, Peppa'smodel kinetics plot of optimized formulation F5.

IV. CONCLUSION

In the present study, an attempt was made to formulate Nanosponge delivery system for lipophilic drug Pitavastatin using Ethyl Cellulose, Polyvinyl alcohol, β- cyclodextrin, Pluronic F68 and Hydroxy Propyl β- cyclodextrin as polymers, which are meant to be used for better anti-hyperlipidaemic action. FT-IR studies were carried out to find out the possible interaction between the selected drug and polymers. FT-IR studies revealed that there was no interaction between the selected drug and polymers. Pitavastatin loaded nanosponges were prepared by Emulsion solvent diffusion method. The method was able to produce Nanosponges of acceptable range and stability. All the formulations showed very high entrapment efficiencies. Nanosponges were formulated by taking 100 to 300mg of polymers. Among the all batches F6 was optimized after considering their particle size, zeta potential, SEM and in vitro drug release profile.

Particle size, SEM, [illegible] and zeta potential of all the Nanosponge formulations were in the acceptable and suitable range. Average entrapment efficiency most of PitavastatinNanosponges was found to be greater than 80 % whereas the optimized formulations F5 was shown 94.23 % entrapment.

Release kinetics studies showed that Pitavastatin release from the nano-sponges follows Non-Fickian diffusion. Based on the observations, it can be concluded that the formulated nanosponge delivery system of Pitavastatin using widely accepted and physiologically safe polymers was capable of exhibiting controlled release properties for a period of 12 hours. They are thus may reduce frequency of dosing, thereby minimizing the occurrence of side effects, improve bioavailability and increase the effectiveness of the drug.

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