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Formulation and evaluation of oxiconazole nitrate 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 and evaluate Oxiconazole nitrate loaded nanosponges. The oxiconazole nitrate nanosponges were prepared by the emulsion solvent diffusion method by using the different polymers (Ethyl cellulose, β-CD, HP-β-CD). The FTIR test is conducted as the preliminary test, by this test there was no interaction between the drug and polymers. Then nanosponges (NS) were evaluated for particle size, poly dispersive index (PDI), zeta potential, entrapment efficiency and *invitro* drug release. The particle size ranged from 480.60 to 753.46nm, PDI ranged from 0.284 to 0.502, zeta potential from -20.9 to -35.9 mV and entrapment efficiency was ranged from 52.72 to 92.72%. The cumulative percentage release from all nanosponges varied from 73.16 to 97.84 % after 12hours depending upon the drug and polymer ratio and F4 formulation showed highest drug release i.e., 97.84%. The release kinetic studies showed that the release zero order diffusion controlled and the n value (0.713) from the Korsmeyer-Peppa's model indicated the release mechanism was non-fickian type.

Keywords: Oxiconazole nitrate; Nanosponges; FTIR; *in-vitro* Drug release

1. Introduction

Nanosponges are made of microscopic particles with few nanometers' wide cavities, in which a large variety of substances can be encapsulated. These particles possess nanosponges made 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].

Oxiconazole nitrate belonging to azole antifungal agent, used for the treatment of Tenia fungal infection. It has intermediate molecular weight, low irritation viability and good skin permeability [3].

It belongs to BCS class-II, the drug having low aqueous solubility and poor systemic absorption. The major drawback of this drug is low aqueous solubility and its hydrophobic nature [4].

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Nanosponges have many advantages which includes, (i) Nanospongescan carry both hydrophobic and hydrophilic molecules. (ii) 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. (iii) Nanosponges have the ability to produce predictable/controlled drug release. (iv) 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. (v)Nanosponges can significantly reduce the irritation of drugs without reducing their efficacy. (vi) Biodegradable in nature and easy scale up for commercial production [5].

Nanosponges have tremendous application in the field of drug delivery which includes the following. (i) Nanosponges are being used for solubility enhancement because of 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 [7]. (ii) 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 [8]. (iii) During protein delivery, nanosponges helps in the maintenance of the native protein structure 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. (iv) 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 [9].

2. Material and methods

Oxiconazole nitrate was purchased from Triveni Chemicals, Gujarath. Ethyl cellulose from Research lab fine chem industries. β-CD and HP-β-CD from Gattefose Hyderabad. All the reagents were analytical grade.

2.1. Determination of λ max of Oxiconazole nitrate in Citro-phosphate buffer of pH 4.5

Accurately weighed quantity of 10 mg of Oxiconazole nitrate was taken in 10 ml volumetric flask and it was dissolved in ethanol and made up to 10 ml using citrophosphate buffer pH 4.5. From the above stock solution, 10µg/ml solution was prepared and scanned between 200-400nm by keeping ethanol as blank. The absorption maxima of Oxiconazole nitrate were obtained 231nm.

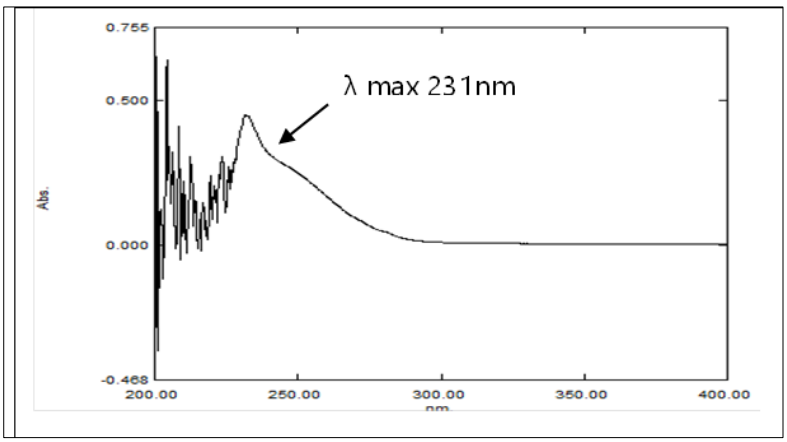

Figure 1 Determination of λ max of Oxiconazole nitrate in citro-phosphate buffer pH4.5

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 (Oxiconazole nitrate), Physical mixture: drug + EC+ β-CD, Physical mixture: drug + EC + HP-β-CD.

2.3. Preparation of calibration curve in citro-phosphate buffer of pH 4.5

Accurately weighed quantity of 100 mg of Oxiconazole nitrate was taken in 100 ml volumetric flasks and it was dissolved in citro-phosphate buffer pH4.5 and (Stock Solution I 1000µg/ ml). 5ml of stock I solution was taken in 50ml of

volumetric flask containing citro-phosphate buffer (stock II) From Stock Solution II, 0.2, 0.4, 0.6, 0.8, 1.2 and 1.4ml was taken and transferred to 10 ml volumetric flasks and volume was made up to 10 ml using volume with citro-phosphate buffer pH4.5 respectively. 2, 4, 6, 8, 10, 12 and 14µg/ml solutions respectively. The aliquots were analysed at 231 nm. The plot of concentration v/s absorbance, was plotted.

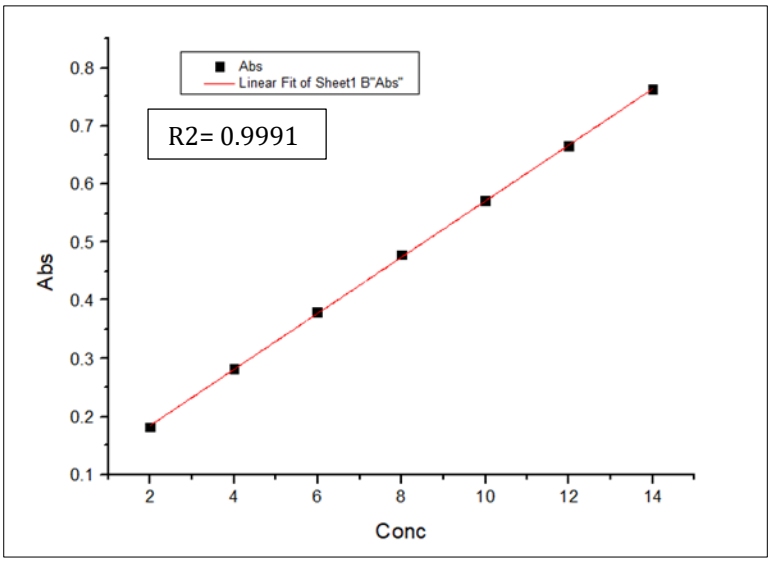

Figure 2 The Standard graph of Oxiconazole nitrate in citrophosphate buffer pH4.5

3. Formulation design

3.1. Preparation of Oxiconazole nitrate nanosponges using Ethycellulose, β-Cyclodextrin, and HP-β-Cyclodextrin

Nanosponges were prepared by emulsion solvent diffusion method, using different proportion of Ethyl cellulose, β-CD and HP-β-CD. Disperse phase consisting of drug (100mg) and requisite quantity of ethyl cellulose dissolved in 5ml of solvent (Ethanol) was slowly added to an aqueous phase containing definite amount of polymer. The reaction mixture was stirred at 1000rpm for three hours on a magnetic stirrer. The formed nanosponges were collected by filtration through whatmann filter paper and dried at room temperature [6].

Table 1 Composition of different formulation of Oxiconazole nitrate nanosponges

Formulation Code	Drug (mg)	EC (mg)	β-CD (mg)	HP-β-CD (mg)	DW (ml)
F1	100	100	100	---	30
F2	100	100	200	---	30
F3	100	100	300	---	30
F4	100	100	400	---	30
F5	100	100	---	100	30
F6	100	100	---	200	30
F7	100	100	---	300	30
F8	100	100	---	400	30

DRUG= Oxiconazole nitrate, EC= Ethyl cellulose, β-CD= β-Cyclodextrin, HP-β-CD =Hydroxy Propyl-β-Cyclodextrin, DW = Distilled Water

4. Evaluation of nanosponges

4.1. 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 [10].

4.2. Polydispersity index [PDI]

In light scattering, the term polydispersity and percentage 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 [11,12].

4.3. Zeta potential

Zeta potential analysis was performed to estimate the stability of the Nano-particles. 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 Nano-particles.

5. Scanning electron microscopy [SEM]

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 [13].

5.1. Drug Content

An accurately weighed amount of 20mg of nanosponges were added to 20ml of ethanol and placed in a thermo-shaker, operated at 100rpm at 25^0 C for 45minutes followed by vortexing for 10min. the solution was filtered through a 45µm membrane filter. Filtrate is observed under UV spectrophotometry [14].

$$\%\ Drugcontent = \frac{Practical\ amount\ of\ the\ drug\ obtained}{\text{Theroretical amount of drug added}} X100$$

5.2. Percentage Drug entrapment efficiency (%DEE)

50mg from the prepared drug loaded nanosponges by emulsion solvent diffusion method using suitable polymer were suspended in 50 ml of ethanol and were subjected for ultracentrifugation for 40min. the percentage of incorporated drug was determined spectrophotometrically. 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 minutes the free drug [15].

$$\%\ EntrapmentEfficiency = \frac{\text{Tota ldrug content} - \text{drug weight in aqueous phase}}{\text{Total weight of drug}} X100$$

5.3. *In vitro* Drug Release Study

In vitro drug release studies were carried out in *Franz* diffusion cell. 20mg of nanosponges dispersed in 2ml of citro-phosphate buffer. The dispersion was used for diffusion study. Nanosponges containing drug were placed in donor compartment while the receiver compartment consists of 22 ml of diffusion medium Citro-Phosphate buffer pH 4.5 maintained at room temperature in Franz diffusion cell. The rpm of the magnetic bead was maintained at 50 rpm. 1 ml of the aliquot was withdrawn at predetermined intervals. The samples were analysed for the drug content by UV spectrophotometer at 231 nm. Equal volume of the diffusion medium was replaced in the vessel after each withdrawal to maintain sink condition. Three trails were carried out for all formulation. From the data obtained the percentage drug release was calculated and plotted against function of time to study the pattern of drug release [13,16].

5.4. 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 [17].

- 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.

6. Results and discussion

6.1. 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 (Oxiconazole nitrate), polymer (ethyl cellulose) and co-polymers (β-cyclodextrin& HP-β-cyclodextrin) used for the preparation of Nanosponges. The FT-IR was performed for drug, polymer and co-polymer physical mixture. The spectra obtained from FT-IR spectroscopy study at wave number from 4000 to 400 cm^{-1} are shown below.

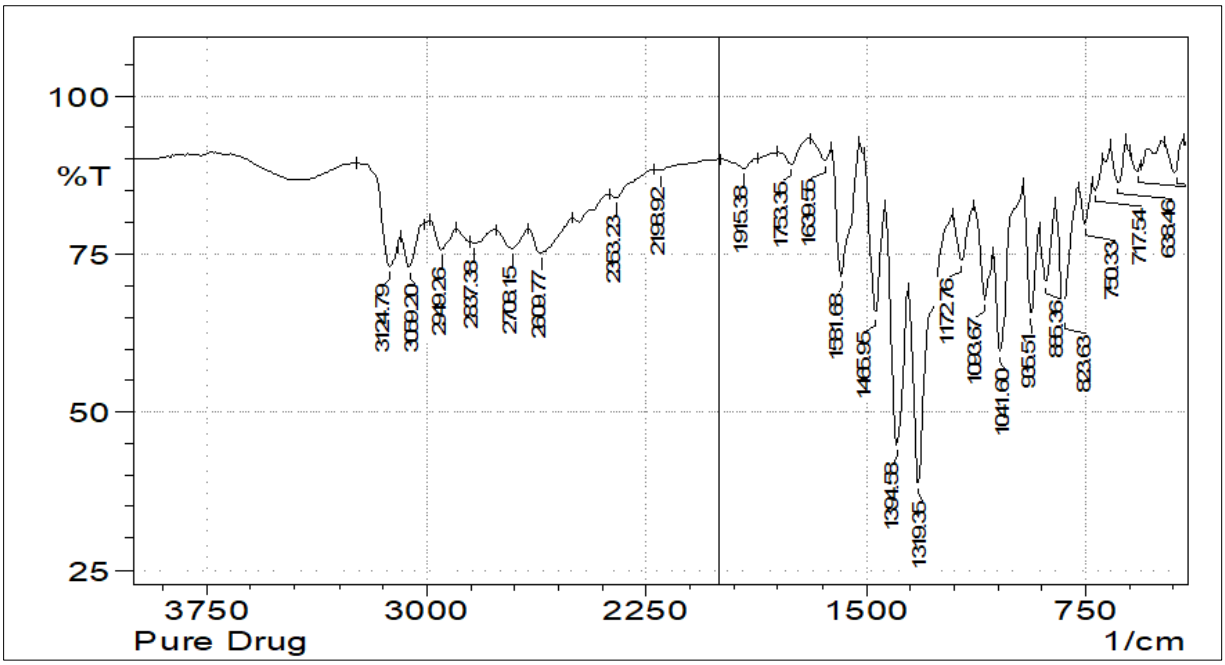

Figure 3 The FTIR spectrum of pure Oxiconazole nitrate

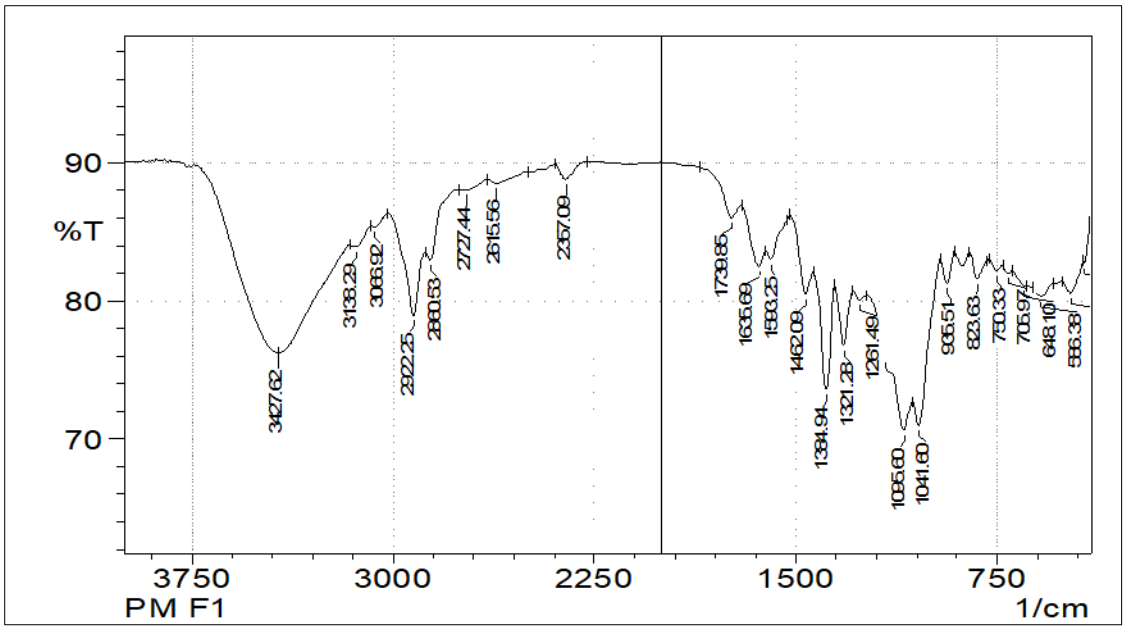

Figure 4 The FTIR Spectrum of drug +EC+β-CD

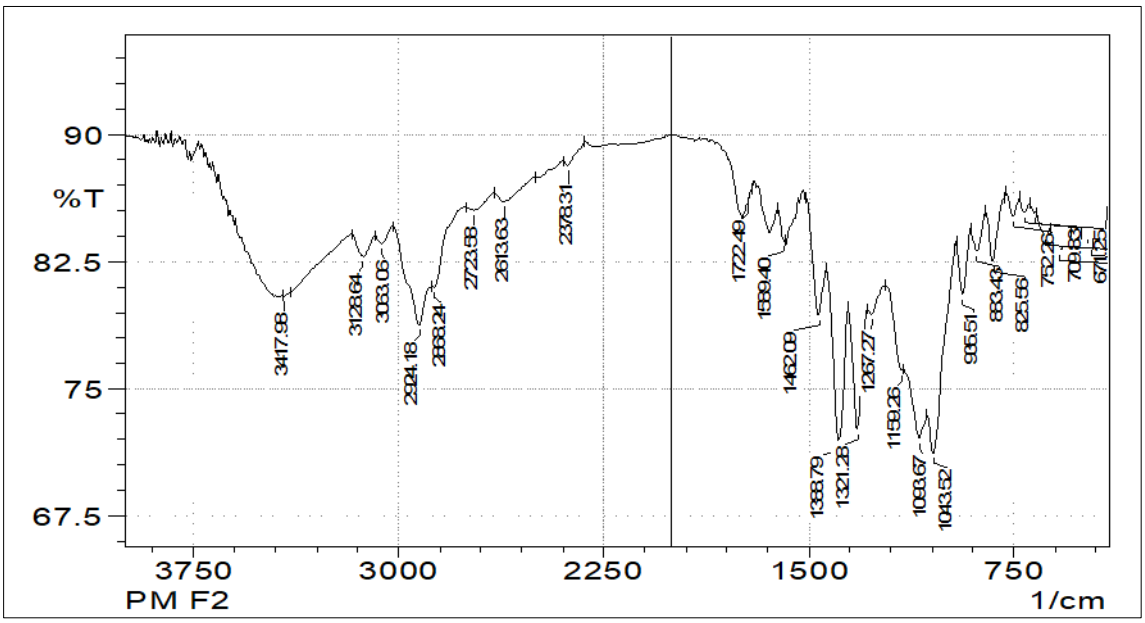

Figure 5 The FTIR Spectrum of Drug+EC+HP-βCD

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

Table 2 Interpretation of FTIR spectra

Sr. No	Name of the Compound	Wave number (cm^{-1})	Functional group
1	Oxiconazole nitrate	3124.79	-OH Stretching
		2949.26	C-H Stretching
		1639.55	C=C Aromatic Stretching
		1581.68	N-H Bending
		1465.30 - 1394.58	C-H Bending
		1041.60 - 1172.76	C-O stretching
		1319.35	C-O-C stretching
2	Oxiconazole nitrate: EC:β-CD (1:1:1)	3138.29	-OH Stretching
		2949.26	C-H Stretching
		1635.69	C=C Aromatic Stretching
		1384.94 - 1462.09	C-H Bending
		1593.21	N-H Bending
3	Oxiconazole nitrate: EC:HP-β-CD (1:1:1)	3128.64	-OH Stretching
		1589.40	N-H Bending
		1394.58 - 1465.95	C-H Bending
		1043.52	C-O stretching

6.2. Characterization of Nanosponges

6.2.1. Particle size, zeta potential and PDI

Report of size, PDI and zeta potential obtained from the zeta sizer, shown in the Table no.3. The particle size ranged from 480.6 to 753.4 nm, PDI ranged from 0.284 to 0.437, zeta potential from -20.9 to -35.96 mV.

Table 3 The particle size, PDI and zeta potential of Oxiconazole nitrate prepared with Ethyl cellulose, β-CD, HP-β-CD

Formulation Code	Particle size (d. nm)	PDI	Zeta potential (mV)
F1	518.60	0.502	-21.8
F2	683.93	0.434	-20.9
F3	658.63	0.384	-21.9
F4	558.63	0.284	-22.9
F5	753.46	0.352	-14.5
F6	673.45	0.405	-19.8
F7	539.60	0.437	-27.6
F8	480.60	0.426	-35.9

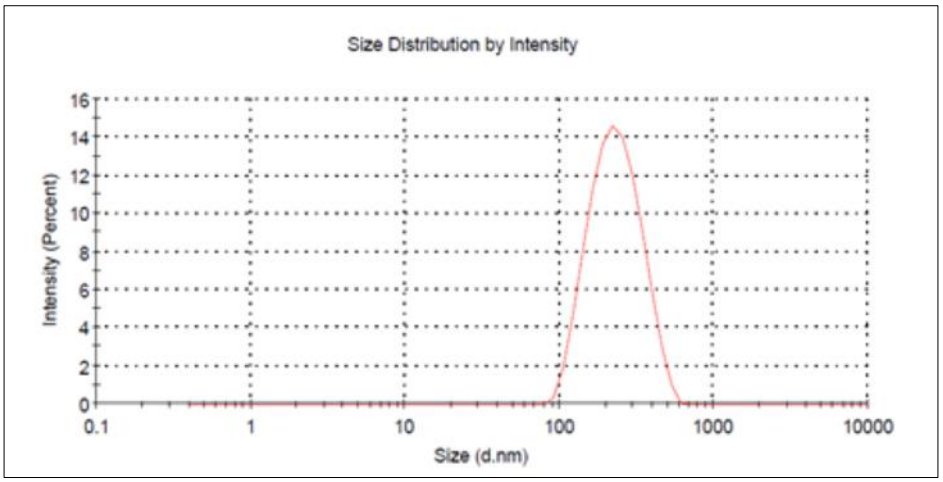

Figure 6 Size distribution of Optimized formulation F4

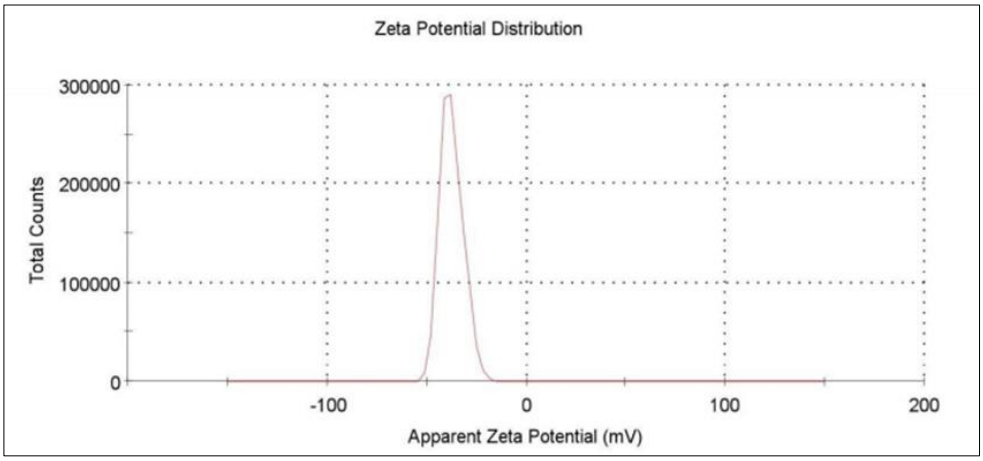

Figure 7 Zeta potential of Optimized Formulation F4

6.3. Scanning Electron Microscopy

SEM analysis of the formulated Oxiconazole loaded nanosponges were performed to evaluate the surface morphology of Nanosponges. The SEM images of Optimised formulation F4 is shown in below.

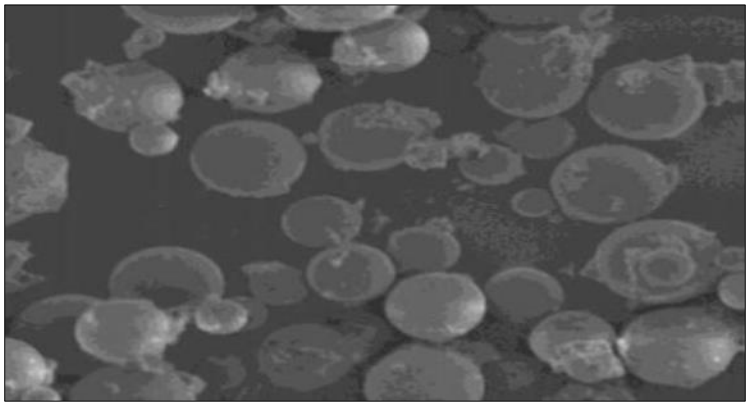

Figure 8 SEM image of Optimised formulation of F4

6.4. Drug content and Entrapment Efficiency

The drug content and the entrapment efficiency results are given in the Table no.4. The drug content results of nanosponges were obtained in the range from 95.39 to 98.85%. Entrapment efficiency of nanosponges were obtained in the range from 52.72 to 92.72%.

Table 4 Data of drug content and Entrapment Efficiency of Oxiconazole loaded nanosponges with Ethyl cellulose β-CD and HP- β-CD

Formulation Code	Drug Content %	Entrapment efficiency %
F1	96.22	66.04
F2	97.46	52.72
F3	98.50	81.38
F4	98.85	92.72
F5	95.39	83.20
F6	96.12	80.02
F7	97.06	76.45
F8	96.38	78.44

6.5. Release studies

The drug releases from the Nanosponges were studied by *Franz* diffusion method. The *in vitro* release profiles of Oxiconazole nitrate from Oxiconazole nitrate nanosponges are shown in Table No.5. The cumulative percentage release of drug from different nanosponges varied from 73.35 to 97.84% depending upon the drug polymer ratio and the type of polymer used.

Table 5 Percentage drug released from different formulations (F1-F8) during 12 Hours

Time (Hours)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	8.18	16.79	8.64	10.25	9.58	8.75	6.4	10.66
1	19.24	23.77	17.11	19.53	14.4	12.45	9.82	20.19
2	22.43	26.13	19.95	29.39	17.11	15.74	14.5	23.48
3	29.52	28.83	23.64	36.16	22.02	18.55	16.81	26.82
4	36.6	36.51	28.35	42.14	27.8	26.55	22.12	33.89
5	50.09	46.26	44.78	50.36	36.4	32.85	27.82	41.73
6	59.07	57.99	53.28	68.67	44.15	39.84	32.85	47.91
8	65.76	76.28	88.72	89.53	86.02	82.39	80.9	85.26
12	73.16	88.76	90.31	97.84	92.77	90.75	89.8	90.04

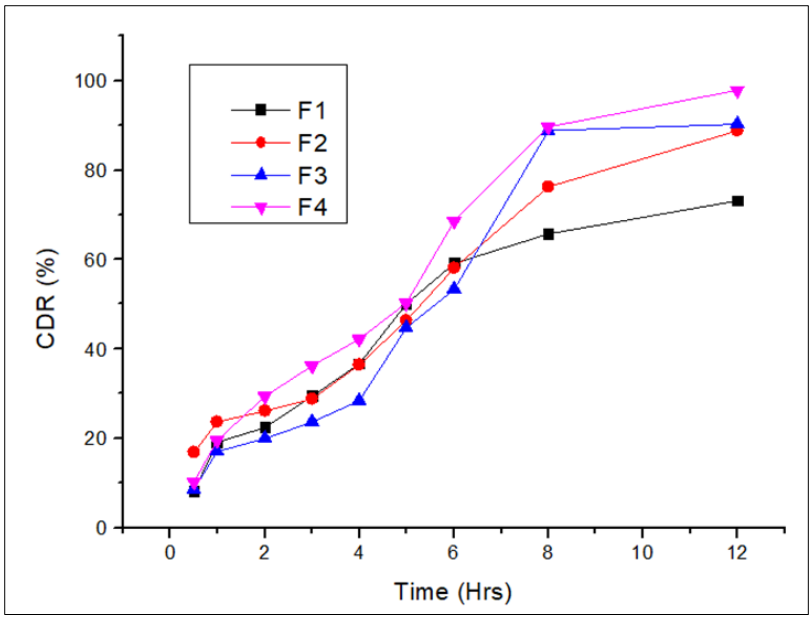

Figure 9 The comparison of percentage of cumulative drug release profile of Oxiconazole loaded Nanosponges (F1-F4)

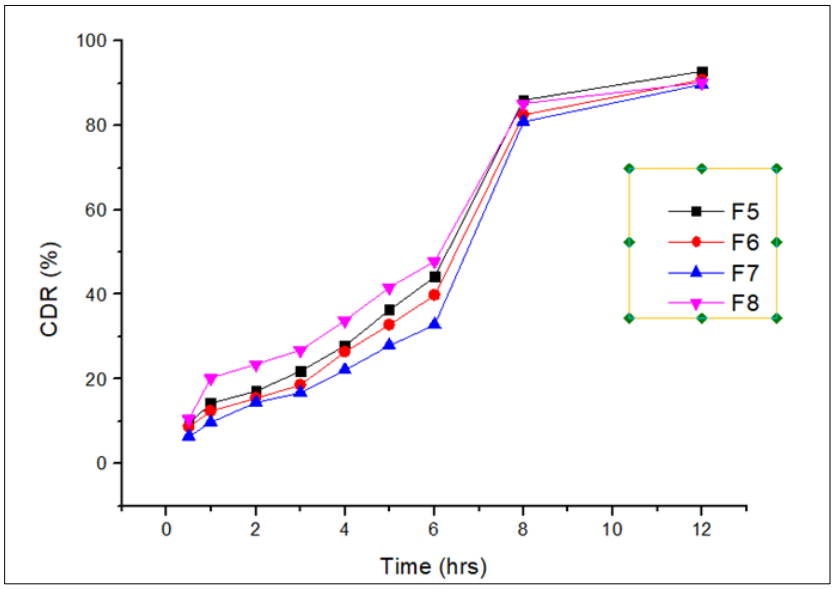

Figure 10 The comparison of percentage of cumulative drug release profile of Oxiconazole loaded nanosponges(F5-F8)

6.6. 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 F4 were shown in Table No. 6 and 7. Figure 11. For remaining formulation, a similar procedure was followed.

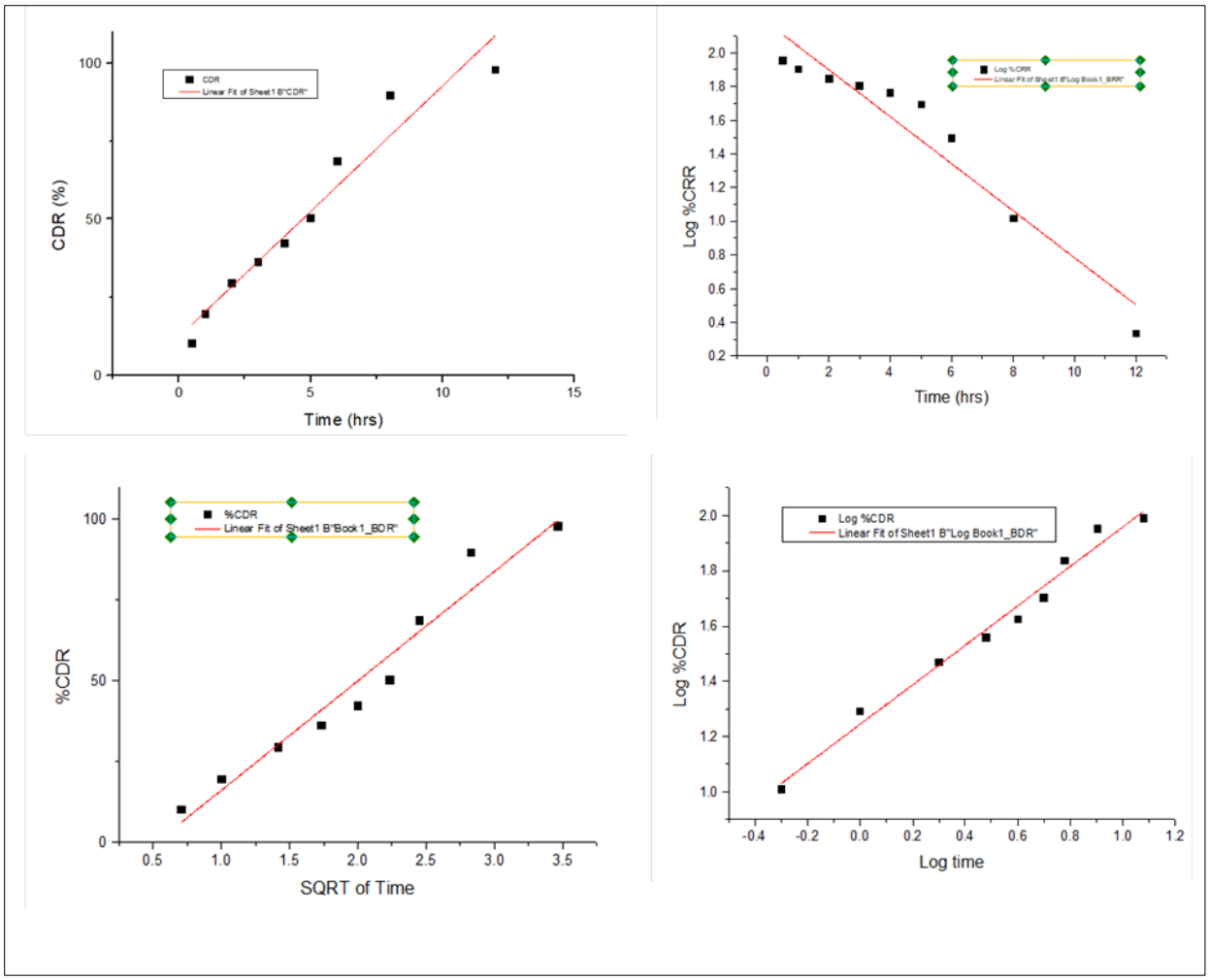

Figure 11 The Zero order, first order, Higuchiand Peppa's model kinetics plot of optimized formulation F4

Table 6 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	0.9374	0.9841	0.901	0.977	0.672
F2	0.9706	0.9379	0.9161	0.985	0.683
F3	0.8956	0.9249	0.8664	0.995	0.654
F4	0.9379	0.915	0.9508	0.981	0.713
F5	0.9852	0.9413	0.9006	0.971	0.655
F6	0.952	0.907	0.8655	0.994	0.663
F7	0.9456	0.913	0.9073	0.996	0.682
F8	0.9059	0.9085	0.8826	0.994	0.658

Table 7 The processing of release data of formulation F4 into different kinetic models

Time (hrs)	Log Time	SQRT	%CDR	Log %CDR	%CRR	Log % CRR
0.5	-0.3010	0.7071	10.25	1.0107	89.75	1.9530
1	0.000	1.000	19.53	1.2907	80.47	1.9056
2	0.3010	1.4142	29.39	1.4681	70.61	1.8488
3	0.4771	1.7320	36.16	1.5582	63.84	1.8050
4	0.6020	2.0000	42.14	1.6246	57.86	1.7623
5	0.6989	2.2360	50.36	1.7020	49.64	1.6958
6	0.7781	2.4494	68.67	1.8367	31.33	1.4959
8	0.9030	2.8284	89.53	1.9519	10.47	1.0199
12	1.0791	3.4641	97.84	1.9905	2.16	0.3344

7. Conclusion

In the present study, an attempt was made to develop Nanosponge delivery system for lipophilic drug Oxiconazole nitrate using Ethyl cellulose, β-cyclodextrin and HP-β-cyclodextrin as polymers, which are meant to be used for better anti-fungal action. FT-IR studies revealed that there was no interaction between the selected drug and polymers. Oxiconazole nitrate 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 F4 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 Oxiconazole nitrate NS was found to be greater than 80 % whereas the optimized formulations F4 was shown 92.72 % 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 Oxiconazole nitrate 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

Acknowledgments

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Disclosure of conflict of interest

The authors have declared that, there is no conflict of interest exist in this research article.

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