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Formulation and evaluation of Glibenclamide loaded Nanosponges

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Abstract

Nanotechnology mediated drug delivery has been reported to enhance the drug efficacy, bioavailability, reduced toxicity and improve patient compliance by targeting the cells and tissues to elicit the desired pharmacological action. The main aim of the study was to formulate Glibenclamide loaded nanosponges and to evaluate them. Glibenclamide loaded nanosponges were prepared by Emulsion solvent diffusion method using different polymers (Ethyl cellulose, β-cyclodextrin, Hydroxy Propyl β- cyclodextrin, Pluronic F68). The FTIR test is conducted as the preliminary test, by this test there was no interaction between the drug and polymers. Then nanosponges were evaluated for particle size, PDI, zeta potential, SEM, entrapment efficiency and *invitro* drug release. The particle size ranged from 640.7 to 876.2 nm, PDI ranged from 0.456 to 0.707, zeta potential from -17.3 to -34.3 mV and entrapment efficiency was ranged from76.21 to 98.23% The cumulative percentage release from all nanosponges varied from 80.35 to 97.56% after 12 hours depending upon the drug and polymers ratio and F5 formulation showed highest drug release i.e., 97.53%. The release kinetic studies showed that the release first order diffusion controlled and the n value (0.8769) from the Korsmeyer- Peppa's model indicated the release mechanism was non-fickian type.

Keywords: Glibenclamide; Nanosponges; FTIR; *In vitro* drug release

1. Introduction

Nanosponges are made of microscopic particles with few nanometres' wide cavities, in which a large variety of substances can be encapsulated. These particles possess the ability to carry both lipophilic and hydrophilic substances and thereby improving the solubility of poorly water-soluble molecules. The studies conducted in this field proves that the tiny mesh-like structures called nanosponges may revolutionize the treatment of many diseases and early trials suggest this technology is up to five times more effective at delivering drugs for breast cancer than conventional methods [1]. The nanosponge is about the size of a virus with a 'backbone' (a scaffold structure) of naturally degradable polyester. They 'cross link' segments of the polyester to form a spherical shape that has many pockets (or cavities) where drugs can be encapsulated. The polyester is biodegradable, which means that when it breaks down in the body, the drug can be released on a known schedule [2].

Glibenclamide is a second-generation sulfonylurea that reduces blood glucose by increasing insulin secretion from pancreatic beta cells [3]. Glibenclamide is effective within a narrow range of plasma concentration (50-200nM), which can be achieved with very low dose of the drug. Dose of the Glibenclamide is 2.5 mg/day. It belongs to BCS II. Glibenclamide exhibits poor bioavailability <70% because of poor water solubility. The prepared nanosponges of Glibenclamide will increases its efficacy of sustain release and improving solubility [4].

Nanosponges have various advantages which includes (1) Being amphiphilic in nature, nanosponges can carry both hydrophobic and hydrophilic molecules. (2) The superior properties of nanosponges have been attributed to

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'tunability', that is the ability to control the structure of particles and control the nature and size of aperture. (3) Nanosponges have the ability to produce predictable/controlled drug release [5]. (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) Biodegradable in nature and easy scale up for commercial production [6]. (7) They mix with water and are used as a transport fluid. They can be used to mask unpleasant flavors [7].

Nanosponges have many applications in the field of drug delivery which includes the following (1) 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 hydrophobic functionality of the complex hides in the interior cavity of the cyclodextrin the net effect is that a water-soluble complex is formed [8]. (2) In drug delivery due to it 's 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 [9]. (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) 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 [10].

2. Material and methods

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

2.1. Determination of λ max of Glibenclamide in phosphate buffer of pH 6.8

Accurately weighed quantity of 10 mg of Glibenclamide was taken in 10 ml volumetric flask and it was dissolved in methanoland made up to 10 ml using phosphate buffer of pH 6.8. From the above stock solution, 10µg/ml solution was preparedand scanned between 200-400nm by keeping phosphate buffer as blank. The absorption maxima of 227 nm for Glibenclamide were obtained and used for further studies.

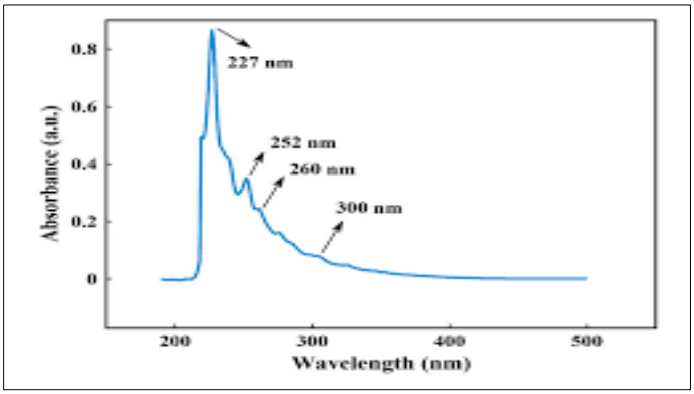

Figure 1 Determination of λ max of Glibenclamide in phosphate buffer pH6.8

2.2. 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.

- Pure drug (Glibenclamide)
- Physical mixture: drug + Ethyl Cellulose + β - Cyclodextrin
- Physical mixture: drug + Ethyl Cellulose+ Hp - β - Cyclodextrin
- Physical mixture: drug + Ethyl Cellulose+ Pluronic F68

2.3. Preparation of calibration curve in phosphate buffer pH 6.8

Accurately weighed quantity of 50 mg of Glibenclamide was taken in 50 ml volumetric flask and it was dissolved in methanol and volume was made up to 100ml using phosphate buffer 6.8 (Stock Solution 1 1000µg/ml) From Stock Solution 1, 2ml was taken and transferred to 50 ml volumetric flask and volume was made up to 50 ml buffer (Stock Solution II 1000µg/ml) From Stock solution II 1,2,3,4,5,6,7 and 8ml was taken and transferred to 10 ml volumetric flask and volume made up to 10 ml using phosphate buffer 6.8. 2,4,6,8,10,12,14, and 16 µg/ml solutions respectively. The aliquots were analysed at 227 nm. The plot of concentration v/s absorbance was plotted.

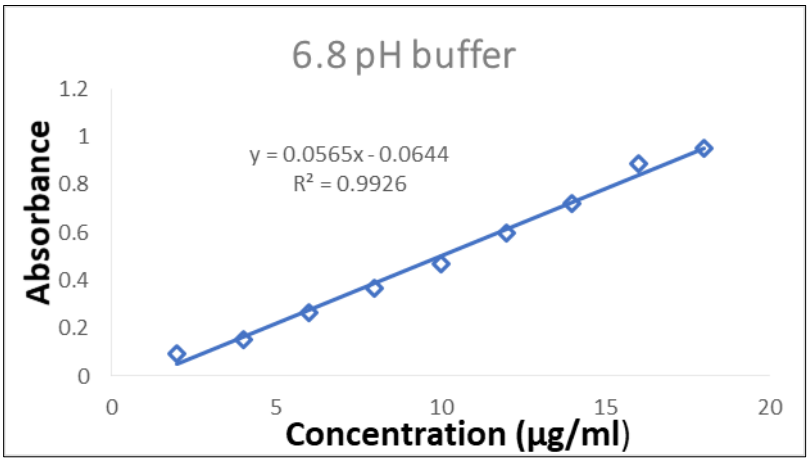

Figure 2 The standard graph of Glibenclamide using phosphate buffer of pH 6.8

2.4. Preparation of Glibenclamide loaded Nanosponges using Emulsion Solvent Diffusion method

Nanosponges using different proportions of ethyl cellulose, β-cyclodextrin, HP-β cyclodextrin and Pluronic F68 were prepared by Emulsion solvent diffusion method.

Table 1 Composition of different formulation of Glibenclamide loaded nanosponges

Formulation code	Drug (mg)	EC (mg)	β-CD (mg)	HP-β-CD (mg)	PL F68	DCM (ml)	Dist.H_2O (ml)
F1	100	200	100	-	-	20	50
F2	100	200	200	-	-	20	50
F3	100	200	300	-	-	20	50
F4	100	200	-	100	-	20	50
F5	100	200	-	200	-	20	50
F6	100	200	-	300	-	20	50
F7	100	200	-	-	100	20	50
F8	100	200	-	-	200	20	50
F9	100	200	-	-	300	20	50

Drug-Glibenclamide; EC= Ethyl cellulose; β-CD= β-cyclodextrin; HP-β-CD=Hydroxy Propyl β-cyclodextrin; DCM= Dichloromethane; Dist.H2O= Distilled water

Disperse phase consisting of drug (100mg) and requisite quantity of ethyl cellulose dissolved in 20 ml solvent(dichloromethane) was slowly added to a definite amount of polymer in100ml of 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 ℃ for 2 hours. The dried nanosponges were stored in vacuum desiccator to ensure the removal of residual solvent [11].

2.5. Evaluation of nanosponges

2.5.1. 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.

2.5.2. 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.

2.5.3. Polydispersity index

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* [12,13].

2.5.4. Scanning electron microscopy

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

2.5.5. Drug Content

An accurately weighed amount of 20 mg of Glibenclamide nanosponges were added to 20 ml methanol and placed in a thermo-shaker operated at 100 rpm at 25ºC for 45 minutes, followed by vertexing for 10 minutes. The solution was filtered through a 45 µm membrane filter, and the drug was determined spectrophotometrically at λ max 227nm, 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 [15].

$$\%Drug\ content = \frac{Practical\ amount\ of\ the\ drug}{Theoretical\ amount\ of\ the\ drug} \times 100$$

2.5.6. Percentage Drug entrapment efficiency (%DEE)

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 Glibenclamide was determined spectrophotometrically at 227nm. 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 Glibenclamide nanosponges was determined using the formula: [16].

$$\%\ of\ drug\ entrapment = \frac{Total\ drug\ content - Drug\ weight\ in\ aqueous\ phase}{\text{Total drug content}} \times 100$$

2.5.7. In vitro Drug Release Study

In vitro drug release studies were performed in triplicate using USP Paddle method at 50 rpm and 37 ± 0.3 in 900 ml of phosphate buffer (pH 6.8). 100 mg of the formulated nanosponges is used for each experiment. Samples were taken at appropriate time intervals for 1 h interval for 10hr. The samples were measured spectrophotometrically at 227 nm. Fresh dissolution medium was replenished each time when sample is withdrawn to compensate the volume [17].

2.5.8. Kinetic Modelling of Drug Dissolution Profiles

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 [18].

3. Results and discussion

3.1. 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 (Lovastatin) and the polymers (EC, β – CD, HP-β -CD and Pluronic F68) used for the preparation of Nano sponges. 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.

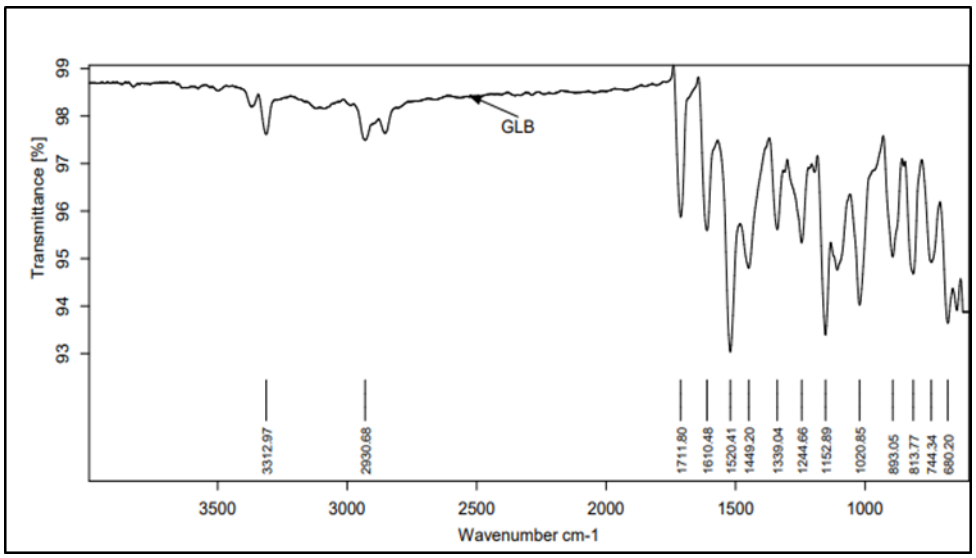

Figure 3 The FTIR spectrum of pure Glibenclamide

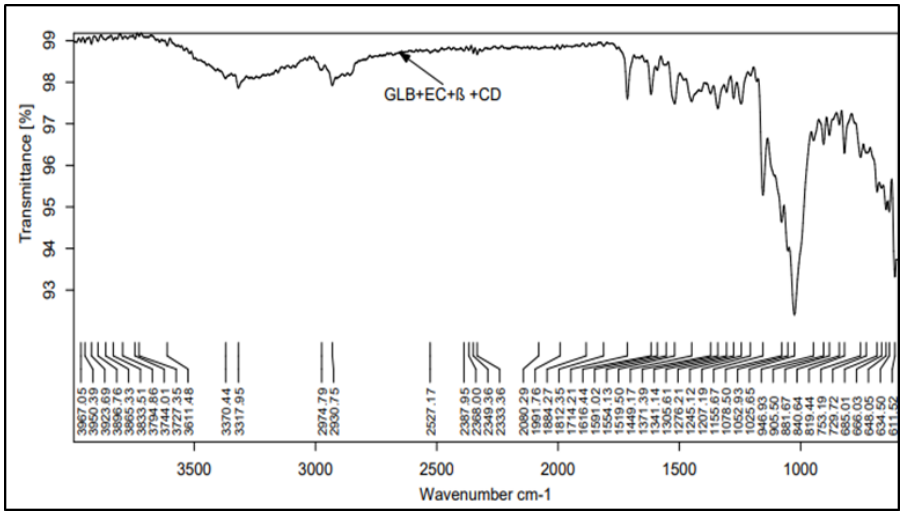

Figure 4 The FTIR spectrum of physical mixture of GLB, EC and β-cyclodextrin

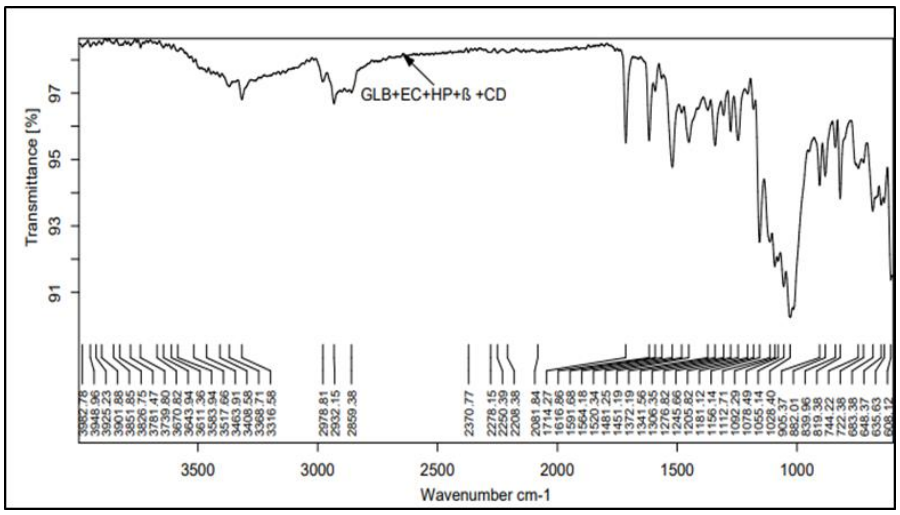

Figure 5 The FTIR spectrum of physical mixture of GLB, EC and HP-β-cyclodextrin

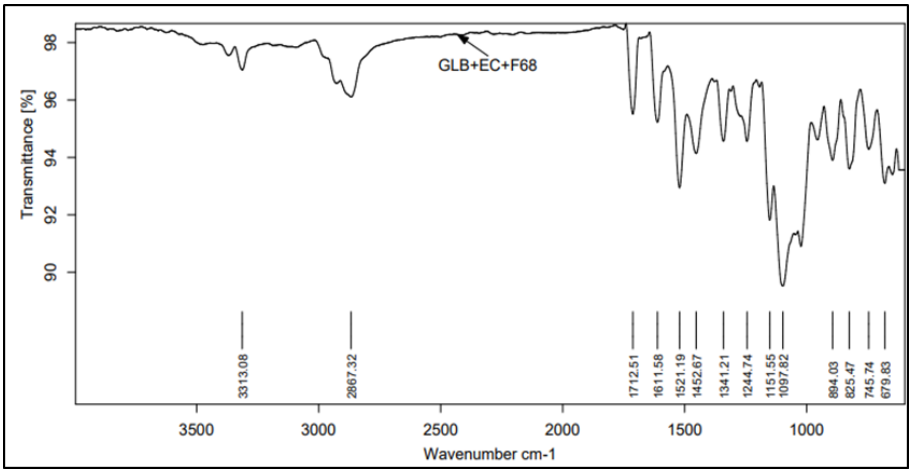

Figure 6 The FTIR spectrum of physical mixture of GLB, EC and Pluronic F68

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

Table 2 Interpretation of FTIR

SL. NO	Name of the compound	Wave number(Cm-1)	Functional group
1	Glibenclamide	893.05 Cm-1	Alkene
		680.20 Cm-1	Aromatic ring
		3312.97 Cm-1	Amines
		1711.80 Cm-1	Ketones
		1244.66 Cm-1	Esters
2	Glibenclamide: EC: β-CD (1:1:1)	685.01 and 819.44 Cm-1	Alkene
		840.64 Cm-1	Aromatic ring
		3370.44 Cm-1	Amines
		1714.21 Cm-1	Ketones
		1245.12 Cm-1	Esters
3	Glibenclamide: EC: HP-β-CD (1:1:1)	683.38 and 819.38 Cm-1	Alkene
		839.96 Cm-1	Aromatic ring
		3368.71 Cm-1	Amines
		1714.27 Cm-1	Ketones
		1245.66 Cm-1	Esters
4	Glibenclamide: EC: PL-F68 (1:1:1)	679.83 Cm-1	Alkene
		825.47 Cm-1	Aromatic ring
		3313.08 Cm-1	Amines
		1712.51 Cm-1	Ketones
		1244.74 Cm-1	Esters

3.2. Characterization of Nanosponges

Glibenclamide 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.

3.3. Particle size, Zeta potential and PDI

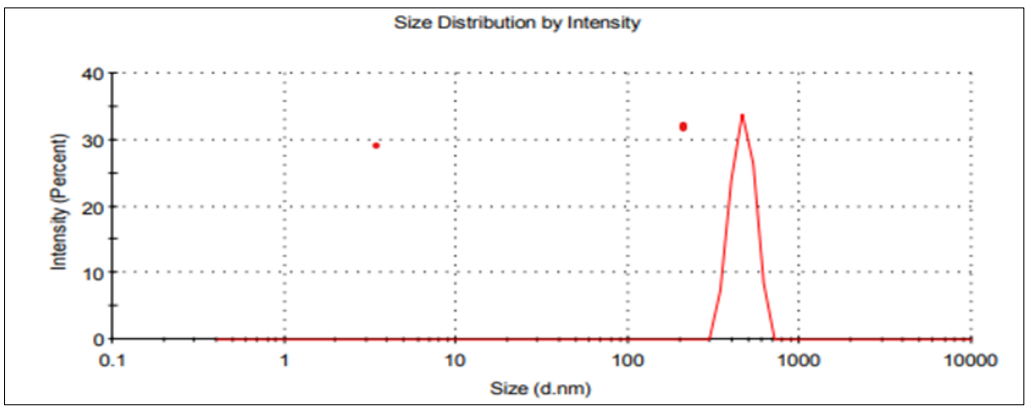

Figure 7 Size Distribution Profile of optimized formulation F6

The particle size ranged from 640.7 to 876.2 d. nm, PDI ranged from0.456 to 0.707 and zeta potential from -17.3 to -34.3 mV.

Table 3 The particle size, PDI and zeta potential of Glibenclamide loaded nanosponges prepared with β – Cyclodextrin, and HP-β-cyclodextrin and Pluronic F68

Formulation code	Particle size (d.nm)	PDI	Zeta potential (mV)
F1	876.0	0.707	-23.2
F2	873.8	0.667	-24.5
F3	785.2	0.587	-29.2
F4	742.2	0.658	-34.3
F5	640.7	0.556	-21.7
F6	665.3	0.456	-23.4
F7	756.9	0.654	-17.3
F8	805.3	0.599	-26.3
F9	711.2	0.562	-28.9

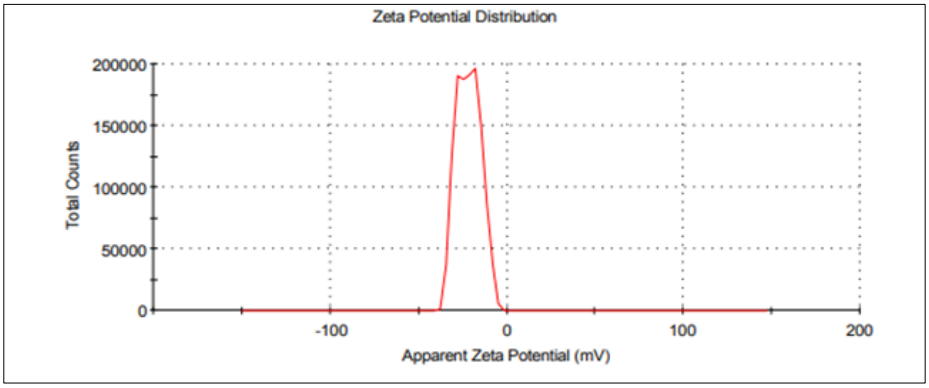

Figure 8 Zete potential profile of optimized formulation F5

3.4. Scanning Electron Microscopy

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

3.5. 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 Glibenclamide using 20 ml of methanol. The drug content results were ranged between 59.55 to 81.38% and drug entrapment efficiency results were ranged between 74.21 to 92.23%.

Table 4 Data of drug content and entrapment efficiency of Glibenclamide loaded nanosponges prepared with EC, β – Cyclodextrin, HP-β-cyclodextrin and Pluronic F68

Formulation code	Drug content in %	Entrapment efficiency (%)
F1	65.85	81.65
F2	75.33	83.25
F3	69.25	79.61
F4	71.26	82.98
F5	81.38	92.23
F6	67.27	74.21
F7	65.96	79.69
F8	66.33	79.31
F9	59.55	75.69

3.6. Release studies

The drug releases from the Nanosponges were studied by Dissolution method. The *In vitro* release profiles of Glibenclamide from Glibenclamide nanosponges are shown in Table No.5. The cumulative percentage release of Glibenclamide from different Glibenclamide nanosponges varied from 80.35 to 97.56% depending upon the drug polymer ratio.

Table 5 Percentage drug released from different formulations (F1-F12) during 12 hours

TIME (hr.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	44.17	51.24	63.13	37.83	30.91	31.38	48.09	54.14	51.73
1	36.58	31.62	32.48	34.29	37.67	42.20	36.34	36.65	38.85
2	40.89	48.85	42.07	29.78	47.49	63.42	40.94	48.10	47.72
3	60.56	61.38	59.22	51.60	54.86	56.90	57.22	58.61	64.50
4	58.61	61.34	71.30	56.63	65.36	66.04	58.39	58.91	67.91
5	76.22	69.14	82.20	60.51	69.75	62.81	72.14	72.96	70.85
6	84.11	68.81	62.92	71.04	70.63	71.34	79.56	79.50	75.54
7	88.62	71.25	85.10	81.98	79.64	79.66	88.29	88.48	79.07
8	84.72	71.72	63.75	82.12	77.50	89.03	84.71	87.11	86.82
9	92.92	80.33	70.43	83.67	87.89	85.08	91.36	91.86	86.56
10	90.71	93.50	83.16	88.65	92.40	90.87	90.93	91.22	87.49
11	94.80	88.55	78.00	91.50	95.82	90.86	92.82	90.78	87.05
12	95.76	95.57	80.35	93.09	97.56	92.57	95.53	93.42	88.23

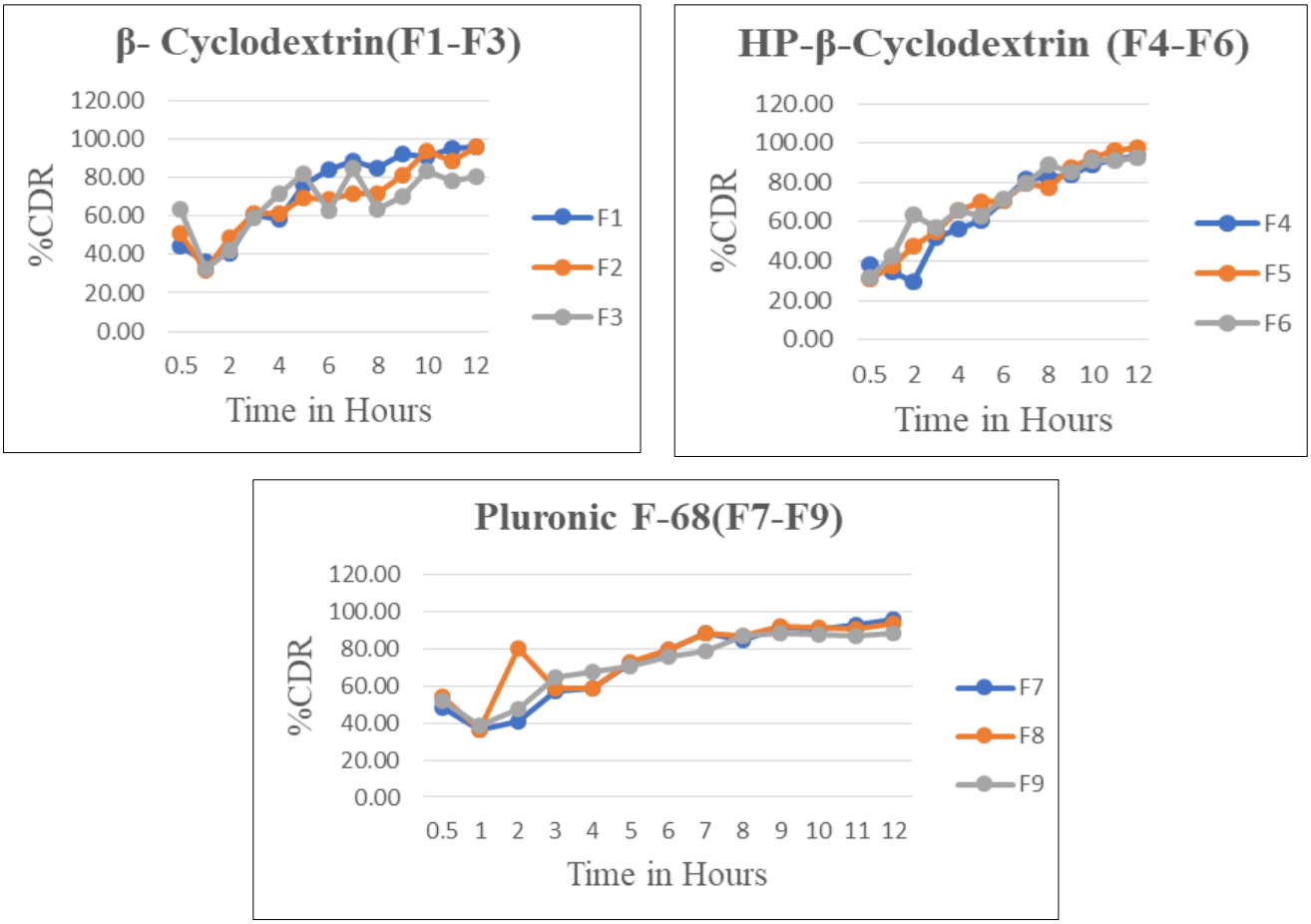

Figure 9 The comparison of percentage cumulative drug release profile of Glibenclamide loaded Nanosponges. (A) F1-F3(B) F4-F6 (C) F7-F9

3.7. Release kinetics

Data obtained from *In vitro* 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 *In vitro* release for F6 were shown in Table No.6 and 7. For remaining formulation, a similar procedure was followed.

Table 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	30.91	1.4900	69.09	1.8394
1	0	1	37.67	1.5759	62.33	1.7946
2	0.3010	1.4142	47.49	1.6766	52.50	1.7202
3	0.4771	1.7320	54.86	1.7392	45.13	1.6545
4	0.6020	2	65.36	1.8152	34.64	1.5396
5	0.6989	2.2360	69.75	1.8435	30.25	1.4807
6	0.7781	2.4494	70.63	1.8489	29.37	1.4607
8	0.9030	2.8284	77.50	1.8893	22.55	1.3521
10	1	3.1622	92.40	1.9656	7.59	0.8806

Table 7 The regression values of kinetic models of different formulations

Formulation code	Regression Factor			Korsmeyer-Peppa's	
	Zero order	First order	Higuchi model	R^2	n value
F1	0.8354	0.9145	0.9409	0.9454	0.6894
F2	0.7657	0.8341	0.8833	0.9568	0.5897
F3	0.7831	0.7132	0.7033	0.9124	0.6861
F4	0.8841	0.9667	0.9496	0.9510	0.6794
F5	0.8832	0.7099	0.9568	0.9496	0.8769
F6	0.7975	0.9155	0.9322	0.9012	0.5328
F7	0.8265	0.9535	0.9285	0.8956	0.6589
F8	0.6621	0.8402	0.8108	0.8741	0.7356
F9	0.8043	0.9435	0.9247	0.9201	0.5895

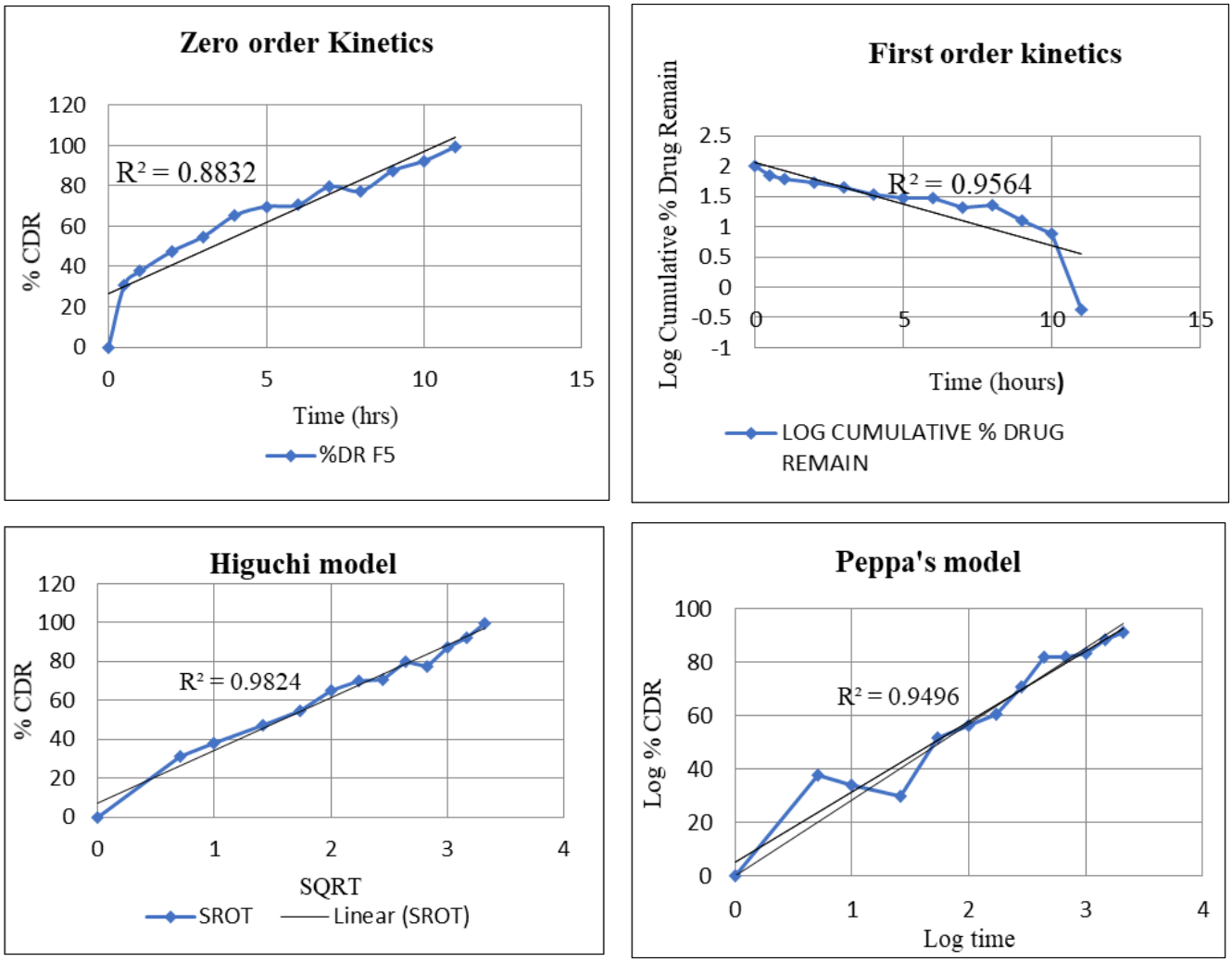

Figure 10 The Zero order, First order, Higuchi, Peppa's model kinetics plot of optimized formulation F5

4. Conclusion

In the present study, an attempt was made to develop Nanosponge delivery system for lipophilic drug Glibenclamide using Ethyl cellulose, β-cyclodextrin and HP-β-cyclodextrin and Pluronic F68 as polymers, which are meant to be used for better anti-diabetic action. FT-IR studies revealed that there was no interaction between the selected drug and polymers. Glibenclamide nanosponges were prepared by emulsion solvent diffusion technique which was able to produce Nanosponges of acceptable range and stability. All the formulations showed very high entrapment efficiencies. Among the all batches F5 was optimized after considering their particle size, SEM, zeta potential and *In vitro* drug release profile. Particle size, SEM, PDI and zeta potential of all the NS formulations developed were in the acceptable and suitable range.Average entrapment efficiency most of Glibenclamide NS was found to be greater than 80% whereas the optimized formulations F5 was shown 92.23% entrapment.

Release kinetics studies showed that drug release from the nanosponge fallows non-Fickian diffusion. Based on the observations, it can be concluded that the formulated nanosponge delivery system of Glibenclamide using widely accepted and physiologically safe polymer 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.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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