Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)

A J P R D

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FORMULATION AND EVALUATION OF KETOCONAZOLE NIOSOMAL GEL

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ABSTRACT

In recent years, treatment of infectious disease through Novel Drug delivery system (NDDS) has undergone a revolutionary shift. Niosomes are a Novel Drug Delivery system which has potential application to treat infectious disease topically. Niosomes are non-ionic surfactant vesicles, in which medication is encapsulated in a vesicle for controlled drug release. Ketoconazole niosomes were prepared by using Cholesterol, Span 60/ Span 40 as surfactants, chloroform, and diethyl ether using rotary vacuum evaporator method. Formulation was then evaluated for particle size, drug content, entrapment efficiency, and in-vitro drug release studies. The Entrapment efficiency and drug content were calculated at 225nm using UV spectrophotometer. The drug content was found to be 70.37% for Span 40 and 72.81% for Span 60.The percentage of drug entrapment in niosomes was 60.3 % for Span 40 and 62.21 % for Span 60. FT-IR studies for niosomes containing Span 40 shows -CH stretching (Aliphatic) at 2891 cm^{-1}and2925 cm^{-1} for niosomes containing Span 60. Ketoconazole niosomal gel was prepared using Carbopol 940, glycerol, Triethanolamine and distilled water. Evaluation of niosomal gel was determined by Physical appearance, pH, viscosity, drug content, entrapment efficiency and *In-vitro* permeation studies.The percentage of the drug release from the niosomal gel was found to be 40.78 % for Span 40 and 33.75% for Span 60 . This delivery system is cost effective and simple to prepare as only the prepared gel of niosomes was introduced in Rotary vacuum evaporator for solvent evaporation.

KEYWORDS: Niosomes, NDDS, Ketoconazole, Cholesterol, Span 60/ Span 40

Article Info: Received: 01 Sep 2018; **Review Completed**: 26 Oct 2018; **Accepted:**28 Oct 2018; **Available online:** 31 Oct 2018

Cite this article as:

Kaur Paninder*, Dua J.S, Prasad D.N., Formulation and Evaluation of Ketoconazole Niosomal Gel, Asian Journal of Pharmaceutical research and Development.**2018;6 (5): 71-75**
DOI: http://dx.doi.org/10.22270/ajprd.v6i5.424

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INTRODUCTION

From last few decades, Novel Drug Delivery system have attracted a considerable attention due to their targeted drug delivery and controlled release of drug.[1] Niosomes are such example of novel drug delivery system in which drug is encapsulated in a vesicle to enhance the bioavailability of drug.[2] Niosomes are made of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and Cholesterol with subsequent hydration in aqueous media. Niosomes are lamellar structures that are microscopic in size.[3] Niosomes are one of the promising drug carriers that have a bilayer structure. Niosomes attracts much attention because of its advantages in many aspects, such as chemical stability, high purity, content uniformity, low cost, convenient storage of non-ionic surfactants, and large numbers of surfactants available for the design of niosomes.[4] Niosomes increase the stability of entrapped drug, therapeutic performance of the drug molecules and protecting drug from biological environment and restricting effects to target cells.[5] Permeability, chemical and physical approaches are the major barrier for a novel drug delivery system. A number of antifungal agents are available in different topical preparations (e.g., creams, ointments, and powders for the purpose of local dermatological therapy). Antifungal drugs are lipophilic compounds, which are practically insoluble in water and having low permeability to stratum corneum. Useful tool for the therapy of skin and soft tissue infections is application of antifungal agent topically. Ketoconazole an antifungal drug, is a substituted Imidazole derivative having broad spectrum activity. Ketoconazole have several disadvantages mild burning at the application site, several allergic reactions, blisters, irritation, pain or redness. Niosomes have been recognized as good vehicles for

the topical delivery of drugs. The encapsulation of drug in a vesicle can reduce the side effects of the drug and enhance the bioavailability of the drug. Surfactants s.a span 60, span 40 acts as the penetration enhancer by removing the mucus layer.[6]

The aim of this study is to prepare and evaluate a Ketoconazole niosomal gel. Niosomes are chemically stable, biodegradable, biocompatible systems. Niosomes can incorporate a large amount of active drug in a small vesicles for the target drug release.

Material and method

Ketoconazole was obtained as a gift sample from Titanes pharma, Cholesterol, Sorbitan Monopalmitate, Sorbitan Monostearate were obtained from Central drug house Pvt. Ltd., New Delhi. Carbopol 940 was obtained from Qualikems Fine Chem. Pvt. Ltd., Barodra. Chloroform was obtained from Thermo Fischer Scientific India Pvt. Ltd., Mumbai. Methanol was obtained from Merck Specialities Ltd.

Formulation of Ketoconazole Niosomes

Niosomes were prepared using Reverse phase evaporation technique. Drug, non- ionic surfactant (Span 40, 60) and cholesterol were weighed accurately and dissolved in sufficient amount of solvent mixture (Chloroform: Methanol 2:1) to give a clear solution. The mixture formed was then poured in to 1000ml of rotary flask and evaporated under vacuum (20- 25mm Hg) at 60°±2°C with the rotation speed of 100 rpm to form a uniform thin dry film. Further, the rotary flask was removed and allowed to return the temperature to room temperature. The thin film formed was hydrated using 20ml of distilled water while rotating the flask under 50rpm and temperature 60°±2°C. The niosomal suspension was then formed completely and allowed to stored in refrigerator in a tightly closed container.[7]

Table: 1 Formulation Code of Niosomes containing surfactant SPAN 40

Formulation Code	Non- Ionic Surfactant	Drug: Surfactant: Cholesterol (m moles)
KTZ40-1	SPAN 40	1:1:1
KTZ40-2	SPAN 40	1:2:1
KTZ40-3	SPAN 40	1:3:1

Table: 2 Formulation Code of Niosomes containing surfactant SPAN 60

Formulation Code	Non-Ionic Surfactant	Drug: Surfactant: Cholesterol (m moles)
KTZ40-1	SPAN 60	1:1:1
KTZ40-2	SPAN 60	1:2:1
KTZ40-3	SPAN 60	1:3:1

EVALUATION OF KETOCONAZOLE NIOSOMES

Particle size analysis

The average particle size of the niosomes was characterize using Malvern's zeta sizer. The niosomal suspension was diluted, filled in a cuvette using suitable blank.[8]

Scanning electron microscopy

Scanning electron microscope was used to determine the sizes of the vesicles.[9]

Drug content analysis

Drug content in the niosomal suspension equivalent to 100mg was determined by lysing the niosomes using n-propanol. 1ml of the lysed niosomal solution was then diluted upto 10ml using 7.4 phosphate buffer. The absorbance of the dilution was then calculated spectrophotometrically at 225nm.[10]

Entrapment efficiency

The free drug concentration in the supernatant was determined at 225 nm using UV- Visible Spectrophotometer after centrifuging 1 ml of the suspension diluted to 10 ml with distilled water at 15,000 rpm for 60 minutes at 4°C using a high speed cooling centrifuge so as to separate niosomes from unentrapped drug. The % drug entrapment was calculated from the following formula.[11]

$$\% \text{ drug entrapment} = \frac{(\text{Total drug} - \text{Drug in supernatant liquid}) \times 100}{\text{Total drug}}$$

FORMULATION OF KETOCONAZOLE NIOSOMAL GEL

Niosomal suspension (10ml) containing ketoconazole equivalent to 2% w/w was incorporated into the gel base composed of Carbopol 940 (1.5%), Glycerol (10%), Triethanolamine (q.s.) and distilled water up to 15ml.[9]

EVALUATION OF KETOCONAZOLE NIOSOMAL GEL[(9)]

Physical Appearance

Clarity, color, homogeneity and the presence of foreign particles in the niosomal gel was determined.

pH

pH of the niosomal gel was determined using digital pH meter.

Viscosity

Brookfield viscometer was used to determine the viscosity of the niosomal gel.

Drug content uniformity

Drug content of the niosomal gel was calculated by dissolving 10mg of the drug in 100 ml of volumetric flask and suitable volume with 50% n-propanol was formed for lysis of the niosomes. The volume was made up to 100ml using methanol. The solution was then filtered and absorbance was measured under UV spectrophotometer at 225 nm.

Entrapment Efficiency[11]

The free drug concentration in the supernatant was determined at 225 nm using UV- Visible Spectrophotometer by centrifuging 0.5 g of the gel equivalent to 10mg of ketoconazole diluted to 10 ml with distilled water at 15,000 rpm for 60 minutes at 4°C using a high speed cooling centrifuge so as to separate the niosomes from the unentrapped drug. The % drug entrapped was calculated from the formula:

$$\% \text{ drug entrapment} = \frac{(\text{Total drug} - \text{Drug in supernatant liquid}) \times 100}{\text{Total drug}}$$

In-vitro drug diffusion studies:

In-vitro diffusion studies of the niosomal gel were carried out using dialysis membrane. The drug release from the niosomal gel was determined from the collected samples. The analysis of the collected samples was done under UV spectrophotometer at 225 nm.[12]

Stability studies

Stability studies of the different formulations were carried out under different temperature conditions so as to check the effect on: physical appearance, entrapment efficiency and drug content. The niosomal formulations were stored at 2- 8°C and at room temperature (30±2°C) in air tight containers for 30 days and 2 ml samples were withdrawn every 15 days and at the end of 45 days. The analysis of the samples was then done spectrophotometrically at 225 nm after lyses of the niosomes and further preparing their suitable dilutions.[(13)]

RESULTS AND DISCUSSIONS

Particle size analysis

The average particle size of KTZ 40-3 formulation was found to be 272.3 nm.

The average particle size of KTZ 60-3 formulation was found to be 226.3 nm.

Drug content and Entrapment Efficiency

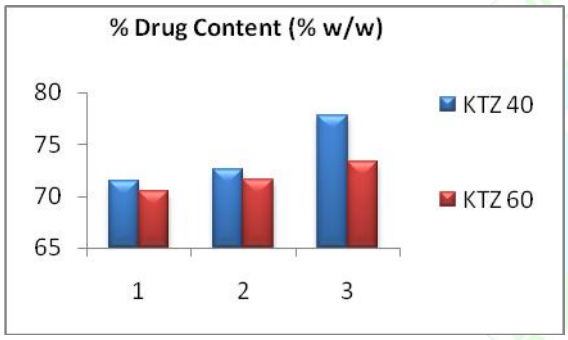

Figure: 1 Drug Content of Ketoconazole Niosomes containing Span-40 and Span-60.

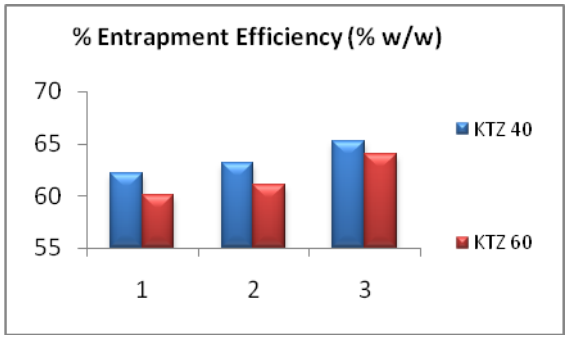

Figure: 2 Entrapment Efficiency of Ketoconazole Niosomes containing Span-40 and Span-60.

Evaluation of Ketoconazole niosomal gel

Physical appearance:

The formed gel is off-white in color. The gel was observed to be bit sticky in nature.

pH:

The pH of the gel formulations were found to be in the range of 6.7 to 6.9.

Table: 3 pH of the different Niosomal gel formulations

S.no	Formulation code	pH
1.	KTZ 40-3	6.72
2.	KTZ 60-3	6.74

Viscosity:

Table: 4 Viscosity of the gel formation

S.no	Formulation code	Viscosity (cP)
1.	KTZ 40-3	8256
2.	KTZ 60-3	8675

Drug content analysis:

The percentage drug content of the formulations were mentioned in the table as follows;

Table: 5 % Drug content of the different gel formulations.

S.no	Formulation code	% Drug content (%w/w)
1.	KTZ 40-3	72.37
2.	KTZ 60-3	70.81

Entrapment Efficiency:

The entrapment efficiency of the different gel formulations are as follows;

Table: 6 Entrapment Efficiency of the different gel formulations

S.no	Formulation code	% Entrapment efficiency (%w/w)
1.	KTZ 40-3	62.3
2.	KTZ 60-3	60.21

In-vitro Drug permeation studies :

Table: 7 *In-vitro* permeation of ketoconazole niosomal gel.

Time (Hr.)	Cumulative % Drug release		
	Plain Gel Ketoconazole	KTZ 40-3	KTZ 60-3
0	0	0	0
1	5.96	2.28	2.47
2	8.9	5.90	5.6
3	15.97	10.1	9.09
4	19.73	13.28	11.06
5	22.84	17.70	15.67
6	25.86	20.90	17.56
7	28.78	23.45	20.42
8	34.79	30.06	25.43
9	40.84	35.76	30.7
10	45.72	40.78	33.75

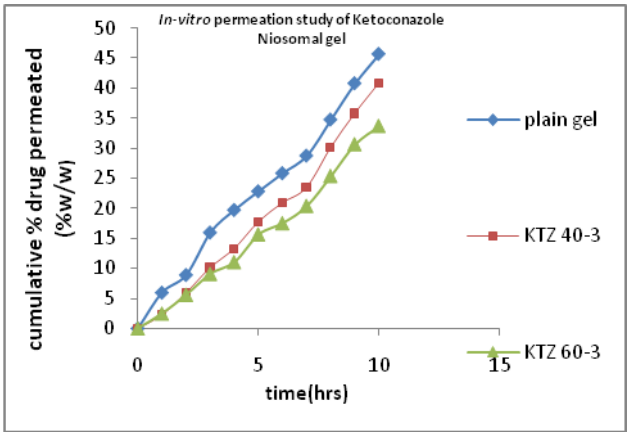

Figure: 3 *In-vitro* permeation study of ketoconazole Niosomal gel.

Stability Studies

Table: 8 Stability study of ketoconazole niosomal gel formulation KTZ 40-3 atdifferent temperature.

Time of storage in days	Temperature of storage			
	Drug Content (%) 4°C - 8°C (Refrigeration tem.)	Entrapment Efficiency (%) 4°C - 8°C (Refrigeration tem.)	Drug Content (%) 25°C ±2°C (room tem.)	Entrapment Efficiency (%)25°C ±2°C (room tem.)
0	54.30	35.2	54.30	35.2
15	54.28	34.7	54.27	34.3
30	53.27	34.2	52.26	33.1
45	53.25	33.1	51.25	32.0
60	53.24	33.1	51.24	31.9

Table: 9 Stability study of ketoconazole niosomal gel formulation KTZ 60-3 at different temperature.

Time of storage in days	Temperature of storage			
	Drug Content (%) 4°C - 8°C (Refrigeration tem.)	Entrapment Efficiency (%) 4°C - 8°C (Refrigeration tem.)	Drug Content (%) 25°C ±2°C (Room tem.)	Entrapment Efficiency (%) 25°C ±2°C (Room tem.)
0	56.10	33.8	56.10	33.8
15	55.01	33.5	55.02	33.7
30	55.03	33.2	54.04	33.6
45	54.01	33.1	54.01	33.0
60	54.00	33.0	54.00	31.8

CONCLUSION

It is concluded that Reverse phase evaporation technique is a useful method for the successful incorporation of poorly water soluble drug Ketoconazole into niosomes with high entrapment efficiency. The prolonged release of the drug from the niosome suggests that the frequency of administration and adverse effects significantly thereby improving the patient compliance. The administration of drug as gel type formulation enhances its penetration. Both of the batches that is Span 40 and Span 60 were successfully formulated as niosomal gel but Span 40 batch shows an excellent result in the release of drug shown in *in vitro* permeation studies graph.

ACKNOWLEDGMENT

I would like to express my special thanks of my teacher as well as our principal. Last but not the least, I would like to thank my parents and my friends.

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