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# Formulation and Evaluation of Ethyl Cellulose Based Fluconazole Nanosponges

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Authors JRY and SCJ did sample selection, designed the study and perform laboratory work as well as interpretation of findings and helped in preparation of the report. Author ARC managed the data analysis and identification of the compounds. All authors interpreted and permitted the submission of the last manuscript. All authors read and approved the final manuscript.*

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## ABSTRACT

Background and Objective: Fluconazole (FLZ) is a novel triazole antifungistatic drug; topical administration of FLZ resulted in systemic absorption and skin inflammation, and thereby failed to achieve mycological eradication, resulting in low patient compliance and undermining therapy effectiveness. The aim of this study was to use the emulsion solvent evaporation technique to create FLZ-loaded nanosponges (NSs) using ethylcellulose (EC) and polyvinyl alcohol (PVA) as a stabiliser. Materials and Method: By varying the drug concentration (FLZ), EC, and PVA, four formulations were developed, each of which was then optimized through particle characterization (polydispersity index (PDI), scanning electron microscopy (SEM), zeta potential (ZP), drug entrapment, and loading efficiency). Results: SEM (Scanning Electron Microscope) analysis showed that the particle sizes of FLZ inclusion complexes ranged from 150 2 to 250 5 nm. The ZP was strong enough to produce stable formulations. FLZ was released from the nano sponges in a regulated manner for 24 hours in both in vitro and in vivo experiments. FTIR and DSC were used to validate the association of the FLZ with the nanosponges. The crystalline nature of FLZ was

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modified to an amorphous state due to the complexation with the nanosponges, according to an XRPD analysis. The FLZ nanosponges were found to be stable in a stability analysis. Conclusion: Therefore, ethyl cellulose-based nanosponges provide a novel method for controlling the release of FLZ for antifungal effects.

*Keywords: Fluconazole; nanosponges; ethylcellulose; emulsion.*

## 1. INTRODUCTION

Nanotechnology is critical because existing formulations have a number of concerns, including significant side effects, inaccurate targeting, and solubility and stability issues [1]. To overcome the above disadvantages, nano-sized (10–1000 nm) drug carriers can be used to boost dissolution rate, absorption, bioavailability, and increase the drug's half-life in biological systems with site-specificity and continuous drug release [2]. Because of their potential for managed drug delivery, nanosponges have emerged as one of science's most exciting fields. The nanosponge delivery system will precisely monitor release rates or target medications to a particular body location, which would have a huge effect on the health-care system. Because of its high stability, high carrier potential, and ability to incorporate both hydrophilic and hydrophobic compounds, this nanosized delivery system has clear advantages for drug delivery. The use of nanosponges for selective and dispersed therapeutic agent delivery is the driving force behind research in this field [3]. The sponge serves as a three-dimensional scaffold or network. Polyester is used for the backbone. To make the polymer, it's combined with cross-linkers in a solution. As a result, spherically shaped particles with cavities where drug molecules can be deposited are created. Since polyester is biodegradable, it degrades slowly in the body. It releases the drug cargo in a linear manner as it degrades. By changing the amounts of crosslinker to polymer, nanosponges can be synthesised to be a certain size and release drugs over time. The ability of nanosponges to contain only small molecules is their biggest drawback. Solvent method, cross linking of -cyclodextrins, ultra sound aided method, and emulsion solvent diffusion method is some of the most efficient and cost-effective methods for making nanosponges. Ethyl cellulose (EC) has been stated to be non-biodegradable, non-toxic, biocompatible, and tolerable with reduced toxicity among the different forms of polymers used in the fabrication of nano matrix [4].

The Food and Drug Administration (US FDA) approved FLZ, an antimycotic agent, in 1990. It is a hydrophilic bistriazole with a wide spectrum. FLZ differs from other azol derivatives in terms of pharmacokinetic properties due to the existence of two triazol rings, which make it less lipophilic and have a lower affinity for proteins [5]. It is quickly consumed after oral administration and has a systemic bioavailability of over 90% [5,6]. The mild lipophilicity (log P=0.5), low protein binding (12%), and neutral charge at plasma pH (pKa=2.03) of FLZ can all be explained by its distribution profile [7]. Fluconazole is administered to the skin after oral administration, where it diffuses and accumulates quickly and deeply in the stratum corneum (SC). The concentration of FLZ in the skin is greater than in the serum, and it is eliminated from the SC at a much slower rate than in the serum or plasma. For most dermatophytes, the concentration inside the skin is much greater than the minimum inhibitory concentration [8,9]. The high affinity of FLZ for the SC due to an association between fluconazole and keratin has been linked to its extended skin retention [10].

FLZ is a topical and oral antifungal drug used to treat oropharyngeal and esophageal candidiasis, vaginal candidiasis, and cryptococcal meningitis. Peritonitis, candida urinary tract infections, candidemia, and pneumonia are among the health complications for which it is used [11]. Since it is an antifungal agent, it also needs a long course of treatment, which may increase the risk of side effects following systemic administration. To prevent these side effects, a topical fluconazole preparation must be created. The majority of topical delivery systems on the market, on the other hand, have insufficient residence time, resulting in ineffective therapeutic effects [12]. Furthermore, owing to their poor delivery potency, these formulations typically require a large volume of active pharmaceutical agent to achieve the desired therapeutic effect. A topical drug delivery device based on nanosponges has the ability to reduce the side effects associated with traditional delivery systems.

The aim of this research was to create and characterise fluconazole-loaded ethyl cellulose nanosponges for long-term drug delivery and

antifungal action. As a result of absorption by the reticuloendothelial system and the hydrophobic inheriting property of EC, nanosponges prepared by EC, rate retarding polymer could prolong the half-life of fluconazole. Drug release is reduced by reducing water entry into the polymer matrix.

## 2. EXPERIMENTAL

### 2.1 Material

Fluconazole (FLZ) was purchased in its purest form from Sai Lifesciences in Hydrabad, India. Sigma Aldrich, USA, provided dichloromethane (DCM), polyvinyl alcohol (PVA), and ethyl cellulose (EC), as well as .Sigma Aldrich, Germany, provided the ethanol (LC-MS grade), acetonitrile, formic acid, and methanol. Deionized water was used to make the ultra-pure grade water used in the analysis (Milli-Q). Except otherwise mentioned, all other chemicals and reagents were of analytical grade.

### 2.2 Methods

#### 2.2.1 Development of fluconazole loaded nanosponges

Fluconazole-loaded nanosponges (FLNS) were generated using an ultrasonication-assisted-emulsion solvent evaporation technique [13-14], with different proportions of polymers (EC and PVA) and the drug in two concentrations. With the aid of sonication, FLZ was dissolved in EC polymeric solution in DCM for 10 minutes. By probe sonication (model CL-18; Fisher Scientific, USA) for 5 minutes with power 60 percent voltage production, the prepared drug solution was emulsified dropwise into 100 ml of aqueous phase (100 ml) containing a different proportion of PVA. At atmospheric conditions, the produced emulsion was held on a magnetic stirrer (Fisher Isotemp Hot Plate and Stirrer; Fisher Scientific, USA) and stirred for around 24 hours at 1000 rpm [15]. The prepared FLZ were then extracted by ultracentrifugation and overnight lyophilization. The collected samples were then packed in a tightly sealed jar (Vial) and used for further characterization. Nanosponges with different concentrations of FLZ, EC, and PVA were developed (Table 1).

## 3. CHARACTERIZATION

### 3.1 Characterization of Fluconazole Nanosponges

#### 3.1.1 Production yield percent

After drying, the fluconazole nanosponges were measured. The following formula was used to measure the percentage yield value [16]:

% yield = Weight of nanosponges×100/Total solids weight

#### 3.1.2 Entrapment efficiency

The entrapment efficiency of fluconazole nanosponges was calculated using a UV spectrophotometric process. At 260 nm, a calibration curve for fluconazole in methanolic HCl was plotted in the range of 5-20 ppm (Beer's Lambert's range) (Shimadzu-1700, Japan). The concentration of fluconazole and its absorbance had a strong linear relationship (r2=0.9992, n=3). Every batch was given 100 mg of fluconazole nanosponges, which were powdered in a mortar and dissolved in 100 mL of methanolic HCl. After required dilution, fluconazole was extracted by centrifuging at 1000 rpm for 30 minutes, purified, and the concentration was calculated from calibration curve results [17].

Percentage entrapment was calculated as follows:

% Entrapment efficiency= Actual drug content in the nanosponge×100/Theoritical drug content

#### 3.1.3 Particle size measurement

Photon correlation spectroscopy (PCS) was used to calculate the average particle size of fluconazole nanosponges using a Nano ZS-90 (Malvern Instruments limited, UK) at a fixed angle of 250. The sample was dissolved in pure water 10 times before being tested for particle size [18].

**Table 1. Composition of FLZnanosponge**

| Formulation Code | Fluconazole (FLZ) : Ethyl Celluose(EC) | Polyvinyl Alcohol (mg) | Dichloromethane (ml) |
|---|---|---|---|
| F1 | 1:0.4 | 50 | 25 |
| F2 | 1:0.6 | 50 | 25 |
| F3 | 1:0.8 | 50 | 25 |
| F4 | 1:1 | 50 | 25 |

### 3.1.4 Zeta potential

The zeta potential was used to determine the particle charge as well as the particle velocity in an electric field. The nanosponges were diluted 20 times with purified water and analysed by Zetasizer using Laser Doppler Micro electrophoresis in the current study (Zetasizernano ZS, Malvern instruments Ltd., UK) [17].

### 3.1.5 Surface morphology

Scanning Electron Microscopy was used to investigate the structure and morphology of nanosponges (LEO 440I). The sample was placed on a glass slide and held under vacuum for the duration of the experiment. A sputter coater device was used to coat the samples with a thin gold/palladium film. An acceleration voltage of 15 kV was used to use the scanning electron microscope[18].

### 3.1.6 Fourier transform infrared spectroscopy studies

A Perkin Elmer Model 1600 was used to take FTIR spectral measurements at room temperature (USA). The pellets were made by dispersing the samples in KBr powder and adding 5 tonnes of pressure. Powder diffuse reflectance on an FTIR spectrophotometer was used to produce FTIR spectra [19].

### 3.1.7 Differential scanning calorimetric studies

To determine drug-polymer compatibility, researchers used differential scanning calorimetry (DSC-60, Shimadzu Corporation, Japan). After calibration with Indium and lead requirements, samples (3-5 mg) were heated in crimped aluminium pans under a nitrogen atmosphere (range 50-400 0C, 100C/min). The fusion enthalpy and melting point is determined automatically [19].

### 3.1.8 Porosity

Pouring the nanosponges into a grated cylinder yielded the bulk volume, which was registered. It is then subjected to 200 taps, with the volume reported as true volume [18].

% Porosity= (Bulk Volume-True Volume/Bulk volume)×100

### 3.1.9 Determination of residual solvents concentration

The residual dichloromethane in fluconazole nanosponges was measured using gas chromatography (Shimadzu GC-14B chromatograph, Japan). Gas chromatography was used to assess the dichloromethane content of nanosponges using an Agilent 7890 Gas Chromatograph with a flame ionisation detector from the United States. 500 mg of nanosponges is dissolved in a small quantity of DMSO in a 10 mL mL volumetric flask and volume was made up to 10 mL with DMSO to estimate residual solvents. The solution was purified and degassed using a 0.45 m filter and a sonicator. 5 µl of the sample was injected into the injection port, the chromatogram was registered, and the solvent peak area was calculated. For dichloromethane in the range of 20-100 ppm, a calibration curve was plotted. The concentration of dichloromethane and its peak area have a strong linear association (r2=0.991). The residual solvent concentration was measured using calibration curve data [20].

### 3.1.10 Preparation of nanogel

The fluconazole nanosponges' nanogel was created using a tweaked emulsification-diffusion process. 50 mg nanosponges dissolved in 20 mL ethyl alcohol, which already had gelatin dissolved due to constant stirring. In 40 mL of aqueous phase, the prepared organic phase dispersion was added. On a high-speed homogenizer set to 8000 rpm, methyl acrylic acid (MAA) was applied to the aqueous phase. The organic solution was added to the MAA-containing aqueous process. The resulting dispersion was then stirring continuously at 10000 rpm for 15 minutes before being sonicated for 15-20 minutes. DDW was also added to the prepared dispersion with continuous stirring for 45 minutes in order to enable the organic phase to quickly disperse into the aqueous phase. The nanodispesion was formed as a result of this. Gels were made from the prepared nanodispersion by adding lecithin as a gelling agent. The procedure was carried out while being constantly stirred. The pH of the nanogel was raised to 7 [21].

## 3.2 Characterization of Fluconazole Nanosponges Nanogels

### 3.2.1 Physical properties

The physical properties of the formulated FLZ nanosponges nanogel were examined, including

transparency, homogeneity, texture, viscosity, and pH.

### 3.2.2 Viscosity

The viscosity of each formed nanogel was measured using a viscometer (NDJ-8S) with S63 at 25.0 ± 0.5OC.

### 3.2.3 pH determination

Using a Digital pH metre, the pH value of all formulated nanogels was measured at 25 ± 10° C. (PHS-3E).

### 3.2.4 Homogeneity

The optical appearance of formulated nanogels was used to check for homogeneity, and clumps were tested with a close eye.

### 3.2.5 Spreadability test

A precise 0.1 g of each formulated nanogel was placed on the focal point of a designated glass slide (1.5 cm) on the front side and squeezed for 5 minutes by a second glass slide using a weight of around 1 kg on the upper glass slide. The length (in cm) of the circle area extended by each nanogel was then measured, and the process was repeated three times (n = 3). The average was used to arrive at the final result.

The spreadability was calculated by using the formula: $S = M \times L / T$
where M represents the weight (g) of the upper slide, L represents the length (cm) of the glass slides, and T represents the time (s) spent spreading the gel between the glass slides.

### 3.2.6 Extrudability

The power of formed gels to flow out of collapsible tubes is measured by extrudability. To determine the ease of extrusion, various nanogel formulations were compared based on their filling effects under stress conditions. The extrudability of formulated nanogels was tested using a hardness tester. The collapsible tube was filled with around 5 g of nanogel, and the plunger was set to keep the tube in place. Over the vent, pressure (approximately 1 kg/cm2) was exerted for 30 seconds. The amount of gel extruded from each tube was registered, and the effect was measured as extrusion pressure in grammes for all gel formulations [22].

### 3.2.7 In vitro release

To analyze release pattern of drug from the prepared nanogel in vitro drug release studies were performed using Franz diffusion cell with a porous membrane. All six nanogel formulations from F1 to F6 were applied on the surface of the membrane. Receiver compartment of the Franz diffusion cell was pre filled with the 1% w/v phosphate buffer saline having pH of 7.4, stirred at 350 rpm. Temperature of the Franz diffusion cell was maintained at 37ºC. The samples were drawn after specified time intervals i.e. 0.5,1 , 2, 4, 6, 8, 12 and 24 h. 0.5 ml of sample was drawn after each moment and Is replaced with the same amount of fresh buffer solution. HPLC method was used to analyze the drug sample [23-26].

### 3.2.8 Stability studies

Stability tests were conducted according to the ICH guidelines. Both seven nanogel samples were filled into glass vials separately and held for three months at temperatures of 30°C and 65 percent relative humidity (ambient conditions) and 40°C and 75 percent relative humidity (accelerated conditions). Visualizing the vials after that time was used to assess the appearance and transparency of the nanogel [27].

## 4. RESULTS AND DISCUSSION

Table 2 shows the percent yield value, drug entrapment performance, particle size, and zeta potential of fluconazole nanosponges.

**Table 2. Evaluation parameters of fluconazole nanosponges**

| Formulation | Percentage Yield | Entrapment Efficiency | Particle size (nm) | Zeta potential (mV) | PDI |
|---|---|---|---|---|---|
| F1 | 58.76±0.67 | 58.15±0.95 | 220.56 | -4.7 | 0.489 |
| F2 | 60.12±1.12 | 71.78±1.36 | 161.98 | -5.4 | 0.299 |
| F3 | 61.25±1.32 | 79.35±0.82 | 121.65 | -5.2 | 0.326 |
| F4 | 59.12±0.98 | 65.23±0.52 | 151.89 | -5.1 | 0.521 |

*(Mean ± SD, n=3)*

F3 has the highest percentage yield value of nanosponges. Owing to the sticky nature of the substance, which cannot be purified, the percent yield decreased as the polymer concentration was increased. For formulation F2, nanosponges were found to have the best entrapment performance. Entrapment quality was found to decline as the polymer content was increased due to the polymer's poor solubility in the aqueous process [28-29]. The nanosponges were discovered to be 121.65 nm to 220.56 nm in height (Table 2 and Fig. 1). The nanosponges' zeta potential was found to be between -4.7 and -5.4 mV. (Table 2 and Fig. 2). Nanosponges' stability is shown by the negative symbol.

Fig. 3 shows the SEM representations of the fluconazole nanosponges. Nanosized spherical particles with multiple pores on the surface were discovered using SEM (fluconazole nanosponges). The pores are tunnelling inwards, which may be due to dichloromethane diffusion from the nanosponges' surface.

Pure FLZ thermograms revealed an endothermic plateau at 142.2°C, which corresponded to its melting point in DSC tests. The thermal activity of the physical mixture was comparable to that of the single drug, but it was less intense. However, after microsponge encapsulation, the melting endotherm of the microsponge formulation was suppressed, corresponding to the partial security of FLZ. The crystallinity of the medication changed dramatically in the microsponge formulation, indicating that it was dispersed in the environment [Fig. 4] [22-26].

The infrared spectrum of the drug sample was registered [Fig. 5], and spectral analysis was performed. FLZ had its signature IR absorption peaks at 1193–1062 cm1 (C O bending), 1278–1215 cm1 (C F stretch), and 1620–1507 cm1 (C = C stretch) in the procured drug sample spectrum, confirming its purity. The findings of the FTIR spectroscopic analysis revealed no new peak occurrence or absence of existing peaks, ruling out any chemical reaction between the substance and the polymer used. In the physical mixture and microsponge composition continuum [Fig. 5], both of FLZ's signature peaks is experiential. As a result of the IR spectroscopy findings, the drug was found to be compliant with a variety of polymers and excipients, as well as having excellent stability in all microsponge formulations.

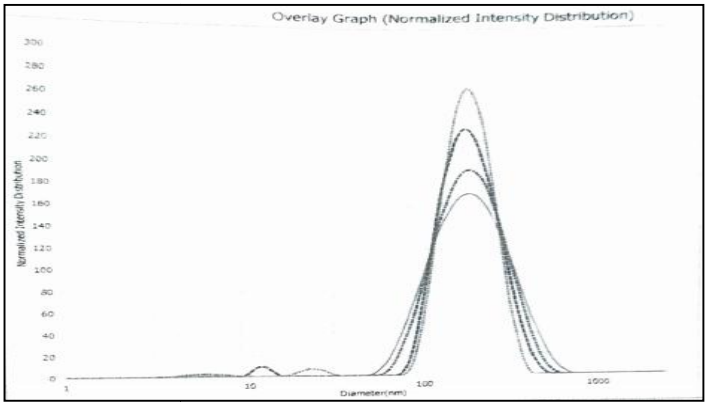



**Fig. 1. Particle size of fluconazole nanosponges (F1-F4)**

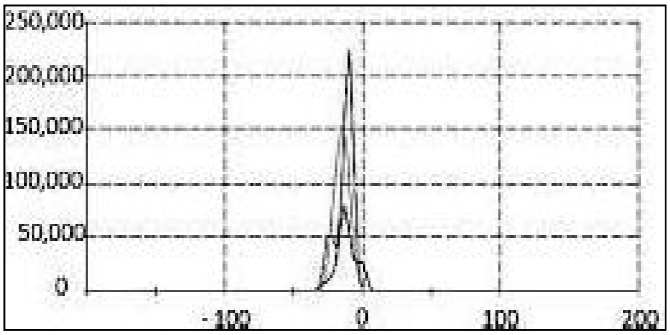



**Fig. 2. Zeta potential of fluconazole nanosponges(F1-F4)**

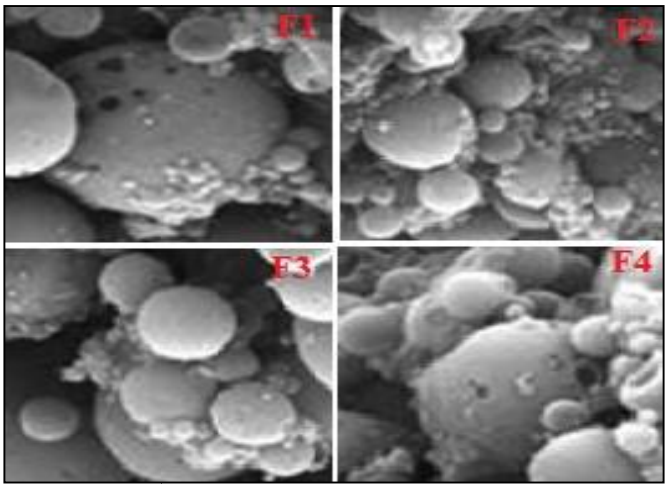



**Fig. 3. Scanning electron micrograph of fluconazole nanosponges**

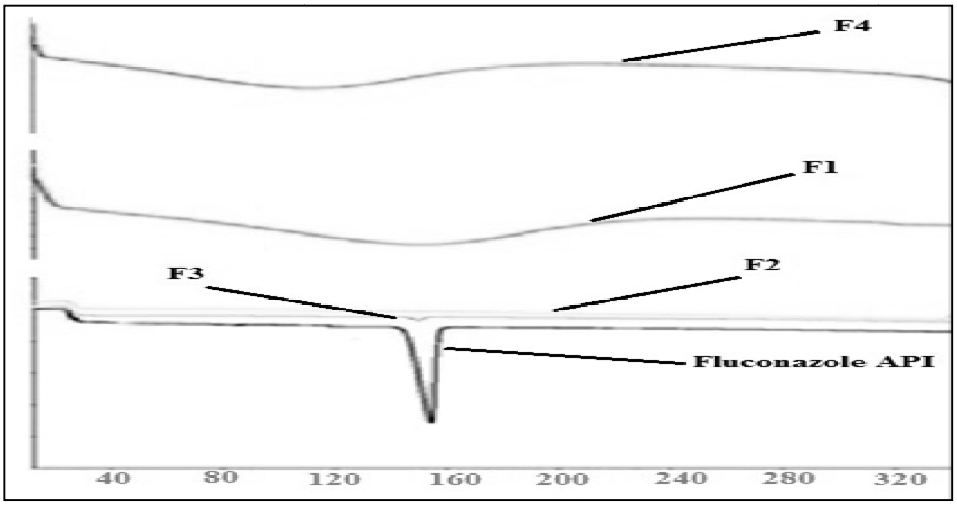



**Fig. 4. DSC thermograms of fluconazole and fluconazole nanosponges**

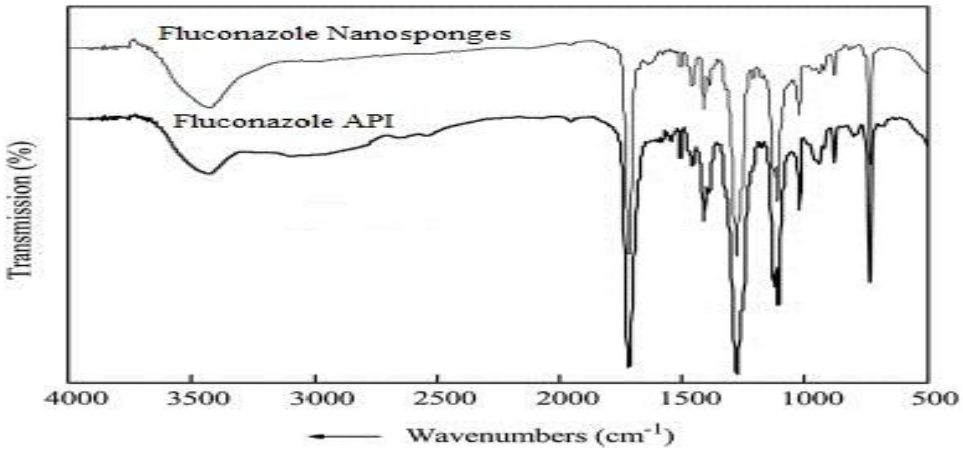



**Fig. 5. FTIR spectra of fluconazole and fluconazole nanosponges**

To determine the degree of nanochannels and nanocavities produced, a porosity analysis is carried out. The density of nanosponges can also be used to determine the porosity of the nanosponges. Nanosponges have a higher porosity than the parent polymer used to make the structure because of their porous existence. The bulk volume of the nanosponges was found to be 70 mL, while the real volume was found to be 25 mL. Porosity of the nanosponges was found to be 70%.

The dichloromethane concentration was estimated to be 350 parts per million. Dichloromethane is a class II solvent (solvents to be limited) according to the ICH Guidelines for Residual Solvents Q3C, so the limits of 600 ppm are suitable without explanation [27-29].

## 4.1 Characterization of Fluconazole Nanosponges Nanogels

### 4.1.1 Physical properties

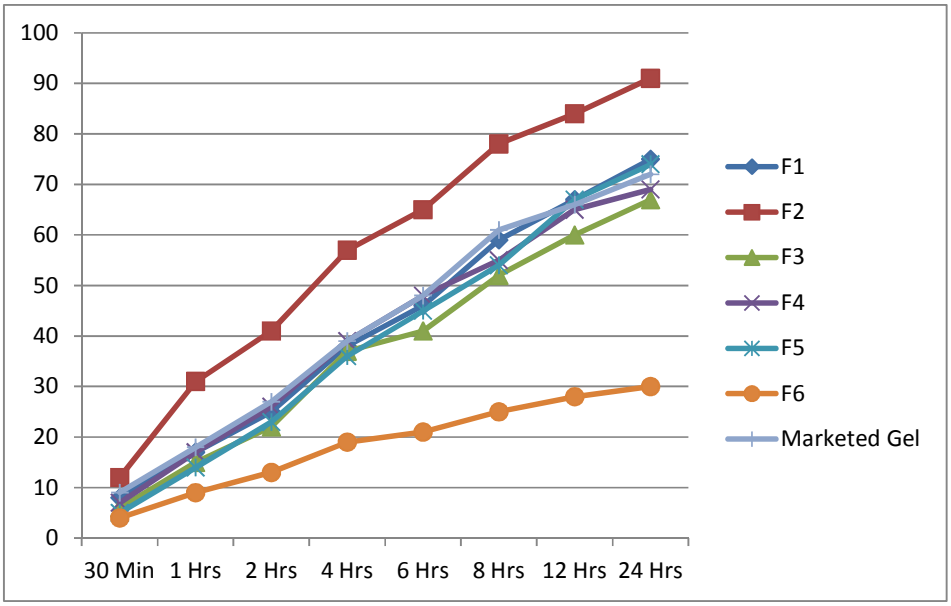
The physical properties of the formulated gel were examined, including transparency, homogeneity, texture, viscosity, pH, and spreadability. All formulated gels are clear, strongly homogeneous, lump-free, and smooth, according to the results. The pH of all prepared gels ranged from 5.8 ± 0.1-6.1 ± 0.1, which is within the standard pH range of skin. Both manufactured nanogels containing the gelling agent carbopol-940 had a spreadability value of 4.5 ± 0.1 - 5.2 ± 0.1 g.cm/s, meaning that F2 is more quickly spread by adding a limited amount of shear stress than other formulations. Extrudability findings revealed that nanogels with a high stiffness do not easily extrude from tubes, whereas nanogels with a low viscosity rapidly flow out of collapsible tubes. Extrudability values range from 1.47 ± 0.01 - 1.16 ± 0.01 g/cm. As a result, a successful gel formulation must have the right stability to extrude from a collapsible tube, as F2 demonstrated (1.16 ± 0.01 g/cm).

### 4.1.2 In vitro drug release

The fluconazole release from the prepared nanogel was observed. After 24 hours, fluconazole nanogel formulations F2 recorded the highest release, approximately 91 percent, while formulations F6 showed the lowest release, approximately 30 percent. During in vitro drug release trials, both formulations were found to adopt 1st order release kinetics. Graph 1 depicts the drug release from all seven formulations.

### 4.1.3 Stability test

Stability tests revealed that all nanogels have good physical characteristics, as no major changes in drug quality, drug release behaviour, viscosity, pH, or humidity were observed after 6 months of storage at 30°C± 10°C and 40°C± 10°C.




**Graph 1. IVRT release of Nanogels along with marketed gel**

## 5. DISCUSSION

The preparation of fluconazole-loaded nanogels made of biodegradable polymers was documented using an updated emulsification-diffusion process. Gelatin was used in greater proportions, along with chitosan, which was used in smaller amounts [2,28,29]. In the aqueous process, FLZ was added at 8000 rpm on a high-speed homogenizer. The organic solution was added to the FLZ-containing aqueous phase. The resulting dispersion was then stirring continuously at 10000 rpm for 15 minutes before being sonicated for 15-20 minutes. The addition of lecithin, a gelling agent, resulted in the creation of nanosponges, which were then transformed into nanogels. The formulated formulations revealed a transparent nanogel with excellent consistency, spreadability, clarity, and flow characteristics. The rheological tests specifically showed that as gelatin content increased, viscosity increased as well, and vice versa. As a result, the viscosity of nanogel formulations was observed to be equal to the volume of gelatin in the formulations. In vitro drug release tests revealed that formulations F2 had the highest release at pH 7.4 and contained the most chitosan, relative to other formulations that had less chitosan and more gelatin polymer. The prepared nanogels were found to be stable under standard storage conditions, but they clustered when the temperature was raised.

## 6. CONCLUSION

Using a modified emulsification-diffusion process, a fluconzole-loaded topical nanogel was successfully developed. SEM analysis revealed that the prepared nanosponges were spherical in nature, while DSC analysis revealed that there was no crystalline structure of drug present in the final nanogel formulation. Both the drug and the polymer had been integrated in the prepared nanogel, according to FTIR analysis. The physicochemical properties of the nanogel showed that it was useful for topical delivery. The formulated formulations revealed a transparent nanogel with excellent consistency, spreadability, clarity, and flow characteristics. The rheological tests specifically showed that as gelatin content increased, viscosity increased as well, and vice versa. As a result, the viscosity of nanogel formulations was observed to be equal to the volume of gelatin in the formulations.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## ACKNOWLEDGMENTS

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Selvamuthu kumar S, Anandam S, Krishnamoorthy K, Rajappan M. Nanosponges: A novel class of drug delivery system-review. Journal of Pharmacy & Pharmaceutical Sciences. 2012;15(1):103-11.
2. ud Din F, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S, Zeb A. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. International Journal of Nanomedicine. 2017;12:7291.
3. Jilsha G, Vidya Viswanad. Nanosponges: A Novel Approach of Drug Delivery System. Int J Pharm Sci Rev Res 2013; 19(2):119-123.
4. Lala R, Thorat A, Gargote C. Current trends in β- cyclodextrin based drug delivery systems. Int J Res Ayur Pharm 2011;2(5):1520-1526.
5. Dash AK, Elmquist WF. Analytical profiles of drug substances and excipients. Harry G Britain, Founding Florey Academic Press. 2001;27:70-113.
6. Martindale The Extra Pharmacopea. 31st Ed. 404.
7. Mathy FX, Ntivunwa D, Verbeeck RK, Pre'at V. Fluconazole distribution in rat dermis following intravenous and topical application: a microdialysis study. J Pharm Sci. 2005;94(4):770– 80.
8. Wildfeuer A, Faergemann J, Laufen H, Pfaff G, Zimmermann T, Seidl HP, et al. Bioavailability of fluconazole in the skin after oral medication. Mycoses. 1994; 37(3–4):127–30.
9. Faergemann J. Pharmacokinetics of fluconazole in skin and nails. J Am Acad Dermatol. 1999;40(6 Pt 2):S14–20.

10. Klimke K, Schäfer-Korting M. Effect of keratin on the efficacy of fluconazole. Mycoses. 1997;40 Suppl 1:43–6.
11. Fetih G. Fluconazole-loaded niosomal gels as a topical ocular drug delivery system for corneal fungal infections. J Drug Deliv Sci Technol 2016;35: 8-15.
12. Abdel-Mottaleb MM, Neumann D, Lamprecht A. Lipid nanocapsules for dermal application: a comparative study of lipid-based versus polymer-based nanocarriers. Eur J Pharm Biopharm 2011; 79(1): 36-42.
13. Wasilewska K, Winnicka K. Ethylcellulose–a pharmaceutical excipient with multidirectional application in drug dosage forms development. Materials. 2019; 12(20):3386.
14. VolmajerValh J, Vajnhandl S, Škodič L, Lobnik A, Turel M, Vončina B. Effects of ultrasound irradiation on the preparation of ethyl cellulose nanocapsules containing spirooxazine dye. Journal of Nanomaterials. 2017;2017.
15. El-Habashy SE, Allam AN, El-Kamel AH. Ethyl cellulose nanoparticles as a platform to decrease ulcerogenic potential of piroxicam: formulation and in vitro/in vivo evaluation. International journal of nanomedicine. 2016;11:2369.
16. Zaman M, Qureshi S, Sultana K, Hanif M, Mahmood A, Shaheryar ZA, et al. Application of quasi-emulsification and modified double emulsification techniques for formulation of tacrolimusmicrosponges. Int J Nanomedicine. 2018;13:4537–48.
17. Swaminathan S, Linda P, Loredana S, Francesco T, Pradeep V, Dino A, Michele T, Gianpaolo Z, Roberta C. Cyclodextrin-based nanosponges encapsulating camptothecin: Physicochemical characterization stability and cytotoxicity. Eur J Pharm Biopharm 2010;74(2):193-201.
18. Ng WK, Saiful Yazan L, Yap LH, Wan Nor Hafiza WA, How CW, Abdullah R. Thymoquinone-loaded nanostructured lipid carrier exhibited cytotoxicity towards breast cancer cell lines (MDA-MB-231 and MCF-7) and cervical cancer cell lines (HeLa and SiHa) Biomed Res Int. 2015;2015:1–10.
19. Swaminathan S, Pradeep V, Trotta F, Cavalli R. Nanosponges encapsulating dexamethasone for ocular delivery: formulation design, physicochemical characterization, safety and corneal permeability. J Biomed Nanotechnol , 2013;9(6): 998-1007.
20. Prasanna Reddy Battu, Reddy MS. Residual solvents determination by HS-GC with flame ionization detector in omeprazole pharmaceutical formulations. Int J PharmTech Res 2009;1(2):230-234.
21. Wu W, Aiello M, Zhou T, Berliner A, Banerjee P and Zhou S. In-situ immobilization of quantum dots in polysaccharide-based nanogels for integration of optical pH-sensing, tumor cell imaging, and drug delivery. Biomaterials. 2010;31(11):3023-3031.
22. Javed HI, Shah SN, Ayaz MM, Javed N, Iqbal FM, Wahid M, Ahmad M, Murtaza G. Formulation development and characterization of diphenhydramine nasal nanogel. AAPS Pharm Sci Tech. 2018; 75(2):491-506.
23. Osmani RA, Aloorkar NH, Ingale DJ, Kulkarni PK, Hani U, Bhosale RR, et al. Microsponges based novel drug delivery system for augmented arthritis therapy. Saudi Pharm J. 2015;23:562–72.
24. Moin A, Deb TK, Osmani RA, Bhosale RR, Hani U. Fabrication, characterization, and evaluation of microsponge delivery system for facilitated fungal therapy. J Basic Clin Pharm. 2016;7:39–48.
25. Aldawsari HM, Badr-Eldin SM, Labib GS, El-Kamel AH. Design and formulation of a topical hydrogel integrating lemongrass-loaded nanosponges with an enhanced antifungal effect: In vitro/in vivo evaluation. Int J Nanomedicine. 2015;10:893–902.
26. El-Housiny S, Shams Eldeen MA, El-Attar YA, Salem HA, Attia D, Bendas ER, et al. Fluconazole-loaded solid lipid nanoparticles topical gel for treatment of pityriasisversicolor: Formulation and clinical study. Drug Deliv. 2018;25:78–90.
27. Ansari KA, Vavia PR, Trotta F, Cavalli R. Cyclodextrin-based nanosponges for delivery of resveratrol:In vitro characterisation, stability, cytotoxicity and permeation study. AAPS PharmSciTech. 2011;12:279–86.
28. Raja CHNV, Kiran Kumar G, Kotapati Anusha. Fabrication and Evaluation of Ciprofloxacin Loaded Nanosponges for Sustained Release. International Journal of Research In Pharmaceutical And Nano Sciences 2013;2(1):1-9.
29. Ansari KA, Torne SJ, Pradeep RV, Trotta F, Cavalli R. Paclitaxel loaded

nanosponges: in-vitro characterization and cytotoxicity study on MCF7 cell line culture. Curr Drug Deliv 2011;8(2):194-202.



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