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DEVELOPMENT AND EVALUATION OF NIOSOMES FORMULATIONS OF KETOCONAZOLE

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ABSTRACT

The poorly water-soluble medication ketoconazole may be successfully incorporated into niosomes with high entrapment efficiency use of thin-film hydration process. The extended-release of the medication from the niosome raises the possibility that it will reduce side effects and frequency of administration. The drug's reduced size and vesicular form, which also boosted its penetration through the stratum corneum, improved the drug's localization in the stratum spinosum, where the infected macrophages are located, and its absorption by the infected macrophages.

KEYWORDS: Ketoconazole, Niosomes, Extended-release.

INTRODUCTION

One of the most promising drug delivery systems is the niosome, which has a bilayer structure and is produced by the self-association of cholesterol and nonionic surfactants in an aqueous phase. Niosomes are biocompatible, biodegradable, and non-immunogenic. They enable for controlled and continuous medication delivery at the desired region and have a long shelf life and are highly stable.[1,2]

In targeted drug delivery systems, drug molecules are specifically targeted at the expected site of action without affecting nearby tissues. The controlled drug delivery method known as niosomes enables a treatment to be delivered over a longer period and in the right pattern. Niosomes are lamellar bilayer-containing nonionic surfactant vesicles.[3,4] When nonionic surfactants are added, niosomes grow tiny multilamellar and unilamellar structures (Diethyl ether and cholesterol, followed by hydration in an aqueous medium). Niosomes are 10-1000 nm in diameter.[5]

Niosomes function as drug storage in the body, releasing pharmaceuticals through their bilayer in a controlled way that permits long-term drug release. Targeted drug delivery is made feasible by niosomes. The area of the body where the drug needs to have a therapeutic effect is where it is administered. As a result, a lower dosage is required to get the desired outcome.[6]

Ketoconazole is an antifungal medication used to treat both systemic and superficial mycoses. Its topical formulation is favorable for its action since it is easily absorbed but incompletely after oral administration[7]. Mild burning at the application site, irritation, redness, and other adverse effects are frequent with ketoconazole medication.

The goal of this study was to create a ketoconazole niosomal gel to create and refine Ketoconazole niosomes by adjusting medication quantities.

Preparation of formulations

The formulations were prepared by altering the concentration of cationic surfactants (Span 20, Span 40, and Span 60)while maintaining a constant level of cholesterol. The effectiveness of trapping was assessed for the synthesized niosomes.[9]

Evaluation parameters for niosomal gel

The formed gel was examined for clarity, colour, homogeneity, and the presence of foreign particles.

pH

A exact weight of 2.5 grammes of gel was used to measure out 25 millilitres of distilled water. The dispersion's pH was measured using a digital pH metre.[10]

Viscosity measurement

The viscosity was measured using a Brookfield-programmed DV III ultra-viscometer. In this experiment, a spindle with the number CP 52 and an ideal speed of 0.01 rpm was used to test the viscosity of the preparation.[11]

Content uniformity

A carefully weighed amount of gel containing 10 mg of the medication was dissolved in a volumetric flask with a suitable amount of 50% n-propanol for vesicle lysis to estimate the gel's drug concentration. The volume was increased using methanol to 100 mL. Filtering the substance included using Whatman filter paper No. 41. In order to achieve the needed volume, methanol was added after 5 mL of the aforementioned solution was added to a 50 mL volumetric flask. The amount of ketoconazole was determined using a blank at 225 nm and a Shimadzu UV/visible spectrophotometer.[12,14]

Estimation of entrapment efficiency

In order to separate niosomes from unentrapped medication, 0.5 g of the gel containing 10 mg of ketoconazole diluted to 10 ml with distilled water was centrifuged at 15,000 rpm for 60 minutes at 4°C. Using a UV- Visible Spectrophotometer at 225 nm, the free drug concentration in the supernatant was determined after the proper dilution. The percentage of drug entrapment in niosomes was calculated using the formula below.% drug entrapment = (Total drug- Drug in supernatant liquid) X 100 Total drug.[15,16]

In vitro drug diffusion study

An in vitro drug diffusion study using a dialysis membrane. An open-ended glass tube with one end connected to the dialysis membrane was filled with a 10 mg niosomal gel. The contribution area was here. The open-ended tube was then placed in the receptor compartment, which was a beaker with 100 mL of phosphate-buffered saline pH 7.4. A magnetic stirrer was used to agitate the receptor medium at 100 rpm while maintaining it at 372°C. 5 ml of the samples were removed after a predetermined amount of time, and they were promptly replaced with an equal volume of fresh PBS pH 7.4 buffer. The sink scenario persisted over the duration of the trial. The materials were measured spectrophotometrically at 225 nm using a UV-visible spectrophotometer.[17-21]

Stability study

The modified niosomal formulations were tested at various temperatures in order to study the impact of temperature on physical properties, entrapment effectiveness, and drug content. Two millilitre samples were obtained every 15 days and at the end of 45 days while the niosomal dispersions were kept in sealed containers for 30 days at 2- 8°C and room temperature (302°C). The samples were spectrophotometrically analysed at a maximum of 225 nm after the vesicles were disrupted with 50% n-propanol.[22]

RESULTS AND DISCUSSION

The gel that has developed has an off-white hue. It has a mildly sticky character. The formulas' entrapment effectiveness is listed follows this order: SPAN 40 > SPAN 60 > SPAN 20. A topical gel delivery method was further developed from the improved Niosomal dispersion. The formed niosomal gel was distinguished by its rheological behavior, pH, and outward appearance. The gel compositions' pH was discovered to be between 6.7 and 6.9 on average.

Table 1: Evaluation parameters of different Niosomal gel formulations.

S. No.	Code	pH	Viscosity (cps)	% Drug content (%w/w)	% Entrapment efficiency (% w/w)
1.	KTZ-S-S 20-3	6.57	8321	98.12	41.4
2.	KTZ-S- 40-4	6.71	8254	96.9	51.0
3.	KTZ-S- 60-5	6.72	8674	94.1	56.0

The formulations' entrapment effectiveness was found to range between 41.4 and 72.1 percent. The formulations KTZ 20-3, KTZ 40-4, and KTZ 60-5 were found to have entrapment efficiencies of 56 percent, 72.1 percent, and 60.3%, respectively. The Span 40 formulation showed the highest entrapment efficiency, while Span 60 niosomes followed in a comparable range. This can be because Span 40 has a greater HLB value than Span 60. The HLB value declined and the entrapment effectiveness fell as

From 6.7 of Span 40 to 4.7 of Span 60, 15.15 Span 20's entrapment effectiveness was found to be lower than that of the other two formulations, although having an HLB value of 8.6. The different phase transition temperatures might be to blame for this. 36,132. The non-ionic surfactants that improved trapping efficiency are listed in the following order: Span 40 > Span 60 > Span 20 For the in-vitro release study of ketoconazole niosomes, a dialysis membrane was employed in an open-ended tube-beaker assembly with phosphate-buffered saline (PBS) pH 7.4 and 10% methanol as the diffusion medium. The cumulative percent drug release at 24 hours increased initially with KTZ 20-1, KTZ 20-2, and KTZ 20-3 at 65.77 percent, 69.43 percent, and 82.21 percent, respectively. Thereafter, the release gradually decreased for the next higher surfactant ratios at KTZ 20-4 and KTZ 20-5 at 73.99 percent and 64.14 percent, respectively. For the Span 40 series, the cumulative percent drug release at 24 hours is 72.97 percent for KTZ 40-1, compared to 74.72 percent, 72.58 percent, 82.69 percent, and 7.96 percent for the formulations KTZ 40-2,

KTZ 40-3, KTZ 40-4, and KTZ 40-5. At 24 hours, it was found that the cumulative percent drug release of Span 60 niosomes increased in the following order: 57.45 percent, 63.25 percent, and 76.68 percent for KTZ 60-1, 60-2, and 60-3, respectively. Following that, for KTZ 60-4 and KTZ 60-5, respectively, the cumulative percent drug release steadily dropped to 63.96 and 58.47 percent.

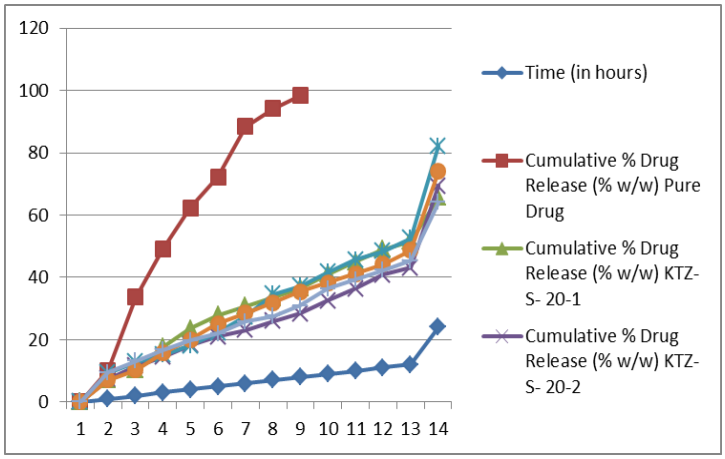

Figure 1: *In-vitro* release profile of niosomes formulations containing Span 40.

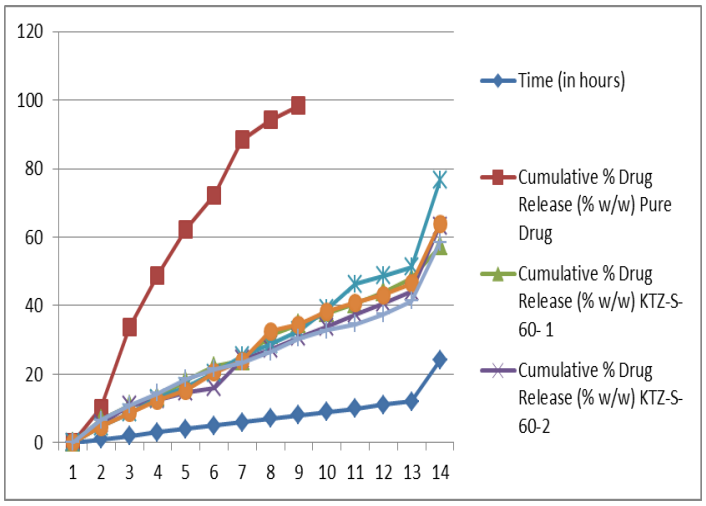

Figure 2: *In-vitro* release profile of niosomes formulations containing Span 60.

Due to Carbopol 940's hydrophilic nature and bio-adhesive capabilities, which may result in an enhanced residence duration of the medication at the site of absorption by interacting with the mucosa, ketoconazole niosomal gel formulations with the optimal ratio of the surfactants were created. The gel formulations' looks, pH, viscosity, drug content, and in-vitro drug diffusion research were all assessed. Ketoconazole gel formulations (KTZ 20-3,) were subjected to stability experiments by being stored at 4°C to 8°C (refrigeration temperature) and 25°C 2°C for 45 days, respectively, following ICH (International Conference on Harmonization) standards.

Table 2: Ketoconazole Niosomal Gel KTZ-S-20-3 Stability Study at Different Temperatures.

Time of storage indays	Temperature of storage			
	Drug Usage (%) 4°C - 8°C (Temperature of a refrigerator)	Entrapment efficiency (%) 4°C - 8°C (Temperature of a refrigerator)	Drug Usage (%) 25°C ±2°C (Temperature of a refrigerator)	Entrapment efficiency (%) 25°C ±2°C (Temperature of a refrigerator)
0	98.11	52.3	98.11	52.3
15	98.02	50.0	94.92	47.4
30	97.83	49.5	92.7	46.2
45	97.5	49.2	91.6	45.5

It was determined how well the medicine was trapped in the niosomal gel right after it was produced and then45 days, every 15 days. The least amount of medication vesicle voccurred at 4°C. This might be explained by the surfactant and lipid phase change that occurs during storage at higher temperatures and causes vesicle leaking.As a result, the niosomes can be kept around 4–8 °C. After being included in the gel basis, niosome stability was enhanced, which may be attributable to the absence of niosome fusion. Niosomal gel may have established as kin's reservoir effect, which improves the medication capacity for retention in the body, which may account for the higher drug skin retention in this case. The stability analyses revealed that 4–8°C was the ideal storage range for the niosomal gel formulations.

CONCLUSION

Study concludes that poorly water-soluble medication ketoconazole may be successfully incorporated into niosomes with high entrapment efficiency use of thin-film hydration process.

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