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Original Research Article

Formulation and in-vitro permeation kinetic studies of β-cyclodextrin complexed ketoconazole drug capped silver nanoparticles

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ABSTRACT

Background: Invasive fungal infections are a growing global crisis due to environmental shifts and growing vulnerable populations. Pathogenic fungi that infect humans are developing resistance against all approved systemic antifungal drugs. Topical drug delivery systems provide a non-invasive way to distribute therapeutic substances directly to the site of action. Ketoconazole (KZ) is a BCS Class II broad-spectrum drug that is used to treat and prevent fungal infections in which Trichophyton rubrum is the main causative agent.

Materials and Methods: The present study utilizes an in-vitro model in which KZ is complexed with β-CD and then capped with AgNPs to formulate a cream and evaluated for the underlying mechanisms and amount of improved passive penetration. The formulated cream is characterized for physiochemical evaluation, Fourier transform infrared spectroscopy (FTIR), kinetic studies indicating the effective stability and encapsulation of the composite.

Results: The prepared sample was evaluated in terms of its appearance, drug content, spreadability, and viscosity. Drug diffusion through the dialysis membrane, and the findings showed the β-CD-KZ-AgNPs formulation had a significantly higher permeability than KZ alone and followed first-order kinetics with an anomalous release pattern. The higher solubility and stability of β-CD and nano-sized AgNPs resulted in improved penetration. This study investigates that β-CD-capped AgNPs can significantly enhance KZ passive penetration and diffusion, providing a potentially useful nanocarrier technology for antifungal treatment.

Conclusion: Enhancing the passive permeation and diffusion characteristics of KZ on β-Cyclodextrin (β-CD)-capped silver nanoparticles (AgNPs) presents a viable approach for enhancing drug delivery efficiency.

1. Introduction

Superficial fungal infections are common; while they are rarely fatal, they can spread to other regions of the skin and become widespread. Furthermore, they have the potential to spread to others and cause other bacterial skin infections, lowering an individual's quality of life. Skin mycoses are caused by three types of fungal agents: dermatophytosis, yeast infections, and mold infections.[1] The only drugs approved to treat these disorders are azoles, echinocandins, and polyenes. Some drugs have led to the development of fungal resistance. Extensive large-scale research is being undertaken on innovative targeting techniques and formulations that have lately gained prominence in efforts to combat drug resistance.[2] Tinea rubrum is an anthropophilic fungus that causes approximately 60% of all dermatophytosis, including Tinea

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corporis, Tinea pedis, Tinea unguium, Tinea inguinalis, and deep dermal infections.[3] To improve pharmacological drugs bioavailability and therapeutic efficacy, effective drug delivery systems must be developed.

The Ketoconazole, a broad-spectrum antifungal drug, is commonly used to treat various fungal infections. However, in addition to its large molecular weight (531.41 Da), low water solubility (0.04 mg/mL), high oral dose (200 mg/day), negative effects on oral administration, and short elimination half-life (3.3 h), its therapeutic efficacy is accompanied by these drawbacks.[4,5] To solve these challenges, nanotechnology-based delivery systems have drawn a lot of attention because of their ability to improve medication solubility, stability, and targeted delivery.

The Cyclodextrin (β-CD) is a cyclic oligosaccharide that has the capacity to create inclusion complexes with different hydrophobic molecules, improving their solubility and stability.[6] Cyclodextrins have long been utilized to improve the water solubility of KZ since they are excellent drug carriers. To improve nasal absorption and fluorescence, β-CD was combined with KZ in a 1:2 molar ratio using freeze-drying, solvent evaporation, and ultrasonic techniques. By complexing ketoconazole with β-CD and citric acid, β-cyclodextrin, and HP-β-CD[7–9] the aqueous solubility was raised from 0.017 mg/mL to 2.58 mg/mL.[10–14]

The AgNps is an excellent capping agent for β-CD formulations, improving nanoparticle dispersion and stability. AgNPs are acknowledged for their distinct physicochemical characteristics, such as their high surface area to volume ratio and ability to interact with biological membranes, both of which can enhance drug penetration and transport,[15] Based on current research, AgNPs and β-CD can combine to form a nanocomposite that enhances the effectiveness and distribution of several drugs, such as antifungal agents.[16]

This study aims to explore the underlying mechanisms and degree of enhanced passive permeation and diffusion of ketoconazole (KZ) when incorporated into an inclusion complex with β-cyclodextrin (β-CD) capped silver nanoparticles (AgNPs), synthesized in our prior research (Bhargavi K et al., 2024).

Our aim is to illustrate how this nanocomposite formulation enhances KZ's passive permeation and bioavailability by thorough characterisation and in vitro diffusion tests. Understanding these mechanisms will not only enhance the therapeutic efficacy of KZ but also contribute to the broader field of nanotechnology-based drug delivery systems

2. Materials and Methods

2.1. Materials

Ketoconazole (KZ) (99.9% purity) and β-Cyclodextrin (β-CD) were purchased from M/s Yarrow Chem, Mumbai. Silver nitrate and other solvents were procured from Himedia Laboratories, Mumbai, India. Dialysis semipermeable membrane (531.43) from Sigma Aldrich, Bangalore. All the other chemicals are of analytical grade.

2.2. Method

2.2.1. Determination of lmax and construction of UV calibration curves

The drug solution (ketoconazole) was prepared in phosphate buffer at a pH of 7.4 at a concentration of 10 mcg/ml. A double beam UV spectrophotometer was used to scan these solutions at wavelengths between 200 and 400 nm, using the phosphate buffer as a blank. The values of the absorption maxima (λmax) were found using the absorbance v/s wavelength plots. To make a stock solution with a concentration of 1 mg/ml, 100 ml of phosphate buffer with a pH of 7.4 was added with an accurately weighed quantity of drug equivalent to 100 mg. A secondary standard solution with a drug concentration of 100 mcg/ml was made by diluting 5 ml of this stock solution to 50 ml. Working standard solutions with concentrations within the beer range were produced by serially diluting this secondary standard solution with phosphate buffer. At 293 nm,[17] the absorbance of the solution was measured using phosphate buffer as a blank.

2.2.2. Construction of standard curves by spectrophotometric method

The concentrations of 10, 20, 30, 40, and 50 μg/ml were created for the KZ standard solutions. The absorbance of these solutions was measured in a Shimadzu UV-1900 UV spectrophotometer (Japan) at a wavelength of 293 nm using phosphate buffer as a blank. The drug's absorbance vs. concentration graph was drawn, and the data were subjected to a linear regression analysis[18] using Microsoft Excel®.

2.3. Preparation of cream[19]

2.3.1. Preparation of oil phase

A specific amount of white paraffin and cetostearyl alcohol are weighed and melted in a porcelain dish. After that, liquid paraffin is added to the mixture and melted. The temperature is carefully maintained between 65 and 70°C throughout the process to ensure that the oil phase is consistent and of high quality.

2.4. Preparation of Aqueous phase

The water was heated in a porcelain dish and maintained at a temperature of 65-70°C. Accurately weighed quantities of propylene glycol and Tween-80 were then added to the measured Distilled water and the mixture was heated at 65-70°C until a uniform consistency was achieved.

2.5. Development of Cream formulation

The oil phase (A) was meticulously added drop by drop to the aqueous phase (B) with moderate agitation, ensuring both mediums were at the same temperature. The mixture was stirred until the temperature reached 40°C, and then the cream was allowed to cool to room temperature, resulting in a thick cream base. The preparation process as tabulated below.

2.5.1. Formulation of the cream with KZ and β-CD-KZ-AgNps inclusion complex

The KZ and β-CD-KZ-AgNps inclusion complex were infused in the cream base to prepare an antifungal cream

Cream Preparation with Amorphous KZ: 2% of amorphous KZ was weighed and added to the 10 gm of the prepared cream base and kneaded the mixture using a mortar and pestle until a uniform mixture is obtained and stored in a cool, dry place until use.

Cream Preparation with β-CD-KZ-AgNps: 2% of the β-CD-KZ-AgNps mixture in a 1:1 ratio to a 10-gm cream base. Once a homogenous cream is created, use a mortar and pestle to knead the β-CD-KZ-AgNps mixture with the cream base. Store the mixture in a cold, dry area until needed.

2.5.2. Preparation of formulated cream – Biophysical evaluation

To enhance the absorption and therapeutic efficacy of the antifungal drug Ketoconazole (KZ), it was encapsulated within β-Cyclodextrin (β-CD) capped with silver nanoparticles (AgNp), forming β-CD KZ-AgNp inclusion complexes. These complexes were synthesized and subsequently analyzed for their biophysical, morphological, and in vitro functional properties (Bhargavi K et al., 2024).

3. Physical and Chemical Evaluation of the Formulated Cream [20,21]

1. *pH:* A Shimadzu pH meter was used to measure the pH of the KZ and formulated cream. The weight of 1 gram of prepared sample was put into a 100 ml beaker containing 50 ml of phosphate buffer (pH 7.4) and measured.
2. *Viscosity Study:* The viscosity of the prepared cream was measured at 37°C using a Brookfield DV-E viscometer. After dipping the spindles S-96 into a cream-filled beaker, the viscosity was measured at various rpm per minute.
3. *Spreadability:* In order to assess the Spreadability of KZ cream and formulated cream, two standard-sized glass slides were chosen. One slide had the sample cream on it, thus the other slide was positioned on top of it so the cream was sandwiched between the two slides. The slides were pressed against one other in order to eliminate the air and remove the adhesive cream. A 50 g weight was gently placed to the upper slide. The time it took for the upper slide to fully separate from the lower slide was noted. The longer it takes to separate two slides, the better the Spreadability. It is calculated using the following formula:

$$S = M \times L / T$$

Where, M = wt. tied to upper slide L = length of glass slides T = time taken to separate the slides.

4. Fourier Transform Infrared Spectroscopy (FTIR) [20,22,23]

FTIR analysis of pure KZ, AgNps, β-CD- and the inclusion complexed formulated cream was performed using a Bruker Alpha II FTIR Spectrophotometer. The scanning range was set between 400 and 4000 cm^{-1}. Samples weighing 50 mg were taken and placed in a holder and scanned.

4.1. Drug content analysis

The amount of drug included in the formulated drug was ascertained by the drug content study. In a 100 ml beaker, 1 gram of the prepared cream was dissolved in 50 ml of methanol. A membrane filter with a 0.2-micron opening was used to filter the resultant mixture. The Formulated Drug in the methanolic extracts was analyzed using a UV-visible spectrophotometer (UV-1900, Shimadzu) at a wavelength of 293 nm, with methanol as a blank. [20]

4.2. Calibration of modified Franz diffusion cell and selection of elution fluid

The Electrolab modified Franz diffusion cell was used, with an area of 1 cm^2 for the dialysis membrane and a receptor compartment capacity of 17 ml made of borosilicate glass. With the aid of a teflon-coated magnetic bead, the receptor compartment was stirred and a water jacket was placed around it. Warm water was run through the jacket in order to keep the assembly as a whole at 37±1°C. The phosphate buffer with a pH of 7.4 was utilized as the elution fluid for the diffusion tests. A 1 mg/ml drug solution in phosphate buffer was added to the receptor compartment and left there for 24 hours in order to conduct the recovery tests. After that, 5 ml of the drug solution were taken out, appropriately diluted with the elution fluid, and subjected to spectrophotometric analysis to ascertain the drug recovery. [24,25]

4.3. Permeability of the drug through dialysis semipermeable membrane

The Electrolab's modified Franz diffusion cell was used to conduct permeability studies of the drug across the dialysis

Table 1:

Oily Phase(A) Ingredients	Quantity (%)	Activity	Ingredients	Aqueous Phase(B) Quantity (%)	Activity
White Paraffin	10	Cream base (Emollient that moisturises the skin)	Propylene glycol	20	Penetration Enhancer
Liquid Paraffin	10	Moisturizer	Tween 80	2	Emulsifier
Cetosteryl alcohol	20	Emulsifying agent	Distilled Water	38	Diluent

Table 2: Physiochemical Evaluation of KZ and β-CD-KZ-AgNp cream

Sl.No	Formulations	Appearance	pH	Consistency	Odour	Viscosity (cps)	Spreadability
1	Standard Drug Ketoconazole cream	Whitish	5.73	Creamy (Semisolid)	Odorless	8210	26.2±0.5
2	Formulated drug -β-CD-KZ-AgNp cream	Dark Grey	5.64	Creamy	Odorless	8479	24.9±0.5

Table 3: Invitro drug release data for KZ and β-CD-KZ-AgNp formulated cream

Time (hr)	Log Time	Square root of time(h)	Cumulative% drug release KZ	Cumulative% drug release β-CDKZAgNp formulation	Log Cumulative% drug release KZ	Log Cumulative% drug release β-CD-KZ-AgNp formulation
0	0	0	0	0	0	0
1	0	1	1.266	26.632	0.102373	1.42537
2	0.30103	1.414214	2.532	33.076	0.403403	1.51951
4	0.60206	2	5.063	38.09	0.704433	1.58081
6	0.778151	2.44949	7.595	45.438	0.880524	1.65742
8	0.90309	2.828427	10.127	55.17	1.005463	1.7417
10	1	3.162278	12.658	67.483	1.102373	1.8292
12	1.079181	3.464102	15.19	74.19	1.181554	1.87035
24	1.380211	4.898979	30.38	83.36347	1.482584	1.92098

Table 4: Regression analysis data of KZ and β-CD-KZ-AgNps cream formulation

Equations	Zero Order kinetics		First Order Kinetics		Higuchis Plot		Koshmeyers Plot	Peppas
Data	Y	R2	Y	R2	Y	R2	Y	R2
KZ	2.1497x	0.8735	0.1585x	0.9859	1.3813x	0.9298	0.3136x	0.8666
β-CD-KZ-AgNps	9.4008x	0.9928	0.1633x+.6885	0.5781	7.9616x	0.9807	0.1878x	0.9907

membrane. The donor compartment was filled with a saturated drug solution as well as a portion of the suspended excess drug. The barrier was mounted between the donor and the receptor compartments. The receptor cell contained phosphate buffer of pH 7.4 as the medium. The medium was magnetically stirred for uniform drug distribution and was maintained at 37±1°C. The samples withdrawn every hour upto 24 h and estimated spectrophotometrically to determine the amount of drug diffused.

4.4. Kinetic modelling for diffusion of KZ cream and prepared Inclusion complexed cream

The kinetics of drug diffusion over the dialysis membrane were investigated by processing the permeation data with zero and first order equations. The numbers 1 and 2, respectively, represent the equations for zero order and first order.

$Q_t = Q_0 + K_0t$ ——————- (1)

$\text{Log } Q_t = \log Q_0 + K_1t/2.303$ ————(2)

where,

Q_t - amount of drug dissolved in time t.

Q_o - amount of drug at time zero.

K_o – zero order release constant.

K_1 - first order release constant

The data was further analysed using Higuchi diffusion model (equation 18) and Korsmeyer–Peppas model (equation 19) to characterize mechanism of drug transport from the systems across dialysis membrane[26]

$Q = K_H t^{1/2}$ ——————- (3)

Q-amount of drug released at time t.

K-rate constant

$M_t / M \infty = K_{KP}\ t^{n}$ ——————- (4)

$M_t / M \infty$- fraction of drug release at time t

K_{KP}- release constant

n - Diffusion exponent

5. Results and Discussions

5.1. Preparation of formulated cream – Biophysical evaluation

To enhance the absorption and therapeutic efficacy of the antifungal drug Ketoconazole (KZ), it was encapsulated within β-Cyclodextrin (β-CD) capped with silver nanoparticles (AgNp), forming β-CD KZ-AgNp inclusion complexes. These complexes were synthesized and subsequently analyzed for their biophysical, morphological, and in vitro functional properties (Bhargavi K et al., 2024).[27]

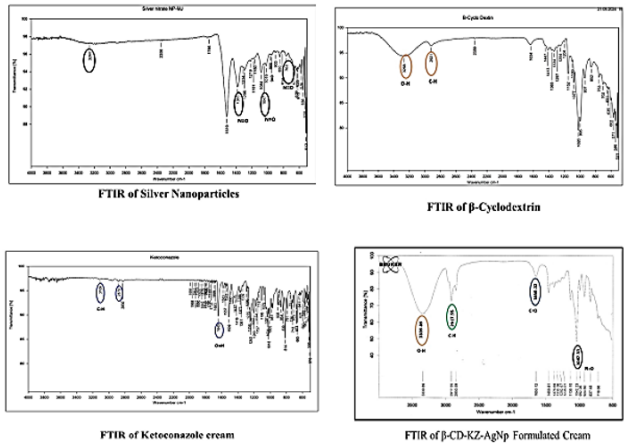

Figure 1: FTIR of **(A)** Silver Nanoparticles (AgNps) **(B)** β-cyclodextrin **(C)** Ketoconazole **(D)** β-CD-KZ-AgNp cream.

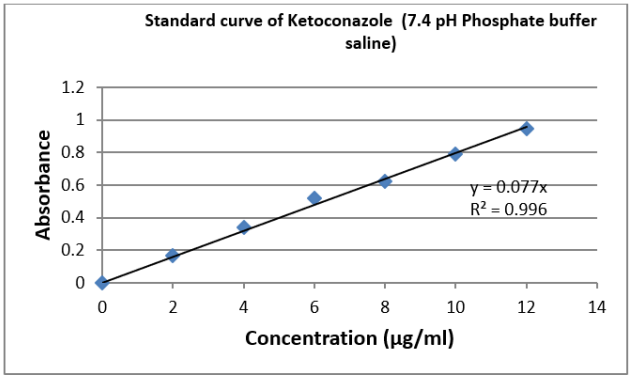

Figure 2: Thestandard curve of Ketoconazole Drug at pH 7.4 buffer.

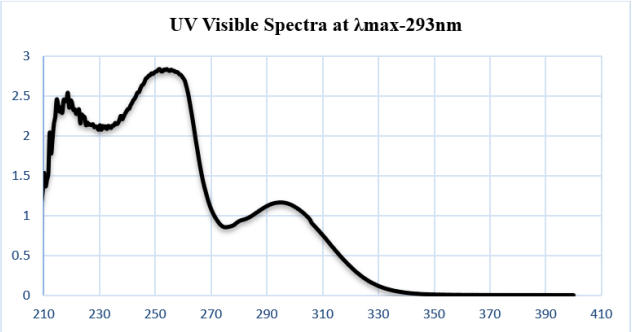

Figure 3: TheUV Visible spectra of KZ peak at 293 nm

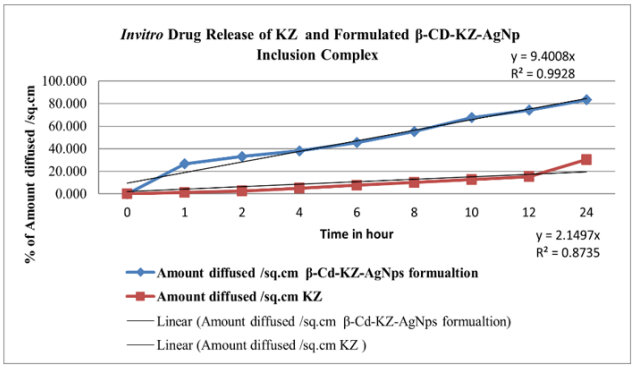

Figure 4: The percentage ofamount diffused/sq cm v/s Time in hour Drug release profile of KZ and β-CD-KZ -AgNp cream over 24 hours; with study carried out at37ºC

5.2. Preparation of formulated cream- Physical examination

The prepared creams were visually evaluated for appearance, odour, and consistency to determine whether they were appropriate for topical use. The physical appearance of the creams revealed that the β-CD-KZ-AgNP cream was dark grey in color, reflecting the addition of AgNPs, while the normal ketoconazole (KZ) cream was whitish in color. Both formulations had the ideal qualities for topical formulations: they were odourless and had a creamy, semi-solid consistency. The pH of prepared creams was tested using a pH meter with standard buffer solutions at pH 7.4. The pH meter electrode was placed into the solution holding the sample.

Viscosity-The Viscosity of KZ and β-CD-KZ-AgNp formulated cream was measured and recorded. The measured viscosity of formulated cream showed that the viscosity was appropriate and effective for topical drug

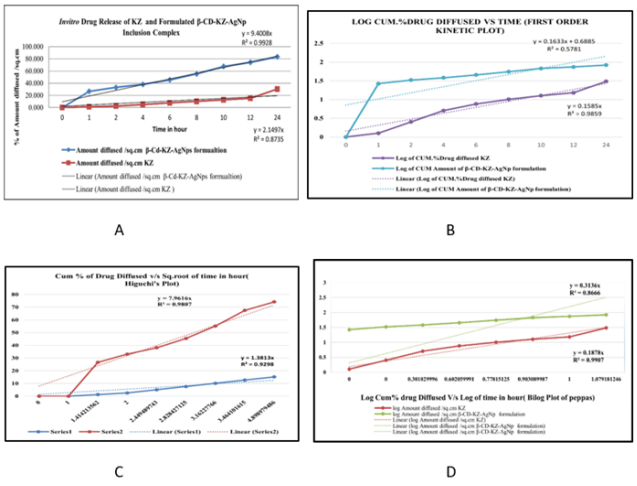

Figure 5: (A) Cumulativepercentage of drug release v/s Time in hour, Zero order drug release kinetics. **(B)** Log of cumulative percentage v/sTime in hour, First order drug release kinetics. **(C)** Cumulative percentage of Drug diffused v/s Square root of Timein hour, Higuchi model drug release kinetics. **(D)** Log of cumulative percentage drug diffused v/s Log of Time inhour, Korsemeyer peppas model drug release kinetics.

delivery.[26]

Spreadability-The spread ability of the drug was not markedly affected by the incorporation of nanoparticles. The spreadability values were very close to the commercially available product that was found to have 24.9±0.5mm indicating good consistency for topical application and the results for all the above are tabulated in Table 3.

FTIR-The Inclusion complex of KZ and β-CD-KZ-AgNps formulated cream was confirmed by FTIR spectra. The Figure 1 -A, B, C, D illustrates the FTIR bands for β-cyclodextrin, KZ, and AgNps and β-CD/KZ/AgNps inclusion complexed cream. The presence of KZ in the inclusion complex is confirmed by its appearance at C=O stretching at 1645, C-H aliphatic stretching at 2879, and C-H aromatic stretching at 3109. The presence of β-CD is confirmed by its appearance at O-H stretching at 3268 and C-H aliphatic stretching at 2921. The presence of β-CD-KZ coated AgNps is confirmed by its appearance at O-H stretching at 3340, C-H aliphatic stretching at 2918, and C=O stretching at 1650, confirming the formation of the β-CD-KZ-AgNp inclusion complex cream.[28,29]

5.3. Drug content

The drug content of the Formulated drug was found to be 99.33%; hence, drug content was found satisfactory.

5.4. UV-Vis Spectroscopic analysis for λmax Determination

UV-visible spectroscopy was the initial step in determining the incorporation of KZ into the inclusion complex. The UV spectra of β-CD-KZ-AgNp (at 1:1) are shown in Figure 2. Literature suggests that pure KZ typically exhibits a UV peak at 293 nm while the spectra for β-CD did not show any discernible peaks. The appearance of the UV peak at 293 nm[7,8] in the spectra of the inclusion complex, independent of concentration, demonstrates that KZ was successfully incorporated into the complex. The peaks were observed to be optimum at 1:1 ratio of inclusion complex. The initial UV-visible spectroscopy validation lays the foundation into the properties and behaviours of the inclusion complex, providing critical information about their composition.

5.5. Construction of standard graph of KZ by UV spectrophotometric method:

The UV Spectrophotometric analysis of KZ showed λmax at 293 nm. The other excipients showed no interference at 293 nm. A calibration curve was constructed. A linear relationship was observed between absorbance and the KZ concentration in phosphate buffer (pH 7.4) in a 0–12ug/mL concentration range as shown in Figure 3. The regression equation is: y= 0.077x; and the value was 0.996.

5.6. In- vitro diffusion studies

5.6.1. The In vitro drug release of KZ andβ-CD-KZ-AgNp through Dialysis Semi permeable membrane in Franz Diffusion Cell.

The Diffusion studies of KZ and formulated β-Cd-KZ-AgNp were studied using a Dialysis Semipermeable membrane using a Franz diffusion cell. The release for KZ in 24 hours is –49.83% and β-Cd-KZ-AgNp diffused 84% in 24 hours. This data shows the formulated β-Cd-KZ-AgNp is better permeable than KZ alone. Hence it can enhance the therapeutic activity against Fungal Infection effectively, the results are shown in Figure 4.

5.7. Drug-release kinetic studies

The diffusion of drugs through the dialysis semipermeable membrane was displayed using Zero-degree kinetics, first order kinetics, Higuchis, and Korsemeyer peppas equations are displayed in Figure 5 A,6B,6C,6D. The diffusion followed first order kinetics, indicating that the release is rapid and concentration-independent. The peppas plot shows that Plain KZ has a y value of 0.3136x and a R value of 0.8666. Similarly, the formulation sample had a y-value of 0.1878x and an R-value of 0.9907. In both cases, the release pattern follows the anomalous transport indicative of the system characterized by the diffusive regime, while the occurrence of the release is representative of first-order

kinetics, in which diffusion serves as the primary release mechanism. The Higuchi plot shows y value 1.3813x and R^2- 0.9298 for KZ and y -7.96 and R^2 -0.9807 for β-CD-KZ complex, indicating that nanoparticles coated to the complex do not cause swelling and are not controlled by swelling mechanism in Tables 3 and 4.[30]

6. Conclusion

The study demonstrates that incorporating Ketoconazole (KZ) into β-Cyclodextrin (β-CD) capped with silver nanoparticles (AgNPs) significantly enhances the drug's solubility, stability, and penetration, making it a more effective antifungal treatment. The formulated β-CD-KZ-AgNP cream showed improved passive permeation and diffusion characteristics compared to KZ alone, as evidenced by the higher permeability and drug release profile. Characterization through FTIR and other analytical methods confirmed the successful encapsulation and stability of the composite. The in vitro diffusion studies indicated that the β-CD-KZ-AgNP formulation followed first-order kinetics with an anomalous release pattern, suggesting a more efficient and rapid release mechanism. This nanocomposite approach provides a promising non-invasive topical delivery system that could potentially address the challenges associated with traditional antifungal treatments and contribute to combating antifungal resistance.

7. Source of Funding

None.

8. Conflicts of Interest

The authors declare no conflict of interest.

9. Acknowledgement

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