Research Article

Microemulsion Formulation for Topical Delivery of Miconazole Nitrate

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ABSTRACT

The aim of present study was to develop micro emulsion system for topical application of miconazole to provide various advantages over conventional dosage forms. Miconazole nitrate is hydrophobic imidazole antifungal agent. Clinical studies show that it is highly effective for topical treatment of fungal infections. Micro emulsion was prepared using oleic acid as an oil phase, tween 20 as surfactant and propylene glycol as co-surfactant. In vitro characterization of micro emulsion of miconazole nitrate was done through measurement of pH, conductivity, viscosity, antifungal activity, drug release kinetics. Miconazole nitrate cream (2%) was used as reference sample for comparison of antifungal activity and release rate. The data obtained from various studies gave satisfactory results. Micro emulsion showed greater antifungal activity against *Candida albicans* as compared to reference sample. In vitro drug release studies were conducted for micro emulsion and reference sample using Franz diffusion cell. Faster drug release rates were observed for micro emulsion formulation than reference sample. Drug penetration from micro emulsion followed Higuchi model whereas drug release from reference formulation followed Korsmeyer-Peppas model. It was concluded that miconazole nitrate can be formulated as micro emulsion with good release and consistency.

Keywords: Miconazole, Penetration, Topical.

INTRODUCTION

Microemulsions can be defined as clear, stable and isotropic mixtures of oil, water, surfactant and co-surfactant. These delivery systems can be used for topical, percutaneous, transdermal, oral, parenteral and ocular application of medicinal agents. They have many advantages over other conventional dermal preparations such as high transparency, better drug loading, high thermodynamic stability, rapid skin penetration, better bioavailability and easy to prepare The droplet diameter of microemulsions are generally within the range of 10-200 nm.[1]

All microemulsions are fluids with low viscosity. Depending upon their structure, microemulsions are of different types as water-in-oil (w/o), oil-in-water (o/w) or bicontinuous systems. Ultra low interfacial tension exists between water and oil phases. Due to the presence of both lipophilic and hydrophilic domains, a wide range of lipophilic and hydrophilic drugs can be incorporated in these systems. Enzymatic hydrolysis and oxidation is prevented trough these flexible delivery systems. The solubilization and bioavailability of lipophilic drugs is improved. These systems can be used for topical, intravenous and oral delivery as well as for the sustained and targeted delivery. The oral bioavailability of many poorly soluble drugs is enhanced.[2]

The validity of miconazole nitrate is well known in antifungal therapy. Clinical studies show that it is highly effective for topical treatment of superficial mycoses, dermatophytoses, cutaneous candidiases and other infections.[3] Miconazole nitrate can be given orally, topically or by parenteral route depending on the type and severity of infection. Topical drug therapy is appropriate for the management of local diseases in order to restrict therapeutic effect to the target site and to decrease systemic drug absorption. The first-pass-effect is also minimized through topical drug delivery systems. Stratum corneum, the uppermost layer of epidermis, is the rate limiting barrier in order to reach therapeutic drug concentrations in the blood circulation or in certain skin layers. The physicochemical properties of the drug and the vehicle used for administration largely affect this process of penetration.[4] Miconazole nitrate is generally applied topically for treating various diseases on skin surface like Athlete's foot, Jock itch, Ring worm and Perioral candidiasis.[5]

Present work was an attempt to develop a stable microemulsion system to provide greater loading capacity, good bioavailability and penetrability of miconazole nitrate across the skin after topical application.

MATERIALS AND METHODS

Materials

Miconazole nitrate (Sharon Biomedicine Ltd. Mumbai, India). Oleic acid, olive oil, cotton seed oil and soybean oil (Avonchem Limited, UK) and Tween 20, Tween 80 and Span 20 (Unichem Limited, UK). Propylene Glycol 400 and n- Butanol were obtained from USA Lab Chemicals. Methanol and ethanol (Merck Chemicals, Darmstadt, Germany), Sabouraud dextrose agar (Himedia Laboratories). Double distilled water was used throughout the study. All chemicals were of analytical reagent grade.

Calibration curve of miconazole nitrate

A calibration curve of miconazole nitrate was constructed in methanol. Dilutions of miconazole in methanol at concentrations ranging from 200 µg/ ml to 12.5 µg/ ml (05 different concentrations) were made. The absorbance of each sample was determined at 272 nm with spectrophotometer. Methanol was taken as blank. The experiments were performed in triplicate and mean absorbance value was taken. A calibration curve was plotted with concentration as x-coordinate and absorbance as y-coordinate. Linear regression analysis was performed.[6]

Solubility studies of miconazole nitrate

Solubility of miconazole nitrate in various oils, surfactants and co-surfactants was determined. Drug powder of miconazole nitrate was added in excess to each vehicle (about 5ml). All samples were placed on magnetic stirrer for 72 hours at ambient temperature to facilitate solubilization. In order to remove un-dissolved drug, the samples were then centrifuged at 10,000 rpm for 10 minutes. The supernatant was taken and analyzed spectrophotometrically after dilution with methanol at 272 nm. Appropriately diluted solutions of oils in methanol were taken as blank.[7]

Selection of oil phase, surfactant and co-surfactant

Oleic acid, tween 20 and propylene glycol were selected as oil, surfactant and co-surfactant respectively on the basis of solubility data.

Construction of Pseudo ternary Phase Diagram

Water titration method was used to construct pseudo ternary phase diagrams. Various ratios of oil to surfactant/co-surfactant mixture ranging 1:9 to 9:1 w/w were used. Three pseudo ternary phase diagrams with different surfactant co-surfactant ratios (1:1, 1:2 and 2:1 w/w), were constructed. For construction of each phase diagram, oil, surfactant and co-surfactant mixtures were prepared. Mixtures were kept on magnetic stirring at ambient temperature and water was added drop by drop. While adding water, a point is reached when system becomes turbid. Appropriate quantities of water, at which mixture remains clear, were identified for each mixture.[8] Percentage quantities of all ingredients were calculated for each diagram and pseudoternary phase diagrams were constructed using Prosim software.

Preparation of micro emulsion

1:1 phase diagram was chosen for preparation of micro emulsion due to better solubility of miconazole nitrate in this mixture as compare to others. According to 1:1 phase diagram quantities of oil surfactant and co-surfactant were weighed. Mixture of oil, surfactant and co-surfactant was prepared with the help of magnetic stirrer and miconazole nitrate was dissolved in this mixture. Stirring was done with a magnetic bar on magnetic stirrer hot plate at room temperature. Fixed amount of water was added continuously while keeping the system on magnetic stirring. The transparent micro emulsion system was immediately formed. Five formulations of micro emulsion containing miconazole (2% w/w) were prepared.[8]

In-vitro characterization of miconazole nitrate micro emulsion

Organoleptic parameters

Color, transparency and homogeneity of micro emulsions were observed in strong light. Presence of un-dissolved drug or other solid ingredient was also checked.[9]

Centrifugation

The formulations were centrifugated at 5000rpm for 5minutes to check phase separation of systems.[10]

pH and conductivity measurements

pH values of the samples were measured by digital pH meter and conductivity was measured by conductivity meter. Measurements were performed in triplicate at room temperature. Results were represented as mean ± S.D.[10]

Refractive index

The refractive index of different formulations was measured by refractometer. Measurements were taken in triplicate and expressed as mean ± S.D. [11]

Determination of droplet size

Average droplet size of the micro emulsion was determined by Zeta sizer.[12]

Measurement of viscosity

The viscosity was determined by Brookfield Viscometer at room temperature. Measurements were taken in triplicate and results were expressed as mean viscosity value for each sample. Viscosity values were taken at 20, 30, 50, 60 and 100 rpm using spindle 2.[13]

In vitro antifungal activity determination

In vitro antifungal studies were performed against *Candida albican* in sabouraud dextrose agar medium. Well diffusion method was used. Suspension of *Candida albican* was prepared in sabouraud dextrose broth. Wells were made in plates containing solidified

sabouraud dextrose agar using borer and plates were inoculated by swabbing technique. Then small amount (1g) of each formulation (micro emulsion, reference cream and placebo micro emulsion) was placed into the wells and plates were labeled appropriately. Formulation of placebo micro emulsion was same as that of miconazole micro emulsion but it was non-medicated. These plates were incubated at 37°C±1°C for 24 hours. The mean zones of inhibition from different formulations were measured in mm.[8]

Drug Release kinetics

Franz diffusion cell was used to determine in vitro drug release of miconazole nitrate from micro emulsion and reference sample (miconazole cream 2%). The effective diffusion area of Franz diffusion cell was 1.628cm² and the receptor compartment was filled with 10 ml of methanol. Total 6 Franz cells were used for each formulation. Diffusion cell was kept on magnetic stirrer hot plate. The temperature was maintained at 37±1°C and continuously stirred at 300 rpm throughout the experiment using magnetic stirrer. Nylon membrane was placed on the top of Franz cell and open cap was fitted on cell with the help of clamp. 2.5g formulation was added in donor chamber and test was started. At different time intervals aliquot of 1ml sample were withdrawn from the receptor compartment using syringe for the period of 12 hours and replaced immediately with an equal volume of fresh methanol. Samples were diluted with methanol and analyzed spectrophotometrically at 272nm. Flux and percentage amount released at different time intervals were calculated for each formulation (micro emulsion and reference cream). Flux values from micro emulsion and reference sample were calculated by using following formula.

$J = m / A t$

Where "J" is the flux of a mass of compound (m), moving through cross sectional area (A) during time (t). Thus the units of flux are $mgcm^{-2}h^{-1}$ or $\mu gcm^{-2}h^{-1}$. The mean cumulative amount of drug released through the membrane (mg/cm^2) was plotted against time for each formulation. Release data from each formulation was expressed as mean ± S.D. To ascertain the kinetics of drug release, the release profile of each formulation was fitted to Zero order, First order, Higuchi, Hixon-Crowell and Korsmeyer-Peppas models.[14]

Comparison of drug release profiles and antifungal activity of different formulations

Drug release profile of micro emulsion was compared with that of reference sample (2% miconazole cream). Mean zones of inhibitions obtained from micro emulsion, reference sample and placebo micro emulsion were also compared.

Statistical data analysis

All measurements were performed in triplicates for each sample and results were represented as mean ± S.D. Analysis of variance (ANOVA) and LSD test at 5% significance were used for analysis using SPSS software (version 16).

RESULTS AND DISCUSSION

Solubility studies of miconazole nitrate

Standard curve of miconazole nitrate was constructed in methanol. Absorbance was taken at 272 nm on UV Spectrophotometer. Standard curve obeyed Beer's law at given concentration range of 200 µg/ml to 12.5 µg/ml when subjected to regression analysis, the value of regression coefficient was found to be 0.9987, which showed linear relationship between concentration and absorbance. The equation of the calibration curve was: $Y = 0.0033X + 0.0252$. The mean correlation coefficient was found 0.9987.

Miconazole nitrate is very slightly soluble in water (0.17 ± 0.0002 mg/ml) or 1 part in 6250 parts of water at 25 °c, 1 part in 75 parts of methanol and 1 part in 312 parts of ethanol. Miconazole is a weak base. It has pka value of 6.7. Solubility of weak basic or acidic drugs depends on the pH of the medium. When pH is decreased, nitrogen becomes protonated and dissolution of miconazole nitrate is improved.[15]

Solubility of miconazole nitrate in various oils, surfactants and co-surfactants was determined using calibration curve. Highest solubility was found in oleic acid (650µg/ml) as compare to other oils and it was selected as an oil phase. Tween 20 as surfactant and propylene glycol as co-surfactant were also selected on the basis of high solubility. In tween 20, solubility was found 14.08 mg/ml and in propylene glycol, it was found 44.38mg/ml. Solubility data of miconazole nitrate is given in Table 1.

Construction of Pseudo ternary Phase diagram

Pseudo ternary phase diagram with 1:1 surfactant co-surfactant ratio was found most appropriate to prepare micro emulsions of miconazole of most acceptable properties. Phase diagram is represented in Figure 1. Five micro emulsions (F1-F5) were prepared.

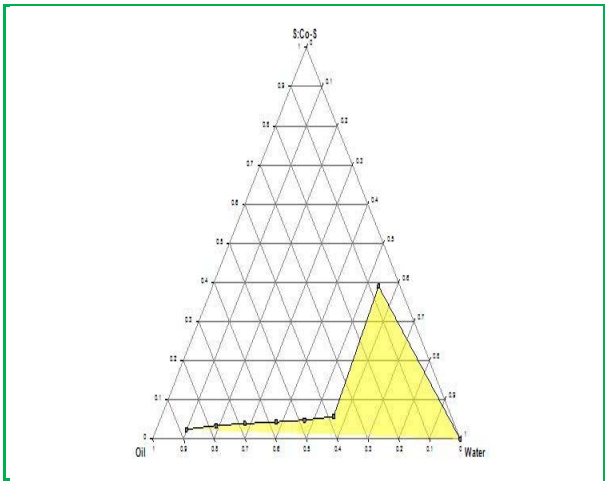

Figure 1: Pseudo ternary phase diagram with surfactant, co-surfactant ratio of 1:1

Table 1: Solubility studies of miconazole in various solvents

Oils	**Solvent**	**Solubility (µg/mL) ± S.D**
	Oleic acid	650 ± 0.032
	Soy bean oil	350± 0.133
	Cotton seed oil	200± 0.127
	Olive oil	150± 0.004
Surfactants	**Solvent**	**Solubility (mg/ml) ± S.D**
	Tween® 20	14.08± 0.203
	Tween® 80	12.43± 0.163
	Span® 20	9.58± 0.091
Co-surfactants	**Solvent**	**Solubility (mg/ml) ± S.D**
	Propylene glycol	44.38 ± 0.005
	Methanol	13.33 ± 0.021
	Ethanol	11.76 ± 0.054
	n-Butanol	8.90 ± 1.006

Table 2: Measurement of pH, refractive index and conductivity (Mean± S.D)

Parameter	F1	F2	F3	F4	F5
PH	3.44 ± 0.224	3.27 ± 0.224	3.31 ± 0.224	3.14 ± 0.224	2.85 ± 0.224
Refractive index	1.414 ± 0.016	1.4401 ± 0.016	1.44897 ± 0.016	1.45206 ± 0.016	1.45197 ± 0.016
Conductivity (µS/cm)	43.0 ± 10.756	39.5 ± 10.756	38.3 ± 10.756	22.9 ± 10.756	15.3 ± 10.756

Preparation and characterization of micro emulsion

In the clinical investigations, topical azole creams at 1-2% concentration are reported well tolerated.[16] In the micro emulsion formulations, drug concentration was kept at 2% w/w. Micro emulsion formulation was characterized with respect to centrifugation, organoleptic parameters, pH, electrical conductivity, refractive index, viscosity, globule size, antifungal activity and in vitro drug release rates.

Centrifugation

To determine behavior of small particles in gravitational field, centrifugation technique is very helpful. If phase separation does not occur after centrifugation, it is a rapid and full proof identification of micro emulsion system.[9]

None of the formulated micro emulsion system showed signs of phase separation on centrifugation at 5000 rpm for 5 minutes. This result provided identification of the system as micro emulsion.

Organoleptic parameters of micro emulsions

The color, clarity and phase separation of all micro emulsions were observed immediately after preparation. The color of micro emulsions was light yellow and all micro emulsions were transparent.

pH, conductivity and refractive index of micro emulsion

The solubility of drug and its potential to cause skin irritation depends on pH of system. Skin surface has pH in the range of 4-6. pH of topical preparations must also be in this pH range. Due to stability problems, pH may change during storage of product.[17] pH of micro emulsions was found in the range of (3.1- 3.4). It was slightly acidic.

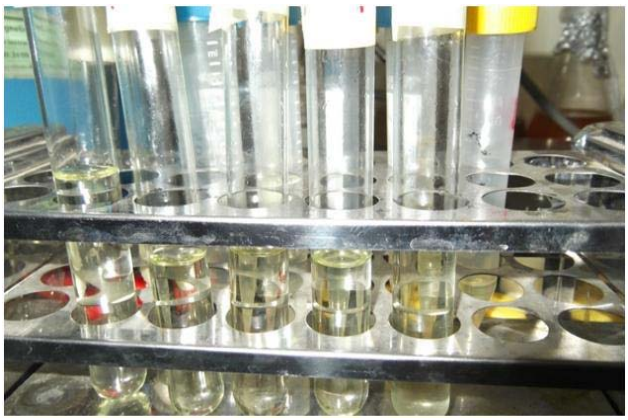

Figure 2: Visual appearance and clarity of micro emulsions

The o/w micro emulsions show higher conductivity values than the w/o micro emulsions due to high conductivity properties of the aqueous external pseudophase. Free basic drugs do not affect the conductivity of respective blank micro emulsion. It is expected that drugs which are in salt form may dissociate in the presence of water and lead to an increased conductivity of microemulsion.[18] Conductivity of micro emulsion formulations was found in the range of (43-15.3µS/cm). Conductivity values of micro emulsion containing more water (F1) showed higher

conductivity. As the water contents decreased, conductivity values also decreased**.**

The refractive index measurements for all tested micro emulsions were in the range of (1.414-1.452). The o/w micro emulsions show low refractive index as compare to w/o micro emulsions due to low refractive index of water (1.3336 ± 0.0004) as external pseudophase.[18] pH, conductivity and refractive index values of micro emulsion formulations are given in Table 2.

Viscosity of micro emulsions

It was represented by rheological behavior of all formulations that systems were non- Newtonian in nature. In pseudoplastic non-Newtonian flow, viscosity values decrease as shear rates increase.[9] Viscosity of various micro emulsion formulations were found to decrease with increasing shear rates as shown in Table 3.

Table 3: Mean Viscosity (cp) values of micro emulsion formulations using spindle- 2

RPM	Viscosity (cp)				
	F1	F2	F3	F4	F5
20	105	89	98	94	101
30	90	85	81	83	85
50	88	81	76	77	78
60	81	75	70	73	74
100	79	72	68	65	66

Measurement of globule size of micro emulsion

Droplet size of micro emulsion formulation was found in the range of (37- 91nm) as shown in Table 4. These results were in accordance with micro emulsion characteristics. The mean droplet diameter of micro emulsion is an important parameter that affects physical stability. The small average droplet diameter obtained was due to the reason that the propylene glycol molecules penetrate the tween 20 film, thus lessening the fluidity and surface tension of the interfacial film and radius of droplet decreased leading to the formation of transparent system.[19]

Anti fungal studies

Antifungal activity of micro emulsion, reference sample (miconazole cream 2%) and placebo was determined against *Candida albican* using well diffusion method. Placebo formulation was same as that of micro emulsion, only difference was that miconazole nitrate was not incorporated in placebo. Sabouraud dextrose agar was used as culture media. Zones of inhibition of formulations were compared. Micro emulsion showed greater zones of inhibition than reference sample. Zones of inhibition are given in Table 5. No significant zone of inhibition was observed in case of placebo which indicates that the components of micro emulsion, except miconazole nitrate, have no antifungal activity.

Statistical analysis of antifungal data by one way ANOVA showed that micro emulsion has highly significant antifungal activity as compare to reference sample. The greater in vitro antifungal activity of micro emulsion than marketed cream may be due to the smaller globule size with its larger surface area as compare to the normal emulsion present in the cream. This may be the reason for greater drug release from micro emulsion preparation.[20]

Table 4: Size distribution of micro emulsion

Size (nm)	Number distribution data %
32.67441559	0
37.83956146	4.2454772
43.82120895	14.90045166
50.74842834	22.7857399
58.77069855	21.78446579
68.06112671	15.88238811
78.82017517	9.724177361
91.28000641	5.275101185

Table 5: Measurement of zones of inhibition of different formulations in mm

Reference sample	Micro emulsion	Placebo
2.3	3.7	0.0
2.1	3.3	0.0
2.2	3.2	0.0
2.4	3.5	0.1
2.1	3.8	0.0

***In-vitro* skin permeation studies**

In-vitro drug release studies were conducted using Franz diffusion cell. 2.5 g of each sample was applied to donor chamber and amount released from hydrophobic nylon membrane was determined for micro emulsion and reference sample (miconazole cream 2%) for 12 hours. Percent amount of drug released from these formulations is given in Table 6. About 80% drug released from micro emulsion within 12 hours. Drug release from reference sample was found 63.48% within 12 hours. It has been shown that release rate from micro emulsion was higher as compare to reference sample. Flux value of micro emulsion was also higher than reference sample which indicate faster drug release from micro emulsion. Flux is the amount of drug permeated per unit area in unit time.

Greater Permeability of drug from micro emulsion may be attributed to different factors. It has been reported that permeation rate is increased with decreasing globular size of micro emulsion. Various components of micro emulsion also have penetration enhancing effect and they promote the penetration across the skin.[21, 22]

Release rates from both formulations were analyzed by one way ANOVA with LSD. Micro emulsion showed significantly higher release rate than that of reference

sample. Release rates from micro emulsion and reference sample were fitted to statistical models like Zero order, First order, Higuchi equation, Hixon-Crowell equation and Korsmeyer-Peppas model. It was observed that Higuchi was best model for drug release from micro emulsion. Korsmeyer-Peppas plots were best fitted to release profile of reference sample.

Table 6: Percentage amount of drug released from different formulations (Mean± S.D)

Sr. No.	Time (Hr)	Percent amount released	
		Micro emulsion	Reference sample
1	0.5	15.68 ± 1.995	6.89 ± 0.411
2	1	24.37 ± 2.543	9.24 ± 0.509
3	2	36.7 ± 3.572	14.72 ± 0.758
4	3	42.3 ± 4.343	22.50± 0.820
5	4	47.05 ± 3.130	27.71 ± 1.323
6	5	52.97 ± 3.124	35.71 ± 0.788
7	6	57.78 ± 3.472	50.93± 2.404
8	12	84.45 ±4.417	63.48 ± 4.591

CONCLUSION

Miconazole nitrate can be formulated as micro emulsion using oleic acid as an oil phase, tween 20 as surfactant and propylene glycol as co-surfactant with good release rate and consistency. pH adjustments and stability studies are required. Although, the antifungal activity of micro emulsion was found greater than that of reference sample, more comparative clinical studies are needed to confirm the advantages over the available marketed products.

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