CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.6583475

Available online at: http://www.iajps.com *Research Article*

DEVELOPMENT AND CHARACTERIZATION OF NOVEL CARRIER FOR DRUG DELIVERY OF ANTIFUNGAL DRUG

Neetesh Jain*, Dr. Akhilesh Kumar Singhai, Ms. Steffi Thomas
School of Pharmacy, LNCT University, Bhopal (M.P.)

Article Received: April 2022 **Accepted:** April 2022 **Published:** May 2022

Abstract:
Fungal infections are the most common diseases found in tropical countries like India, but these infections are neglected and hence spread to other parts of the body. The most commonly used antifungal agents are Miconazole, these molecules being imidazole derivatives with high lipophilicity. It act against most pathogenic fungi and some Gram- positive bacteria. Usually, they are well tolerated and their low toxicity allows them to be safely used for treating several cutaneous or systemic infections. Encouraging results have been obtained on the treatment of topical fungal infections with liposomal or novel vesicular formulations of these antifungal drugs, but due to their size and rigid lipid bilayer they were not able to penetrate efficiently across the skin layer. The transfersome preparations containing Miconazole are conceptually sophisticated; they are characterized by simplicity in their preparation, good stability, safety and efficacy that can highly expand their application in the treatment of fungal infections.

Keywords: *Fungal infection, Miconazole, Transfersome ,Drug delivery system, Antifungal drugs.*

Corresponding author:
Neetesh Jain,
School of Pharmacy, LNCT University, Bhopal (M.P.)
jainofneetesh@gmail.com

QR code

Please cite this article in press Neetesh Jain et al, ***Development And Characterization Of Novel Carrier For Drug Delivery Of Antifungal Drug.,*** *Indo Am. J. P. Sci, 2022; 09(5).*

INTRODUCTION:

The term Transferosome and the underlying concept were introduced in 1991 by Gregor Cevc. In broadest sense, a Transferosome is a highly adaptable and stress responsive, complex aggregate. Its preferred form is an ultra-deformable vesicle possessing an aqueous core surrounded by the complex lipid bilayer. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and selfoptimising. This enables the Transferosome to cross various transport barriers efficiently, and then act as a Drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents Delivery via the transdermal route is an interesting option in this respect because a transdermal route is convenient and safe. This offers several potential advantages over conventional routes [1] like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter-and intra-patient variations, and most importantly, it provides patients convenience. To date many chemical and physical approaches have been applied to increase the efficacy of the material transfer across the intact skin, by use of the penetration enhancers, enhancers, iontophoresis, sonophoresis and the use of colloidal carriers such as lipid vesicles (liposomes and proliposomes) and nonionic surfactant vesicles (niosomes and proniosomes)[2-5].

Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility. Transferosomes can deform and pass-through narrow constriction (from 5 to 10) times less than their own diameter) without measurable loss. This high deformability gives better penetration of intact vesicles. They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anaesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes. They have high entrapment efficiency, in case of lipophilic drug near to 90%. They protect the encapsulated drug from metabolic degradation. They act as depot, releasing their contents slowly and gradually. They can be used for both systemic as well as topical delivery of drug. Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives [6-8]

Around the world fungal infections have recently emerged as a growing threat to human health, especially in persons whose immune systems are compromised in some way. For example, fungi are associated with complex disease entities in complex medical patients (e.g., cryptococcosis in AIDS patients or aspergillosis in bone marrow or organ transplant patients). Fungi usually make their homes in moist areas of the body where skin surfaces meet between the toes, in the genital area, and under the breasts. Many fungi that infect the skin (dermatophytes) live only in the topmost layer of the epidermis (stratum corneum) and do not penetrate deeper. Obese people are more likely to get these infections because they have excessive skin folds. People with diabetes tend to be more susceptible to fungal infections as well. Strangely, fungal infections on one part of the body can cause rashes on other parts of the body that are not infected. For example, a fungal infection on the foot may cause an itchy, bumpy rash on the fingers. These eruptions (dermatophytids or id reactions) are allergic reactions to the fungus. They do not result from touching the infected area.

Keeping in view rising prevalence of superficial fungal infections and possible role of vesicles in providing controlled drug delivery in dermatological disorders, proposed research was aimed at encapsulation of miconazole nitrate as transfersome preparation for prolonged and controlled permeation through skin. In proposed study, a challenge was to ensure that rate and extent of delivery should be sufficient enough to provide sustained pharmacological action. A sincere attempt was made to formulate, characterize, evaluate and optimize miconazole nitrate transfersome by using suitable methods. In proposed study, miconazole nitrate appeared to be a promising candidate for topical vesicular drug delivery in treatment of superficial fungal infection because Miconazole is used to treat skin infections such as athlete's foot, jock itch, ringworm, and other fungal skin infections (candidiasis). This medication is also used to treat a skin condition known as pityriasis (tinea versicolor), a fungal infection that causes a lightening or darkening of the skin of the neck, chest, arms, or legs. Miconazole is an azole antifungal that works by preventing the growth of fungus.

In superficial fungal infections, with targeted topical therapy of MN; systemic drug levels which may lead to gastrointestinal disturbances and cardiac damaging effects, will be reduced. Thus, proposed formulation with improved patient safety and limited risk of drug – drug interaction, will be highly beneficial in all

respects. Hence, an attempt was made to develop novel provesicular formulation that would increase residence time and selective uptake of drug in stratum corneum, thereby, reducing chance of relapse or recurrence and provide clinical efficacy against dermatomycosis including candidiasis.

MATERIAL AND METHODS:

Preparation of Vesicular Formulations

Transferosomes were prepared by conventional rotary evaporation sonication method described by [9]. The ethanolic solution of phospholipid and surfactant were taken in a clean, dry, round bottom flask and the drug solution in 20 ml mixture of methanol and chloroform in the ratio of 1:1 was added to it. The organic solvent was removed by vacuum rotary evaporation above the lipid transition temperature. Final traces of solvent were removed under vacuum overnight. The deposited lipid film was hydrated with drug solution in saline phosphate buffer (PBS) (pH 6.5) by rotation at 60 rpm for 1 h at room temperature. The resulting vesicles were swollen at room temperature to get large multilamellar vesicles (LMLVs). To prepare smaller vesicles, LMLVs were probe sonicated at 40 ˚C at 40 W for less than 30 min.

SIZE AND SHAPE ANALYSIS

The average size of transferosome was determined by microscopy. A sample of transferosome was suitably diluted with distilled water in order to observe individual vesicle and a drop of diluted suspension was examined under a microscope (magnification 15 x 45 X) using calibrated eyepiece micrometer with stage micrometer. The diameters of 150 vesicles were determined randomly. The average diameter was calculated using the formula [10] .

$$\text{Average diameter } (d_{ave}) = \frac{\sum nd}{\sum n}$$

n = number of vesicles
d = diameter of the vesicles

Images of the vesicles were transferred to computer (IBM, China) through a video camera (JVC,Japan).Shapes of vesicles were analyzed automatically using special software developed by Leica imaging systems,UK.

Drug entrapment studies (% Entrapment Efficiency studies)

The entrapment efficiency of drugs (MICO) into transferosome vesicles was determined by ultracentrifugation. 10 ml of transferosome formulation were mixed with 1 ml of 1 % triton X-100 solution. Each sample was vortexed for 2 cycles of 5 minutes with 2 minutes rest between the cycles. 1.5ml of each vortexed sample and fresh untreated transferosome formulations were taken into different centrifugal tubes. These samples were centrifuged at 20,000 rpm for 3 hours. The supernatant layer was separated, diluted with water suitably and drug concentration was determined at 260.2 and 222.4nm respectively in both vortexed and unvortexed samples [11].

The entrapment efficiency was calculated as follows

$$\text{Entrapment Efficiency} = \frac{t-c}{t} \text{ X } 100$$

'T' is total amount of drug detected from supernatant layer of vortexed sample. 'C' is the amount of drug unentrapped and detected from supernatant layer of vortexed sample.

In vitro Diffusion Studies

In vitro diffusion studies of all the formulation of transferosomes of Miconazole nitrate were carried out in pH 7.4 phosphate buffer. The study was performed for 12hrs and cumulative percentage drug release was calculated at different time intervals. The in vitro drug release profile for the formulation (F1 to F6). The plot of time Vs cumulative % drug release formulations (F1 to F6) were plotted and depicted in (Table 2). Effects of various surfactants and their concentration on drug release were studied [12].

RESULTS:

Particle size analysis showed that the sizes of different formulations were in the range of 368 nm and 866 nm indicating that these vesicles were all of a small size. From formulation F1 to F6 particle size are listed in (Table 1) Drug content uniformity was determined as triplicate by dissolving in methanol and dissolved transferosomes were undergone centrifugation at 3000rpm for 2hrs and filtered with Whatmann filter paper (0.45,) Whatman, Maidstone, UK). The solution was diluted to Beer's range and observed in UV-Spectrophotometer). The value range from 81.43% to 94.15% as shown in (Table 1). The entrapment efficiency of deformable vesicles formulations was found to be in the range of 65.41 to 80.11. The percentage entrapment efficiency for span8 0 was maximum F3 for i.e. 80.11 and minimumfor F6 i.e. 65.41.

Table 1: Particle size, Entrapment Efficiency of F1 to F6 Formulations

S. No.	Formulation code	Particle Size (nm)	Drug Concentration (%)	Entrapment Efficiency (%)
1	F1	620	87.65	74.14
2	F2	741	81.43	69.42
3	F3	368	94.15	80.11
4	F4	721	90.31	71.78
5	F5	866	87.41	70.65
6	F6	871	88.91	65.41

Table 2: *In vitro* percentage Cumulative drug release of F1 to F6

S. No.	Time (Hrs.)	*In vitro* percentage Cumulative drug release					
1	0	**0**	**0**	**0**	**0**	**0**	**0**
2	0.5	12.54±0.02	13.50±0.48	16.87±0.09	13.27±0.25	11.44±0.12	11.68±0.01
3	1	20.66±0.22	16.09±0.25	20.41±0.24	23.36±0.31	27.57±0.25	23.48±0.05
4	2	29.99±0.35	20.82±0.43	23.99±0.26	26.91±0.16	30.13±0.19	27.96±0.09
5	3	32.57±0.02	29.01±0.38	27.60±0.06	31.60±0.09	37.29±0.24	34.61±0.10
6	4	39.73±0.12	32.72±0.27	33.49±0.09	35.22±0.13	42.23±0.35	39.20±0.33
7	6	56.68±0.32	46.65±0.36	45.65±0.14	46.65±0.36	58.85±0.55	46.65±0.36
8	8	75.65±0.25	69.65±0.21	63.32±0.25	62.23±0.25	69.41±0.32	73.32±0.25
9	10	85.65±0.14	73.36±0.14	83.32±0.17	74.48±0.25	73.32±0.74	84.45±0.25
10	12	89.98±0.26	78.85±0.25	98.85±0.32	83.32±0.41	86.65±0.25	92.32±0.14

CONCLUSION:

Transferosomal drug delivery system offers a simple and practical approach to achieved increase bioavailability, avoids first pass metabolism and modify drug release profiles essential for sustained, site specific and localized drug action. In vitro release obeyed zero order kinetics with mechanism of release zero order followed by non fickian diffusion due to more lipophilic nature of polymers used. The drug permeation was slow and study of Miconazole nitrate could permeate through the skin into the pilosebaceous unit in 12hrs. Among all the formulations, F3 possess satisfactory swelling index, and in vitro drug release studies were extended period of time so F3 was considered to be the best formulations. So, Miconazole nitrate used for the treatment of pain as transferosomal gel can produce fast absorption. The study conducted so far reveals promising result suggesting scope for pharmacodynamic and pharmacokinetics evaluation.

REFERENCES:

1. Panigrahi L, Ghosal SK, Pattnaik S, Maharana L, Barik BB. Effect of permeation enhancers on the release and permeation kinetics of lincomycin hydrochloride gel formulations through mouse skin. Ind J Pharm Sci. 2006; 68: 205-11.
2. Csóka I, Csányi E, Zapantis G, Nagy E, Fehér-Kiss A, Horváth G, Blazsó G, Eros I.In vitro and in vivo percutaneous absorption of topical dosage forms: Case studies. Int J Pharm.2005; 291:11-19.
3. Ng SF, Rouse JJ, Sanderson FD, Meidan V, Eccleston GM. Validation of a static Franz diffusion cell system for in vitro permeation studies.AAPS Pharm Sci Tech. 2010; 11: 1432-41.
4. Simon GA, MaibachHI. The pig as an experimental animal model of percutaneous permeation in man qualitative and quantitative observations – an overview.Skin Pharmacol Appl Skin Physiol.2000; 13: 229–34.
5. Dick IP, Scott RC. Pig ear skin as an in vitro model for human skin permeability. J Pharm Pharmacol.1992; 44: 640–45.
6. Barry AL, Pfaller MA, Rennie RP etal. Precision and accuracy of fluconazole susceptibility testing by broth microdilution, Etest, and disk diffusion methods. Antimicrob Agents Chemother. 2002; 46: 1781-84.
7. Yenisehirli G,Tuncoglu E,Yenisehirli A,Bulut Y.In vitro activities of antifungal drugs against dermatophytes isolated in Tokat, Turkey. Int J Dermatol 2013; 52:1557-60.
8. Goswami S, Nakhuru KS, Das J , Srivastava RB. Phytochemicals and antidermatophytic activity of methanolic extract of Cestrum nocturnum leaves. Ind Drugs. 2009 ; 46: 619-22.
9. Pakshir K, Bahaedinie L, Rezaei Z, Sodaifi M, Zomorodian K. Invitro activity of six antifungal drugs against clinically important

dermatophytes. Jundishapur J Microbiol. 2009; 2: 158-63.
10. Barros ME, Santoro DA, Hamdan JS. In vitro methods for antifungal susceptibility testing of Trichophyton sp. Mycol Res. 2006; 110: 1355-60.
11. Crowley P.J., Martini L.G.Drug-excipient Interactions, Pharm Technol.2001; 13, 1-6.
12. Barboza F., Vecchia D.D., Tagliari M. P., Silva M. A. S., Stulzer H. K. Differential scanning calorimetry as a screening technique in compatibility studies of acyclovir extended release formulations, Pharmaceutical Chem Journal .2009; 43:363-368.