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COMPARATIVE CHARACTERIZATION OF GEL LOADED OXICONAZOLE NITRATE NANOSPONGES FOR TOPICAL DELIVERY

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ABSTRACT

Recent advances in nanotechnology paved path for design of nanogels with many potential applications in the field of nanomedicine. Nanogels being dispersions of hydrogel nanoparticles or nanosponges offer high drug loading compared to other nanocarriers and are thus suitable for solving issues related to stability, solubility and delayed release of actives and to formulate drug delivery systems for various administration routes besides the oral one. The objective of the present study was to formulate Oxiconazole nitrate nanosponges for topical delivery. Oxiconazole nitrate nanosponges were formulated using ethyl cellulose as polymer, polyvinyl alcohol as cross-linking agent and dichloromethane as solvent with different concentration. Which were evaluated for drug entrapment efficiency, surface morphology, particle size analysis, Zeta potential and percentage yield. Among all six different formulations F5 batch considered as the best with 88% of drug entrapment efficiency and least particle size (164.9nm). From the SEM analysis it's concluded that nanosponges are spherical, discrete with smooth surface and was loaded into the Carbopol 934 gel which were evaluated for viscosity, spreadability, pH, drug content, in- vitro drug diffusion study, release kinetics (R2 for Zero order 0.986), comparative study and stability studies. Overall, this study showed that nanosponges have a porous nature that creates a pathway for the release of the drug, and the process is simple and reproducible.

KEYWORDS: Oxiconazole nitrate, Nanosponge, Topical gel, Ethyl cellulose, Zero order.

INTRODUCTION

The Pharmaceutical and health care industry has been creating and using nano-scale materials for resolving many physical, biological and chemical problems related with the treatment of disease. The hydrophobic nature of most of the drugs present a challenge for effective in vivo delivery. Shrinking materials to nano-size has profoundly enhanced the efficacy of such drugs. A number of polymers have been studied and used for formulating Novel drug delivery systems (NDDS).[1]

Novel drug delivery systems (NDDS) are the key area of pharmaceutical research and development. The reason is relatively low development cost and time required for introducing a NDDS ($20-50 million and 3-4 years, respectively) as compared to new chemical entity (approximately $500 million and 10-20 years, respectively).[2]

The most emerging branch in pharmaceutical sciences known as "Pharmaceutical nanotechnology" presents new tools, opportunities and scope, which are expected to have significant applications in disease diagnosis and therapeutics.[3]

Nanosponges are porous polymeric delivery systems that are small spherical particles with large porous surface. These nanosponges can be effectively incorporated onto topical systems for prolonged release and skin retention thus reducing the variability in drug absorption, toxicity and improving patient compliance by prolonging dosing intervals Nanosponges can significantly reduce the irritation of drugs without reducing their efficacy.[4]

Oxiconazole nitrate belonging to BCS Class II is a broad spectrum imidazole antifungal agent. It has also been shown to inhibit DNA synthesis and suppress intracellular concentration of adenosine triphosphate, like other imidazole antifungal, it can increase membrane permeability.[5]

The aim of the present investigation is to assess the applicability of nanospongesloaded gel in delivering Oxiconazole nitrate through skin by enhancing solubility of the drug and to overcome the shorter retention on skin surface, entrapment of the drug in the nanosponges which will provide increased skin permeability, availability of the drug and incorporating into gel provides synergetic effect of prolong retention time due to the viscosity of the formulation and better patient compliance.

MATERIALS AND METHODS

MATERIALS

Oxiconazole nitrate was supplied from Yarrow Chem Products, Mumbai. All other excipients and solvents used were of the analytical pharmaceutical grade.

METHODS

Organoleptic characteristics[6] : The color and appearance of the drug are characterized and recorded.

Determination of melting point[6]

Melting point is determined by capillary method. Fine powder of Oxiconazole nitrate is filled in a glass capillary tube (sealed at one end).The tube was placed in melting point apparatus attached with thermometer. Note down the temperature at which drug melts completely.

Determination of Solubility[7]

The solubility study was performed out by dissolving an excess of the drug in 10ml of solvents (methanol, water, and 6.8 phosphate buffer). The samples were then agitated for 24 hours at 25±0.5˚C in a water bath shaker. The samples werefiltered and diluted appropriately. At λmax, the samples were spectrophotometrically evaluated.

Preparation of standard calibration curve[8]

The solution containing 10µg/ml concentration of Oxiconazole was prepared and scanned over range of 200-400nm against 6.8 pH phosphate buffer as blank using double beam UV spectrometer and absorbance was measured at 209 nm. A graph of concentration Vs absorbance was plotted.

Compatibility studies using FT-IR Spectroscopy[9]

The pure drug, drug and polymer were prepared and scanned from 4000-400 cm-1 in FTIR spectrophotometer. The results are shown in fig 1 and 2.

Preparation of Oxiconazolenitrate nanosponges by emulsion solvent diffusion method[10]

Nanosponges were prepared by varying concentration of ethyl cellulose and keeping drug concentration constant. The dispersed phase containing drug and ethyl cellulose dissolved in 20 ml of Dichloromethane was slowely added dropwise to polyvinyl alcohol in aqueousphase of 100 ml with 1500 rpm continuous stirring with magnetic stirrer along with Probe sonication every 10 min time interval for 2 hours. The formed nanosponges were collected by centrifugation at 4000 rpm for 15 min and dried for 24 hrs.

Table 1: Formulation of Oxiconazole nitrate nanosponges by emulsion solvent diffusion method.

INGREDIENTS	F1	F2	F3	F4	F5	F6
Oxiconazole nitrate (mg)	100	100	100	100	100	100
Ethyl cellulose (mg)	100	100	100	200	200	200
PVA(mg)	100	200	300	100	200	300
Dichloromethane (ml)	20	20	20	20	20	20

Formulation of Gel Containing Oxiconazole Nitrate Loadednanosponges[11]

Accurately weighed amount of Carbopol 934 (1% w/w) was taken and moistened in water for 2 hrs. Dispersed by constant stirring with the aid of magnetic stirrer to get smooth and uniform dispersion. The prepared dispersion was allowed to stand for 15 minutes to expel the entrapped air. The prepared nanosponges formulation selected nanosponge were added in to the gel, propylene glycol was added as a penetration enhancer, Methyl paraben was added as preservative and make up the volume with distilled water.

EVALUATION TEST FOR NANOSPONGE CONTAINING OXICONAZOLE NITRATE

Percentage yield[12]

The percentage yield of the nanosponges can be calculated by following equation after determining accurate initial weight of the raw materials and final weight of the nanosponge obtained.

$$\text{Percentage yield (PY)} = \frac{\text{Pratical mass of nanosponges}}{\text{Theoretical mass (drug+ polymer)}} \times 100$$

Drug entrapment efficiency[13]

Entrapment efficiency is defined as the percentage amount of drug which is entrapped by the nanosponges. The entrapment efficiency was determined by measuring 10mg of Oxiconazolenanosponges of each batch, powder in a mortar and pestle and crushed material was dissolved in 10 ml of phosphate butter pH 6.8 and then the dispersion were centrifuged at 1200 rpm for 30 minutes in order to separate entrapped from the unentrapped drug. The free drug concentration in supernatant layer after centrifugation was determined at 209 nmusing UV Spectrophotometer. The percentage entrapment efficiency (%EE) was calculated by following formula.

%Entrapment efficiency= Drug added- free drug/ Total drug * 100

Average Particle size[14]

The particle size of nanosponges was determined using Malvern zeta sizer. From this, the mean diameter can be measured. Measurements were made at the fixed angle of 90˚ for all the samples (F1 - F6). The samples were suitably diluted with distilled water for every measurement.

Zeta potential[15]

Measurement of zeta potential of the nanosponges was done by using Malvern nano zeta sizer instrument. Measurements were performed on the samples prepared for size analysis. Zeta potential indicates the degree of

repulsion between adjacent, similarly charged particles in dispersion system.

Scanning electron microscopy (SEM)[16]

Morphological studies of selected nanosponges formulations were carried out by scanning electron microscopy with auto imaging systems. Particles were placed on aluminum stub and coated with gold by using sputter coater operated under vacuum for 25 sec at 40mA.

CHARACTERIZATION OF GEL CONTAINING OXICONAZOLE NANOSPONGES[17,18,19,20]

Determination of pH

The pH of the prepared nanosponge loaded gel formulations were determined by using a digital pH meter. One gram of gel was dissolved in 100 ml of distilled water and stored for two hours. pH meter was calibrated and measurement was performed for each formulation in triplicate and average values were calculated.

Viscosity determination

The measurement of viscosity of the prepared gel was done with Brookfield viscometer (Brookfield DV- II + Pro). The reading was taken at 0.6 rpm using suitable spindle no.

Spreadability

The spreadability of the gel formulation was determined by taking two glass slides (14*5cm) of equal length. On one glass slide, 1gm gel was applied. To the other slide, weights (125g) are added and the time taken for the second glass slide to slip off from the first glass slide was determined. A shorter interval indicates better spreadability. Spreadability was calculated by using the formula,

$$S=M*L/T$$

Where, S = spreadability, M = Weight kept on upper slide, L = Length of glass slides, T = Time taken to slip off the slides completely from each other.

Drug content

The amount of drug contained in the prepared nanosponge based gel was determined by dissolving 100mg of prepared gels in 5ml of Methanol and volume was made upto the mark using phosphate buffer (pH 6.8). The mixture was analysed by spectrophotometrically at λmax against same blank.

***In-vitro* diffusion study[21]**

In-vitro drug diffusion study of prepared oxiconazolenanosponges loaded in gel was carried out by using Franz diffusion cell. The formulation was taken in the donor compartment and Phosphate buffer pH 6.8 was taken in the receptor compartment. The cellophane membrane previously soaked overnight in the diffusion medium was placed between the donor and receptor compartment. 1 g of the formulation was spread uniformly on the cellophane membrane, which is in contact with the receptor medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer with continuous stirring and the temperature of the medium was maintained at 37± 0.5˚C. At specific intervals, 1 ml of sample was withdrawn from the receptor compartment and replaced with an equal volume of Phosphate buffer pH 6.8. After suitable dilutions, the absorbance of the sample was determined by UV-visible spectrophotometer at 209 nm.

Kinetic studies[22]

To analyze the mechanism of drug release from the topical gel, the release data were fitted to following equations

1. Cumulative percent drug released Vs. Time (Zero order kinetics)
2. Log cumulative percent drug retained Vs. Time (First order kinetics)
3. Cumulative percent released Vs. The square root of Time (Higuchi model)
4. Log cumulative percent drug released Vs. Log Time (Korsmeyer-Peppas model)

To compare the *in-vitro* diffusion study with marketed formulations[23]

In-vitro diffusion study was carried out in phosphate buffer 6.8 for 8 hrs by using Franz diffusion cell and the samples were analyzedspectrophotometrically at $\lambda_{max.}$

Stability studies[24]

Best formulation is subjected to stability testing at 40 ± 2^0C, 75± 5 % RH conditions for 3 months. Parametrs such as appearance, drug content and in-vitro diffusion were examined for 3 months.

RESULTS AND DISCUSSION

PREFORMULATION STUDIES OF PURE DRUG

Table 2: Preformulation studies of pure drug.

PROPERTIES	REPORTED		OBSERVED	
Description	White crystaline powder		White crystalline powder	
Colour	White		White	
Melting point	137-138˚C		137˚C	
Solubility	Water	0.091mg/ml	Water	0.089mg/ml
	Methanol	3 mg/ml	Methanol	2.8 mg/ml
	Phosphate buffer pH 6.8	2 mg/ml	Phosphate buffer pH 6.8	1.3 mg/ml

COMPATIBILITY STUDIES USING FT-IR SPECTROSCOPY

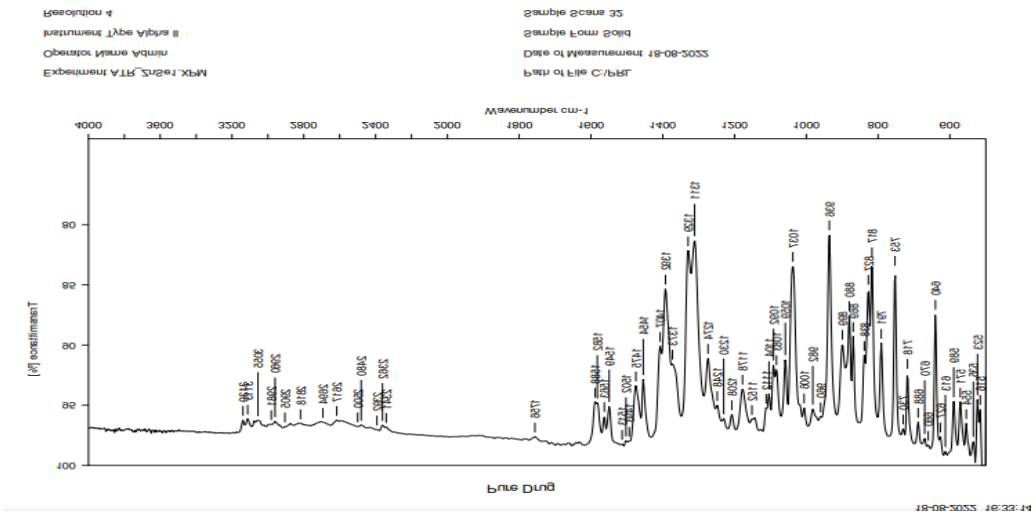

Fig 1: FTIR spectra of pure drug.

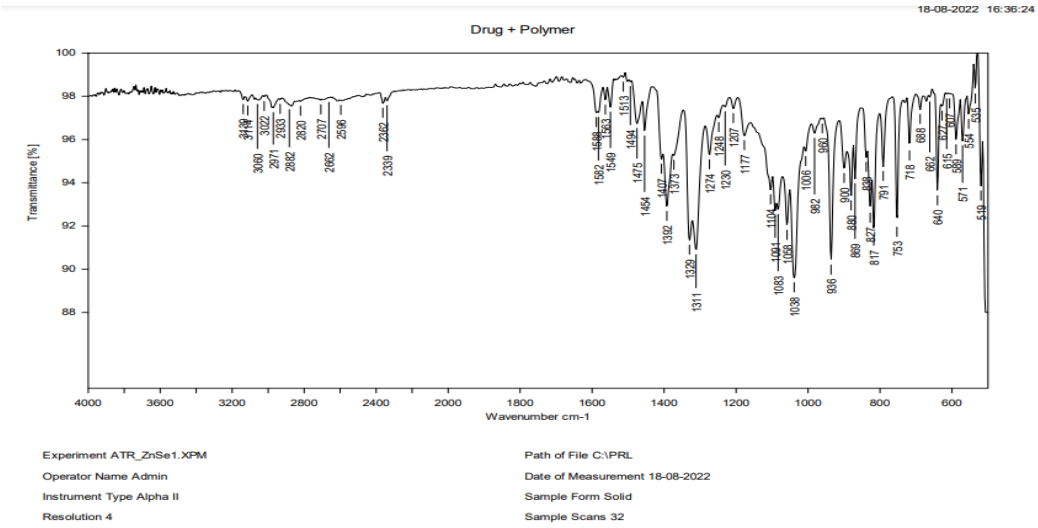

Fig 2: IR-spectrum of Drug + Polymers.

After the compatibility study of Oxiconazole with excipients, the IR spectra of pure drug and drug-excipient physical mixture were analyzed. Fig 1 and 2 indicate no interaction between drug and excipients when compared with spectra of the pure drug as all functional groups were present.

PREPARATION OF A STANDARD CALIBRATION CURVE OF OXICONAZOLE NITRATE

The curve was found to be linear in the concentration range of 2-10 µg/ml at 209 nm.

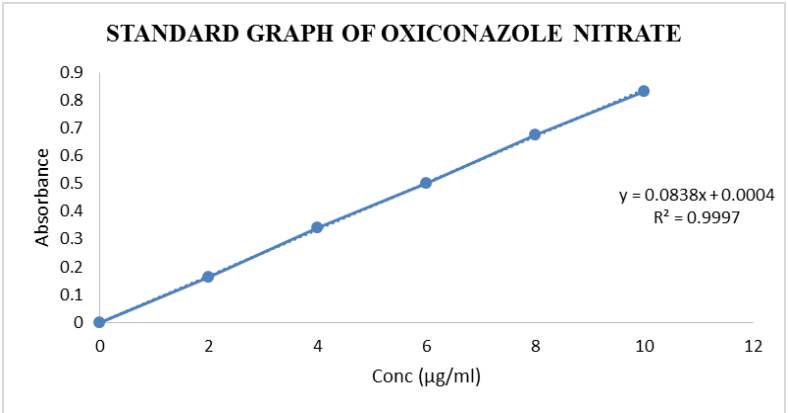

Fig 3: Standard calibration curve of Oxiconazole nitrate in phosphate buffer pH 6.8.

EVALUATION OF OXICONAZOLE NITRATE NANOSPONGES

Table 3: Evaluation parameters of nanosponge formulations.

Formulation code	Percentage yield	Entrapment efficiency	Particle size (nm)
F1	76.08±0.02	62±0.05	584.37
F2	79.15±0.05	66±0.05	409.4
F3	84.05±0.04	70±0.05	418.1
F4	78.91±0.04	73±0.04	340.3
F5	88.15±0.03	88±0.05	164.9
F6	84.23±0.05	86±0.02	230.5

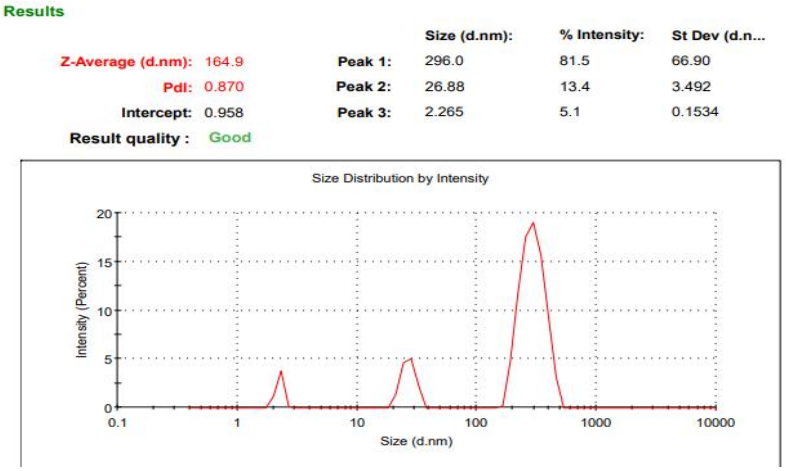

Fig 4: Particle Size of F5 by Malvern zeta sizer.

Particle size analysis of nanosponges was determined using Malvern zeta sizer instrument. The results showed that as the ethyl cellulose concentration increases, the particle size decreases. Out of all six formulations F5 (164.9nm) shows lesser particle size.

Zeta potential

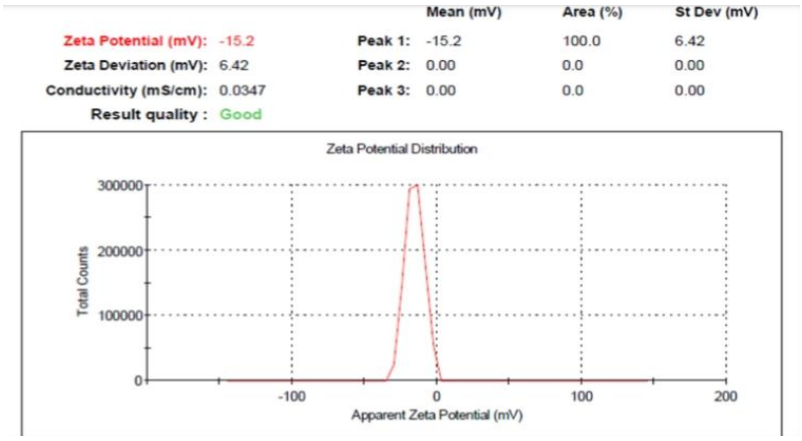

Fig. 5: Zeta Potential of Nanosponge Formulation F5.

Zeta potential of the Oxiconazole nitrate nanosponges was determined by Malvern nano zeta sizer instrument. It was found that the zeta potential of F5 formulation was negative, i.e -15.1Mv (Fig 5). Negative potential indicates that the particles stay in separate entity making the whole system stable.

Scanning electron microscopy

The SEM images showed that the surface of prepared nanosponges was spherical in shape and uniform in size and its surface was porous in nature.

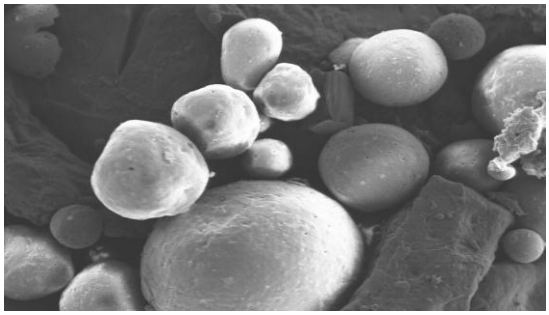

Fig 6: SEM image of F5 formulation of nanosponge.

EVALUATION TEST FOR FORMULATED NANOSPONGE GEL

Table 4: Physiochemical Evaluation Data.

Formulation code	Appearane	pH	Spreadability (gms.cm/sec)	Consisteny	Drug content (%)	Viscosity (cps)
F5	White-gel	6.3±0.05	16.03±0.03	Good	88.98%	1358±0.05

Physical examination

The prepared nanosponge gel formulation (F5) was white to cream preparation with a smooth and homogeneous appearance and there was no phase separation in any of formulation.

Measurement of pH

pH of the formulations is shown in the Table no.11. The pH values of the prepared formulation ranged from 6.3±0.05, which is considered acceptable to avoid the risk of irritation upon application to the skin because adult skin pH is 5.5.

Viscosity Study

Viscosities of the formulation were evaluated by using Brookfield viscometer at 27^{o}C using spindle no.64 at 0.6 rpm. The viscosity of the nanosponge gel was found to be 1358 cps enhancing better retention time on skin.

Spreadability

The values of spreadability were shown in Table No. 11. The nanosponge gel formulation showed 16.03±0.03g.cm/ sec. The results indicate that the polymers used gave gels spread by small amount of shear providing good permeation.

In vitro diffusion study

The *in vitro* drug release studies were carried out using Franz diffusion cell for 8 hrs. The percentage of cumulative drug released from the formulations was tabulated in Table 4.

Table 5: *In vitro* diffusion study of gel containing nanosponges.

Time(hr)	% Cumulative drug release
0	0±0.00
1	12.25±0.01
2	18.99±0.04
3	27.38±0.02
4	38.67±0.05
5	49.66±0.04
6	61.35±0.01
8	81.93±0.03

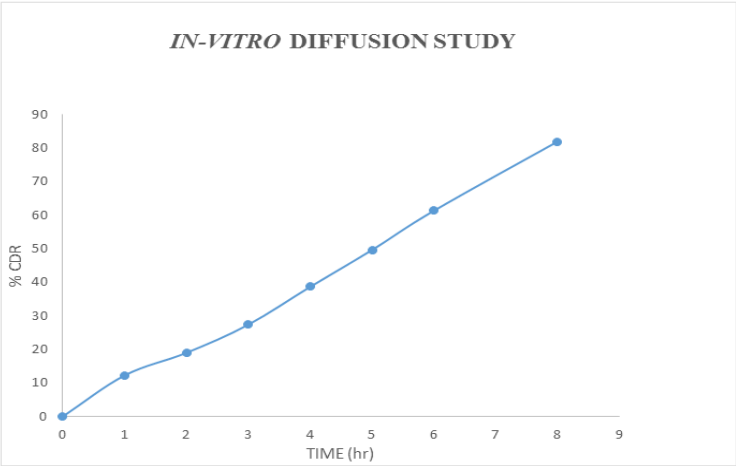

Fig. 7: Release profile of Nanosponge gel F5.

The nanosponge gel formulation (F5) showed drug release of 81.93% at the end of 8 hours. This indicates that as the concentration of ethyl cellulose is increased, the release concentration of the drug is increased. When the formulation is incorporated in the gel, it shows higher drug release.

Kinetics of drug release of Nanosponge gel

The in vitro drug release data of all the Oxiconazole nitrate nanosponge loaded formulation gel was subjected to the goodness of fit test by linear regression analysis according to zero order and first orders kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain mechanism of drug release.

Zero order kinetics release

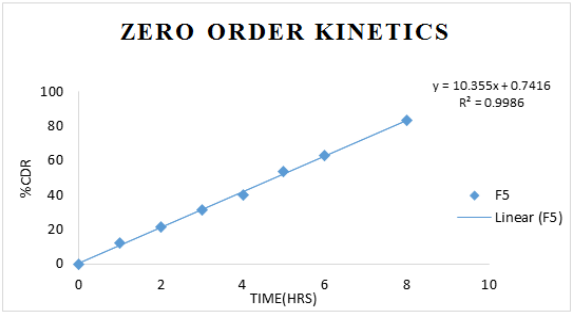

Fig 8: Plot of Percentage CDR v/s Time (Zero order kinetics).

First order kinetics release

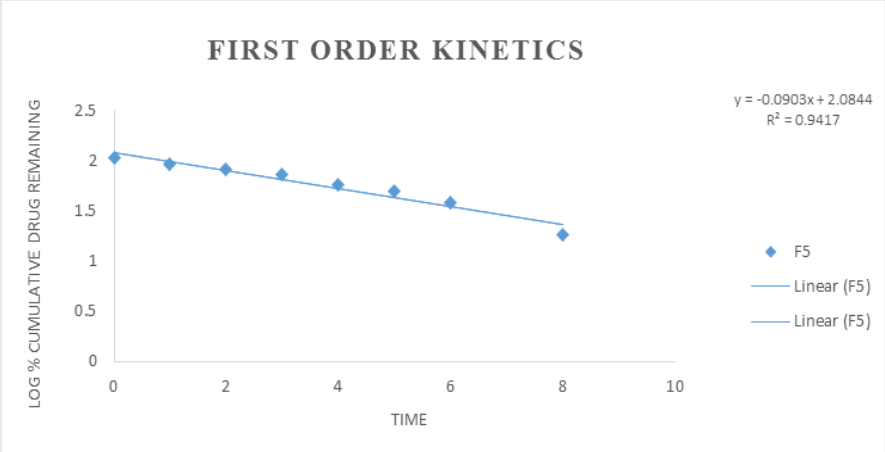

Fig. 9: Plot of Log % CDR v/s Time (First order kinetics).

Higuchi Model

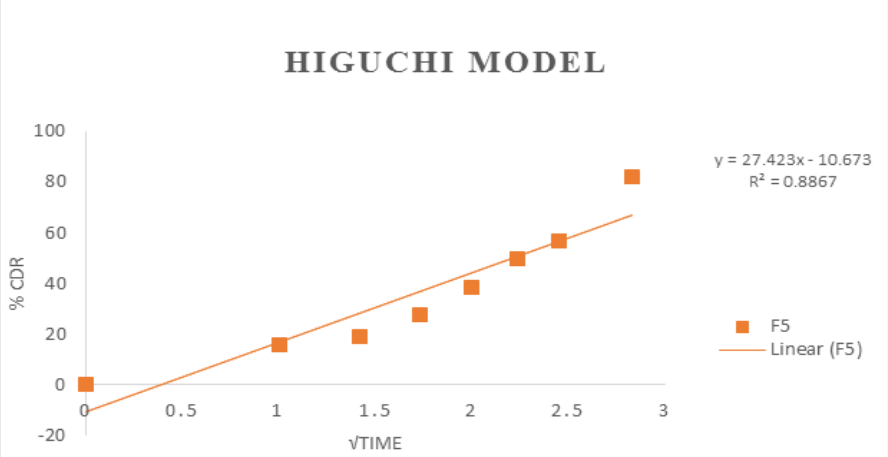

Fig. 10: Plot of Percentage CDR v/s √ Time (Higuchi model).

Peppas Model

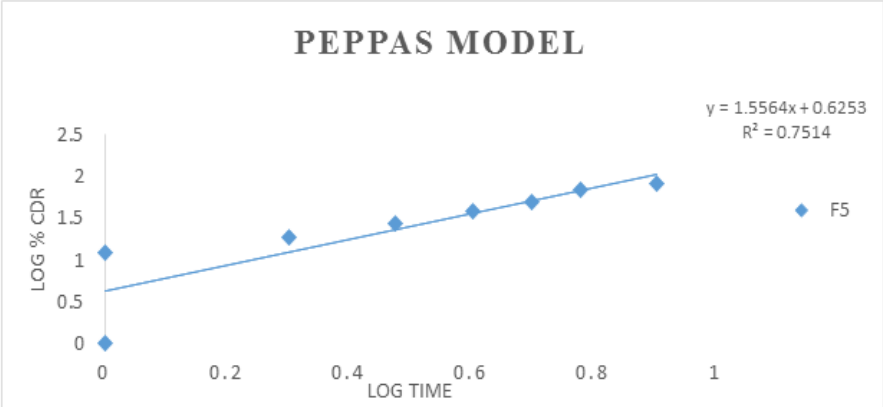

Fig. 11: Plot of Log Percentage CDR v/s Log Time (Peppas exponential equation).

Table 6: Regression Data of Kinetic Drug Release.

Kinetic Model	R^2 Value
Zero Order Kinetics	0.9986
First Order Kinetics	0.9417
Higuchi Model	0.8867
Peppas Model	0.7514

Based on the highest regression values (R^2 = 0.998), the best fit model for the Nanosponge gel formulation is Zero order.

Comparison of *in vitro* diffusion study of formulations with Marketed product

Table 7: Drug release profile of F5 Nanosponges and Marketed product.

TIME	% CUMULATIVE DRUG RELEASE (F5)	% CUMULATIVE DRUG RELEASE
0	0	0
1	12.25	13.87
2	18.99	19.11
3	27.38	26.99
4	38.67	35.11
5	49.66	46.34
6	61.35	57.23
8	81.93	80.11

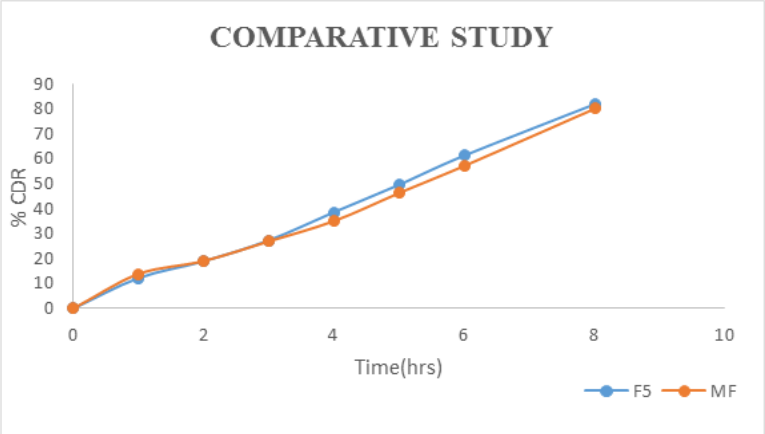

Fig. 12: Comparison of *in vitro* diffusion study of formulations with Marketed product.

At the end of 8 hours, F5 containing 0.1% w/w Gel showed 81.93% whereas Marketed formulation (1%) shows drug release of 80.11% which proves there is decrease in drug exposure compared to the conventional treatment.

Stability Studies

Table 8: Evaluation of F5 for stability study.

Evaluation Parameters	Time (days) Accelerated condition 40±2°C at (75±5%RH)			
	0 day	30 days	60 days	90 days
Colour	White	White	White	White
Drug content (%)	88.98%	87.75%	86.36%	86.12%
In vitro diffusion in 8 hr	81.93%	80.92%	80.26%	79.57%

CONCLUSION

The present study has been a satisfactory attempt to formulate nanosponge for the controlled topical delivery of Oxiconazole nitrate using Ethyl cellulose as polymer, polyvinyl alcohol as surfactant and dichloromethane as solvent.. From the reproducible results of the executed experiments, it can be concluded that:

- Preformulation studies of Oxiconazole nitrate comply with the reported literature limits.
- The IR spectra revealed that, there was no interaction between Oxiconazole nitrate and polymer, thus indicating the compactibility of Oxiconazole nitrate with the polymer used.
- The Oxiconazole nitrate nanosponge were prepared by emulsion solvent diffusion method, the nanosponges was evaluated for parameters like percentage drug entrapment efficiency, surface morphology, particle size analysis and zeta potential. Based on the characterization, nanosponges with high entrapment efficiency and least particle size (F5) was selected for topical gel formulation.
- The Formulation F5 were incorporated into gel and evaluated for pH, drug content, spreadability, viscosity, *in-vitro* drug diffusion study, release kinetics and stability studies.
- The percentage cumulative drug release after 8 hrs was found to be 81.93%. Formulation displayed a Zero-order kinetics (R^2 = 0.998).
- Comparative study of prepared nanosponge gel F5 and Marketed formulation was carried out and drug release of prepared F5 was found more than the marketed product.
- Stability studies of the formulation F5 were carried out for 3 months and there was no significant

changes found in the evaluation of nanosponge gel which indicates that the formulation is fairly stable at storage conditions.

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