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Research article

Development and evaluation of fluconazole-loaded selenium nanoparticle gel

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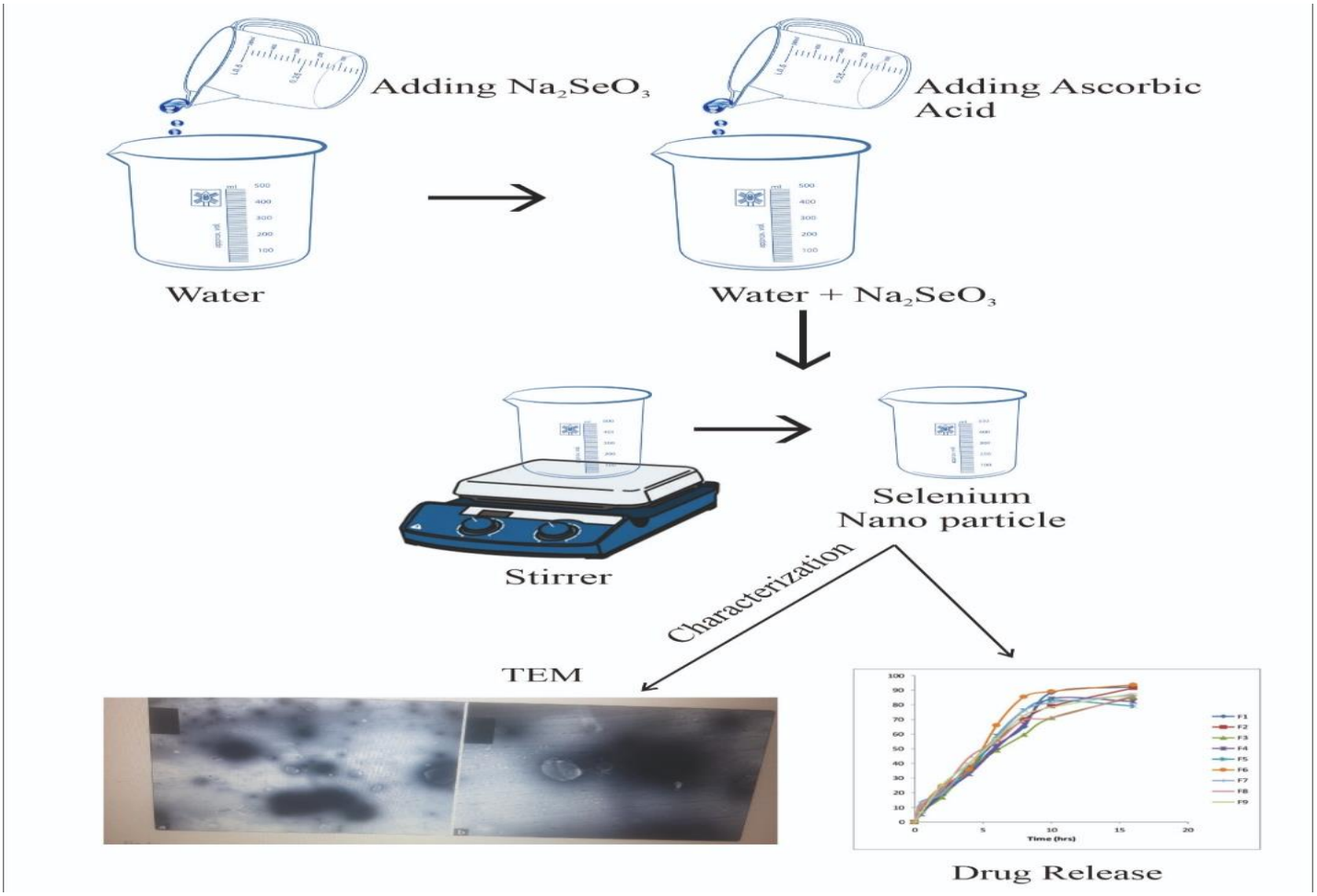
ABSTRACT

The purpose of the current research work was to formulate, optimise, and evaluate fluconazole-loaded selenium nanoparticulate gel for the cure of *Tinea corporis.*



Selenium nanoparticle gel wereeffectively prepared by chemical reduction method and optimized by 3^2factorial design (response surface methodology, design expert version 12)therewere two independent variables was evaluated on (concentration of sodium selenite and sonication time) and two dependent variables with use particle size and entrapment efficiency).The prepared formulation wasassessed in terms of particle size, in vitro drug release, encapsulation efficiency, zeta potential, viscosity and spreadability. Based on response surface methodology, F6 formulation the highest trapping efficiency with of 92.25%, in-vitro drug release of 76.08% in 8 hrs and mean particle diameter of 62.76 nm. The stability studies revealed that all the formulations were stable as none of them exhibited significant change in drug content over time. The study indicated successful development of fluconazole loaded selenium nanoparticulate gel with improved penetration, good homogeneity, enhancement of duration of action. It can thus be concluded that the developed gel could be an effective treatment for management of skin fungal infection.

Keywords: QbD, Fluconazole, Selenium nanoparticles, Drug release.

INTRODUCTION

Humanity has been plagued by various infectious diseases throughout history, and the ongoing COVID-19 invasive fungal infection is altering cancer [1]. The fungal infection is spread by function and biofilms, which are often resistant to existing treatments and, in fact, are considered to essentially contribute to the high death rates associated with invasive fungal infection [2, 3]. Fluconazole is a representative of the triazole family and one of the most often used antifungal medications [4, 5]. It was ZFDA-approved in 1990 for clinical use in the management of inflammatory diseases like Tineacorporis, peritonitis, and systemic Candida infections, including candidemia, disseminated candidiasis, pneumonia, and cryptococcal meningitis [6]. But the efficiency of fluconazole is compromised due to multidrug resistance [7].The literature review shows that novel formulations of selenium nanoparticles can effectively prohibit the growth of fungi (Candida, Aspergillus, Tinea, etc.) and are also able to counteract multidrug resistance caused by fungus strikes [8,9].Therefore, an attempt was made to formulate fluconazole-loaded selenium nanoparticles, followed by their conversion into gel bases for topical application to the affected area. The topical route of intake is the most non-invasive route of drug intake, as it delivers the medication into the body through the skin, offers the advantage of drug retention, and increases patient compliance by reducing the quantity of dose with high efficacy and safety [10, 11].

MATERIALS AND METHODS

The medication and excipients utilised in the present study, namely fluconazole, sodium selenite Polysorbates, and ascorbic acid, were purchased from Merona Scientific, Roorkee. Tween 80 and carbopol were purchased from Nice Laboratory Reagents, Kochi. All reagents were of the highest analytical grade.

Pre Formulation Study

The active pharmaceutical ingredient (API) was identified by using a UV spectrophotometer in phosphate buffer at pH 7.4 with a Shimadzu-1700 UV-Visible Spectrophotometer [12, 13], in addition to FT-IR analysis [14, 15]. The melting point was calculated by using a DSC.

The solubility and partition coefficient of the medication were measured using the shaking flask method [16].

The drug's compatibility with excipients was evaluated using FTIR analysis. The medication was completely combined with excipients in a 1:1 ratio, and all samples were stored in closed vials at 40 °C and 75% RH for 21 days before being scanned using FTIR. The spectra of pure medication and drug-excipient mixtures were matched to standards to determine any physical or chemical incompatibility [17, 18].

Methods of Preparation of Selenium Nanoparticle

SeNPs were produced using a chemical reduction technique. 30 mg of sodium selenite (Na2SeO3.5H2O) was mixed with 90 mL of water. Ascorbic acid (10 mL, 56.7 mM) was added dropwise to the sodium selenite solution while vigorously stirring. Polysorbates (10 µL) was added after each 2 mL of ascorbic acid. Ascorbic acid led to the formation of selenium nanoparticles. All solutions were prepared in a sterile cabinet with double-distilled water. The mixtures were allowed to react with each other in a concentrated state until the color changed from colorless to bright orange. Selenium nanoparticles were sonicated at different rpm. Soon after the colour change was observed, the mixture was diluted to 25 ml with distilled water [19, 20].

Preparation of Gel

The produced selenium nanoparticle was transformed into a gel by adding 1% Carbopol while stirring continuously at 1500 rpm and characterized using various parameters.

Optimization of Selenium Nanoparticles Formation of Gel by Response Surface Methodology

We developed nine formulations of fluconazole-loaded selenium nanoparticles using a 32-factorial design. Table 1 [21 , 22] shows the selection of two independent variables: sodium selenite concentration (X1) and sonication time (X2). Two dependent variables were also chosen: particle size (Y1) and entrapment efficiency (Y2) [23].

Table 1: Test Factors for Optimization of Process Parameters

Factor	Name	Units	Low Level	Middle Level	High Level
A (X_1)	Conc. of sodium selenite	mM/L	50	60	70
B (X_2)	sonication time	Min	20	30	40

Characterization of Selenium Nanoparticle

Particle size analysis by Malvern Mastersizer

Particle size of the selenium nanoparticle was evaluated by Malvern Mastersizer [24].

Surface and Shape Analysis by TEM

The form and surface properties of selenium nanoparticles were analysed using 48 Transmission Electrons (Model H-7500 Hitachi, Japan) [25].

Zeta Potential Analysis

The surface charge of selenium nanoparticles was evaluated by the Malvern zetasizer [26, 27].

Drug Entrapment Efficiency (%)

Dialysis method was used to determine the drug concentration in selenium nanoparticles. 10 ml of nanoparticle dispersion was sonicated for 1 minute and filtered. The filtrate is diluted appropriately and drug content was measured using a UV visible spectrophotometer at 259 nm wavelength [28-29].

The percentage medication trapped efficiency was determined by using the following equation.

$$Entrapment\ Efficiency = \frac{observed\ drug\ content}{Initial\ drug\ conent} \times 100$$

***In-Vitro* Drug Release Studies**

In-vitro drug release experiments were conducted using Franz diffusion cells and cellophane 18 membranes. To maintain the correct temperature, the assembly was placed on a magnetic stirrer and stirred at 100 rpm [30, 31]. The diffusion cell's receptor compartment was filled with appropriate phosphate buffer (pH 7.4). A selenium nanoparticle with 200 mg of medicine was applied to the egg membrane. To maintain sink conditions, a 1 ml aliquot of the receptor medium was removed at regular intervals and immediately replaced with an equal volume of fresh phosphate buffer (pH 7.4) [32, 33]. The substance underwent spectrophotometric analysis at λ max 259 nm for in-vitro drug release tests.

Characterization of Drug Loaded Selenium Nanoparticle Gel

Physical Appearance

The selenium nanoparticle gel was visually inspected for colour, clarity, homogeneity, and appearance [34].

pH Stability Study

2.5 g of gel was properly weighed and distributed in 25 milliliters of distilled water. The pH of the dispersion was measured using a digital pH monitor [35].

Spreadability

The spreadability of gel compositions was determined using spreadability equipment. The lowest 32 slides contained 1.0 g of gel sample, while the upper slide was placed on top. Spreadability was determined using the following formula [36].

$$S = m \times lt$$

Viscosity

The viscosity of the Selenium nanoparticle gel was measured at 25oC using a Brookfield viscometer [37].

Gel Strength

To measure gel strength, use a plunger with a pan that holds weights at one end and immerses the other end in gel. Gels were placed in a glass container and marked 1cm below the fill point. The weight required for the plunger to sink to a depth of 1 cm in the prepared gel was established for each formulation [38, 39].

Stability Studies

Stability tests were carried out on the optimised formulation, F6. The formulation was kept in an airtight container at 25±2°C/60±5% relative humidity (RH) and 40±2°C/75±5% (RH) for 90–16 days. Samples were analysed for residual drug concentrations at 15, 30, 45, 60, and 90 days [40, 41]. Each formulation had an initial drug content of 100%.

RESULTS AND DISCUSSION

Pre-formulation Studies of Drug

The substance was identified by several procedures, such as melting point, UV-51 spectroscopy, and FTIR spectroscopy. All metrics were within acceptable limits and met official Compendia standards.The drug's UV spectra showed peak absorption at 259 nm. The drug's partition coefficient was found to be 1.01, which falls below the permissible range.

The medication was found to be substantially soluble in phosphate buffer, propylene glycol, and methanol but very faintly soluble in filtered water.

Physical and chemical incompatibility studies indicate that the API is compatible with all excipients used in formulations.

Optimization of Various Parameters by Full Factorial Design

The results obtained after implementing 3^2 Full Factorial design are mentioned below.

The regression equation for cumulative Particle size obtained after calculation of main and interaction effects is represented in given equation and the corresponding 3D surface graph.

$$(Y_1=70.22-14.50A-13.17B-0.7500AB+2.17A^2+0.1667B_2^2)$$

From the equation and graph it was observed that as the concentration of sodium selenite and sonication time is increased and particle size reduced, hence both the variables negatively affect the particle size.

Y2: Entrapment Efficiency

The regression equation for entrapment efficiency obtained after calculation of main and interaction effects is represented in given equation and the corresponding 3D surface response graph is shown in figure 2.

$$(Y2= 80.00 +10.67A-0.3333\ B-2.25AB\ -1\ A^2-6\ B^2_2)$$

From the equation and 3D surface graph it was observed that as the concentration of sodium selenite was increases, entrapment efficiency is accordingly increased. Howeversonicationaffects the entrapment efficiency.

Figure 1: 3D surface plot showing the effect of independent variable on particle size

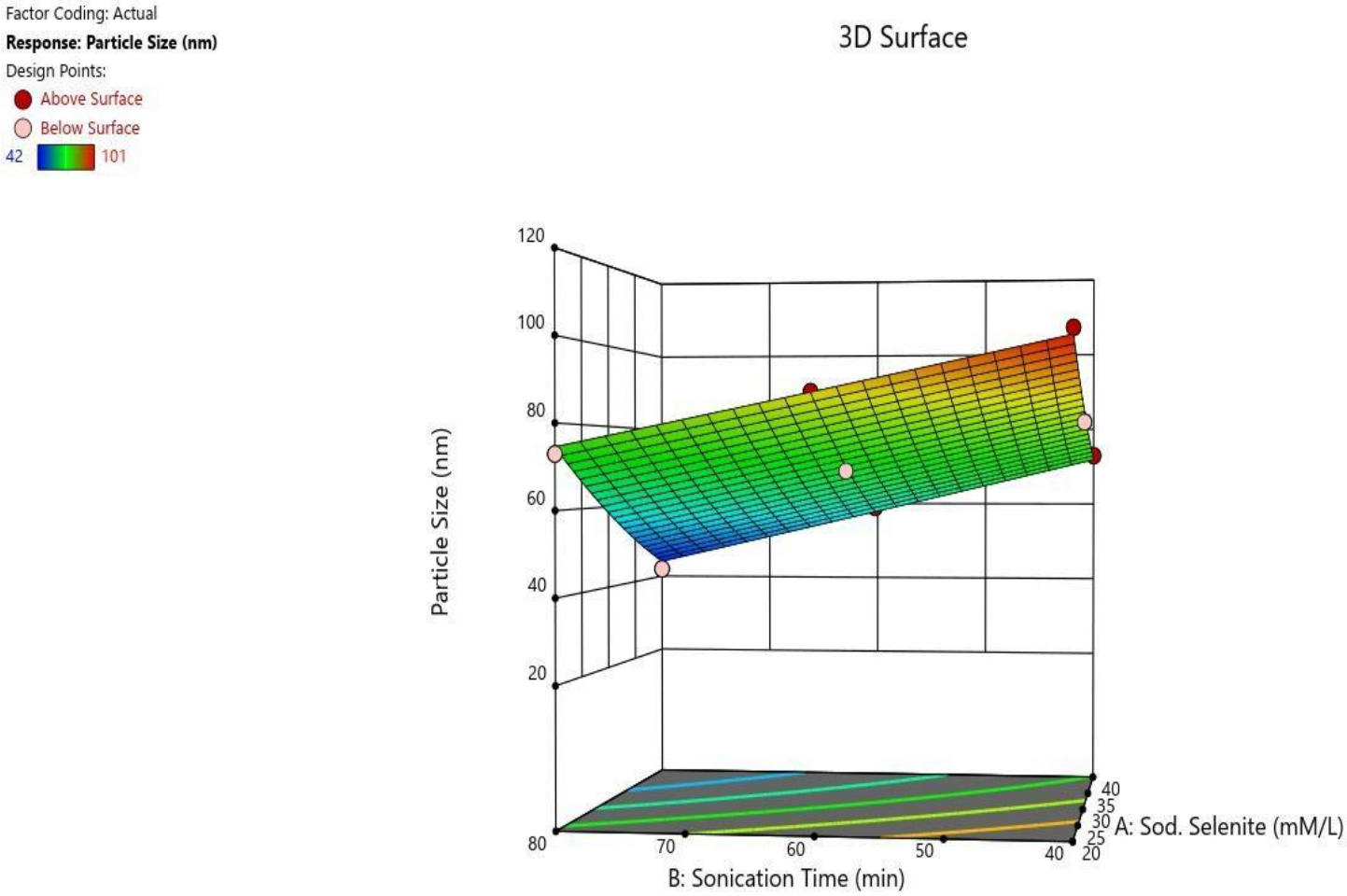
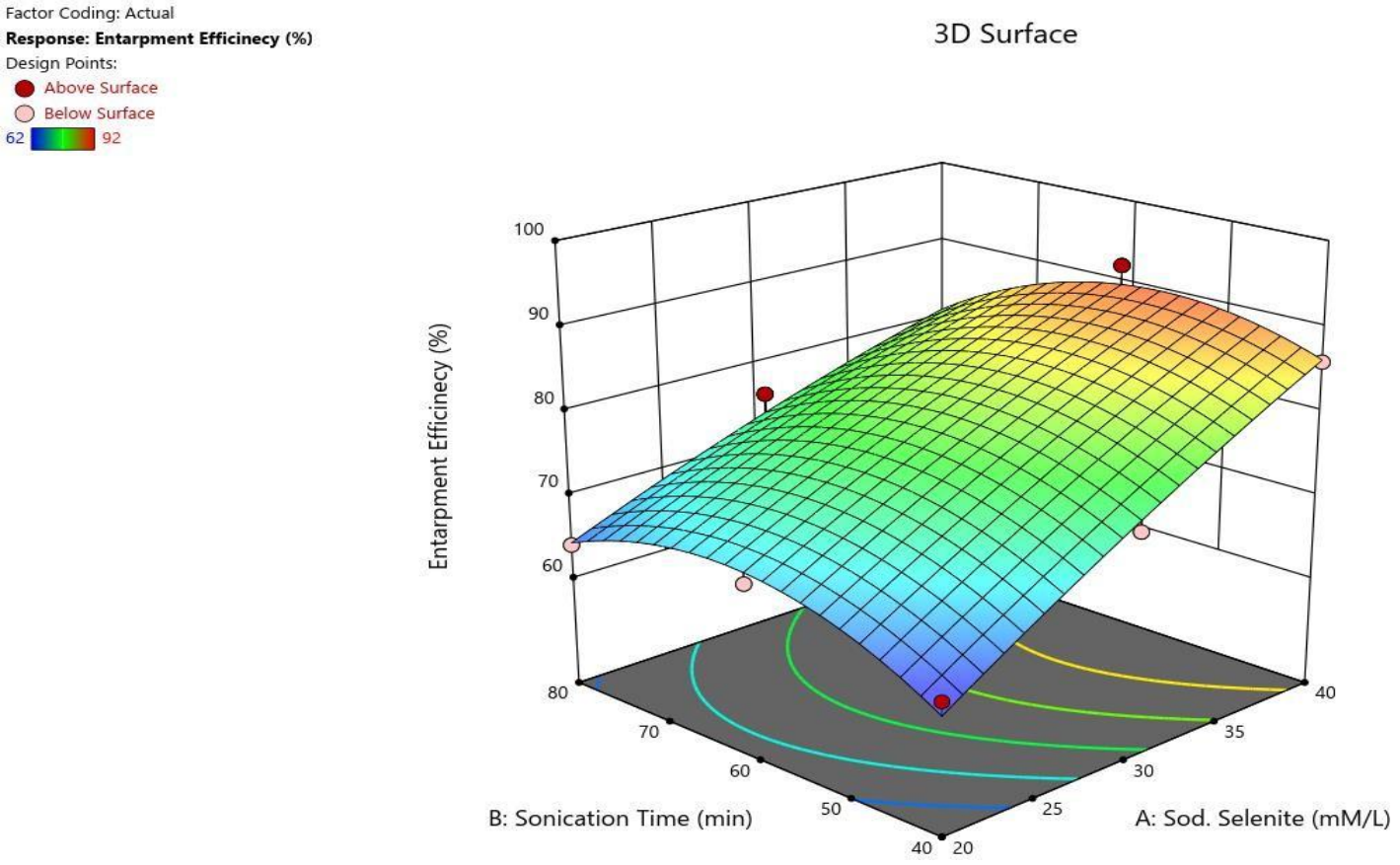


Figure 2: 3D surface plot showing the effect of independent variables on entrapment efficiency



Characterization of Selenium Nanoparticle

Particle size analysis by Malvern Mastersizer

Particle size analysis was performed by Malvern Mastersizer and average size of particles were found to be 62.76nm as shown in Figure 3.

Surface analysis and shape by TEM

Surface morphology of the selenium nanoparticle was examined by TEM. Selenium nanoparticle were observed spherical, smooth, even sized, a small no of irregular selenium nanoparticle had also been observed in pic as shown in Figure 4.

Zeta Potential analysis

Zeta potential analysis was performed by Malvern Zetasizer, and average Zeta potential was reported as -0.628 (mV) as shown in Figure 5.

Figure 3: Particle size distribution

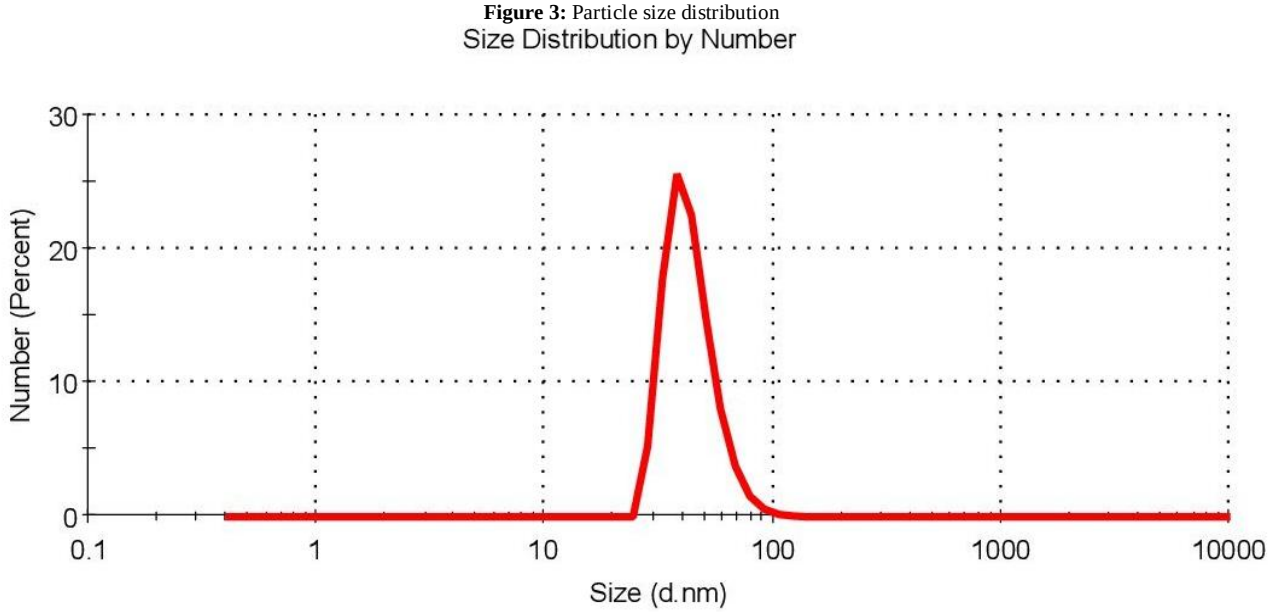


Figure 4: TEM of fluconazole-loaded selenium nanoparticle

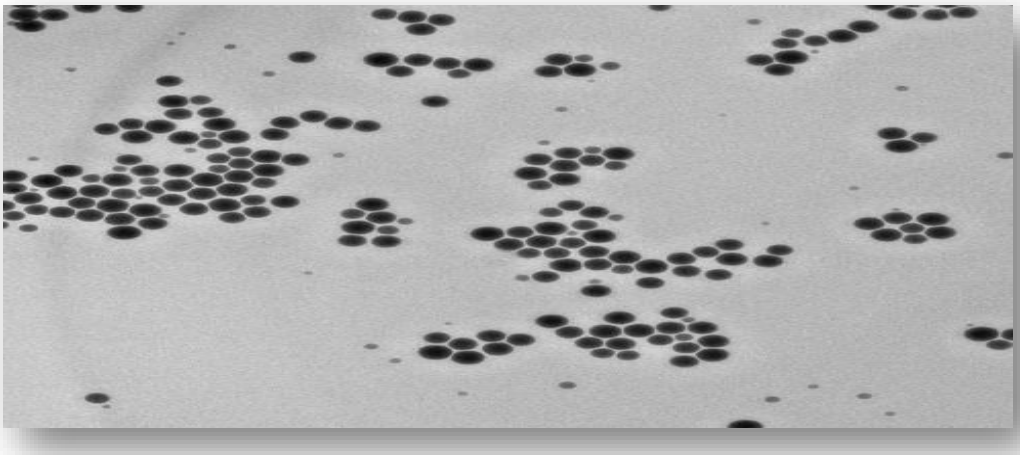


Figure 5: Zeta Potential Analysis

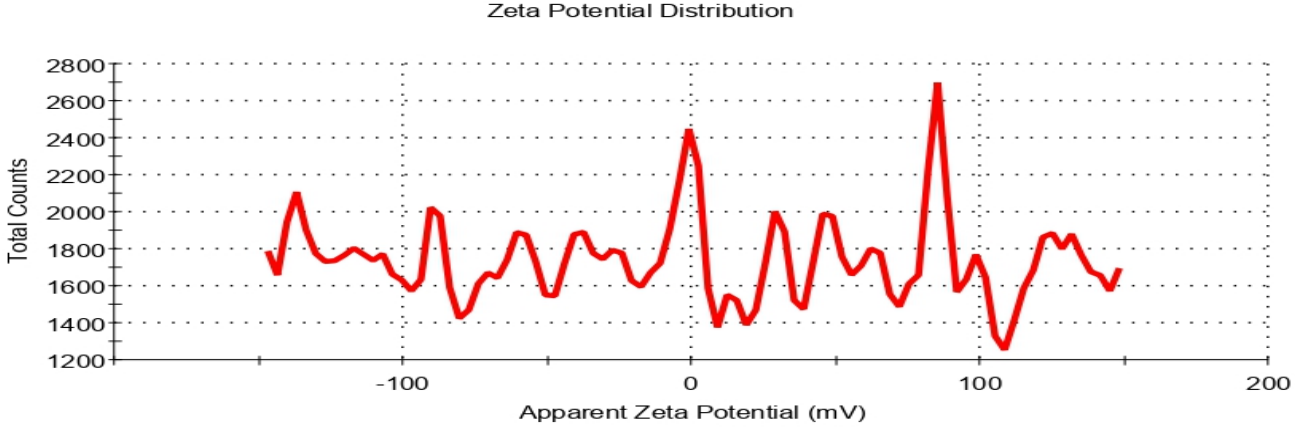
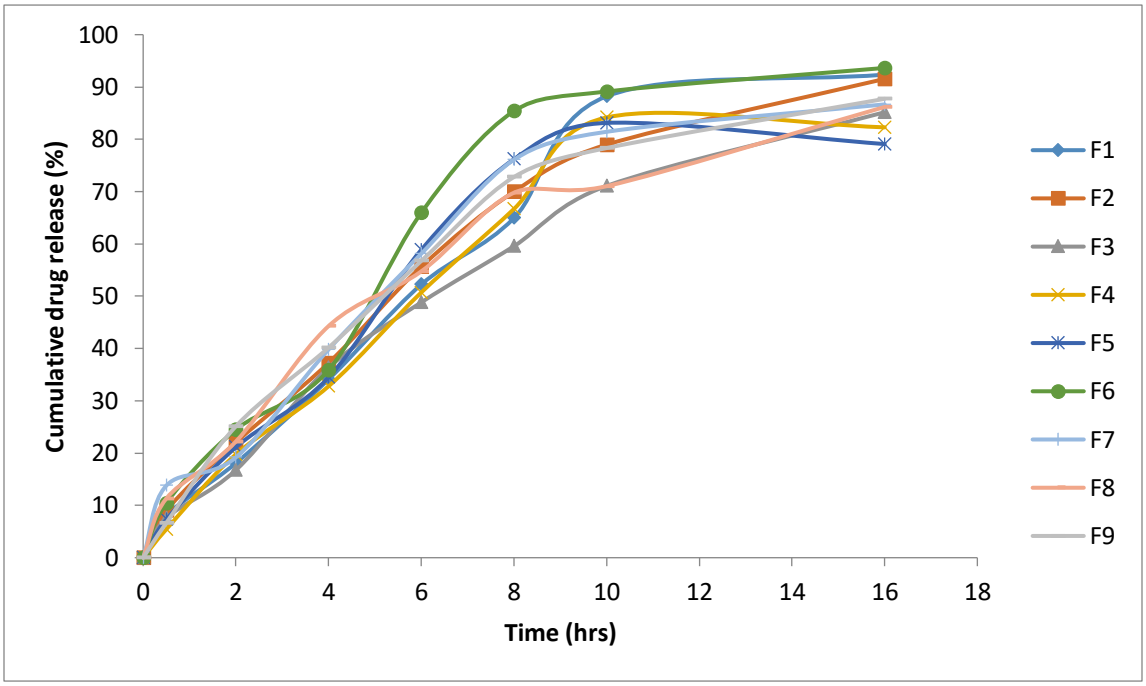


Figure 6: *In Vitro* drug release profile of selenium nanoparticle



Entrapment Efficiency

Entrapment efficiency of nine formulations (F1-F9) is summarized in Table 2.

Table 2: Entrapment efficiency of selenium Nanoparticle

Batch Code	Entrapment Efficiency (%) ± S.D.
F1	67.23 ± 0.59
F2	69.03± 1.12
F3	71.15± 0.89
F4	74.18± 1.19
F5	87.39± 1.34
F6	92.25± 0.17
F7	84.73± 1.15
F8	80.72± 1.90
F9	74.43± 0.43

In-vitro drug release

Drug dissolution study of nine formulations (F1-F9) is summarized in Figure 6.

Characterization of drug loaded selenium nanoparticle gel

Appearance

The developed selenium nanoparticle gel was observed as white translucent with a homogeneous and soft texture.

pH Measurement

The pH of the fluconazole-loaded Selenium nanoparticle gel was observed within acceptable ranges, indicating compatibility for skin application.

Spreadability study of gel

The spreadability of drug loaded selenium nanoparticle gel was found to be 18.75 gm cm/sec±0.1 which is in an acceptable range.

Viscosity

The viscosity of selenium nanoparticle gel was found to be 22.01 Pa, 22.10 Pa, and 6.95 Pa.

Stability studies

The stability investigations at 25±2 °C/60±5% RH (room temperature) showed good stability of all formulations, with no notable changes in drug content. At 40±2 °C/75±5% (RH), drug degradation was rapid. Thus, the optimal temperature is ambient temperature

CONCLUSION

The study demonstrated the successful preparation of fluconazole-loaded selenium nanoparticle gels with better penetration, high homogeneity, and an increased duration of action. The prepared selenium nanoparticle gel formulations were examined for particle size, entrapment effectiveness, in-vitro drug release, and zeta potential. According to the results of the response surface methodology, the F6 formulation is the best formulation in terms of entrapment efficiency and in-vitro drug release rate. The findings of the stability studies show that the formulation was stable at room temperature with minimal drug loss. Thus, the proposed gel may be an effective treatment for skin fungal infections. Furthermore, the nanoparticle-loaded gel was evaluated for homogeneity, pH, spreadability, and viscosity.

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