Development And Optimization of Sertaconazole Nitrate Emulgel for Topical Antifungal Therapy

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***Abstract*—To improve the delivery and release qualities, this work studies formulation and assessment of a topical emulgel formulation holding Sertaconazole nitrate, an antifungal drug of the imidazole class. Synthetic polymer and surfactants were the building blocks of the emulgel recipe. Ingredients including glycerin, propylene glycol, isopropyl myristate, tween 80, carbopol 940, and methyl paraben are also present. Nine distinct formulations (F1-F9) were created to investigate the effects of concentration on physiochemical properties and medication release. The in-vitro drug diffusion, viscosity, spreadability, pH, and physical appearance of the formulations have all been assessed. These pH levels, which fall within the permitted range for topical treatment, ranged from 6.00 to 6.25. Because of its role as a gelling agent, carbopol 940 raises the formulation's viscosity with increasing concentration. As the amount of carbopol 940 increases, the amount of increase in viscosity makes the spreadability of the prepared emulgel decrease. The content of the drug in all formulations was found to be consistent ranging from 98.45% to 101.35%. Experiments on drug diffusion in vitro demonstrated that formulation F7 released 95.09% of the medication in 8 hours overall. The outcomes show that antifungal drugs like sertaconazole nitrate can be more effectively distributed using the emulgel technology. F7 showed superior drug dispersion, stability, and physical qualities compared to the other formulations, suggesting it may be a viable substitute for the standard topical antifungal medicines that were examined.**

***Index Terms*—Sertaconazole nitrate, Topical drug delivery, Emulgel, Antifungal therapy, Factorial design.**

I. INTRODUCTION

Topical drug delivery has great potential as a substitute to traditional drug delivery modalities, offering less side effects when applied topically [1]. It is possible to optimise the drug concentration to a low level because drug metabolism is not present. [2] Emulgel and ointments work well with hydrophobic drugs, while gels and creams work well with hydrophilic ones. Traditional topical formulations like these have been around for a while, but they have a few issues, such as inconsistent drug absorption and product compatibility limitations. The fungal infections have become more common and particularly the dermatophytes, yeasts and molds have caused superficial fungal infections, which has led to a greater need for efficient topical formulations for antifungal therapy.

The traditional formulations are poor soluble, greasy, unstable and have poor drug penetration. So, the topical delivery system, like advanced topical carries, has become much more significant in the pharmaceutical research. Sertaconazole nitrate, a hydrophobic drug, is a good candidate for emulgels since they are a blend of the advantages of emulsions and gels. There are several benefits to administering medication topically rather than orally. These include avoiding first-pass metabolism, reducing gastrointestinal irritation, making the medication easier to apply, increasing patient compliance, and targeting the infection site. Topical preparations include ointments, creams, gels, lotions, pastes, sprays and newer vesicular and emulsion- based system. Of these dosage forms, gels have become very important due to their non-greasy formulation and patient aaceptability. [4]

II. MATERIAL AND METHODS

Sertaconazole nitrate was purchased from Swapnaroop Agencies, India. The drug was described per the specification of the USP. IR and HPLC were the methods used for identification [5,6]. The physiochemical properties such as appearance, solubility, melting point, residue on ignition and impurities were determined.

Method of preparation: Emulsion-gel mixing method
Preparation of the emulsion: Both the aqueous and oil phases (containing the hydrophilic and lipophilic surfactants, respectively) are heated separately in an appropriate amount, and then mixed by stirring to obtain emulsion.
Gel base is prepared by dispersing gelling agents (Carbopol or HPMC) in distilled water, neutralizing (usually with NaOH or triethanolamine) and allowing them to hydrate completely.
The emulsion is added to the gel base in a specific proportion (usually 1:1) and the mixture is continuously stirred or homogenized to obtain the emulgel. [2,3,12]

Evaluation of sertaconazole nitrate emulgel:
1. Preformulation Studies
Prior to formulating Sertaconazole nitrate, it was necessary to conduct preformulation tests to assess its physicochemical characteristics.

2. Drug Characterization
Qualitative evaluation was conducted by visual means of the drug for colour, odour and appearance.

3. Melting Point
Open capillary technique was used to measure melting point. The drug sample was introduced into melting point device through a capillary tube by one closed end. The range of temperatures at which the medication melted was documented.

4. Solubility Study
Solubility of Sertaconazole nitrate was investigated in various solvents like methanol, dimethyl sulfoxide (DMSO), dimethylformamide (DMF) and water. The drug was sonicated for 10 minutes in 10 mL of solvent and approximately 20 mg of the drug was added. The solubility was determined by eye. [6,8,10,11]

III. CHARACTERIZATION OF SERTACONAZOLE NITRATE EMULGEL:

1. UV-Visible Spectrophotometric Analysis
Spectrophotometer used for UV spectrophotometric examination was methanol. A stock solution of Sertaconazole nitrate was made and then further diluted to produce other dilutions of 5–25 µg/mL. Absorbance measured at 260nm by a UV-Vis spectrophotometer and then a calibration curve was plotted.

2. FT-IR Study
FTIR analysis of Sertaconazole nitrate was carried out using Shimadzu IRAffinity-1 FTIR spectrophotometer. The spectra were taken by KBr 400 – 4000cm^{-1} and characteristic functional groups recognized.

3. Drug–Excipient Compatibility Study
Excipient compatibility tests with Sertaconazole nitrate were conducted using Fourier transform infrared spectroscopy. For one-month, physical mixes containing the medication and excipients were mixed in a 1:1 ratio and kept at 40 ± 2°C/75 ± 5% RH. [5]

Preparation of sertaconazole nitrate emulgel
Prepared of emulsion-gel method.
Accurately weighed sertaconazole nitrate was dissolved in isopropyl myristate to prepare oil phase. Tween 80 was added to oil phase and thoroughly mixed. Carbopol 940 was dispersed independently in purified water and hydrated it 1-2 hours. The methyl paraben was subsequently added to the aqueous phase in a separate beaker after being gently heated in propylene glycol. Glycerin was added to water phase even though stirring it. To create an emulsion, oil phase was introduced to water phase in stages while stirring constantly. Hydrated gel basis was gradually added to the produced emulsion. Next, a homogeneous emulgel was achieved by adjusting the pH to 5.5-6.5 with the dropwise addition of triethanolamine [9]

IV. OPTIMIZATION OF FORMULATION

Optimization of formulation by using a 3^2-factorial design. Independent variables chosen were concentration of isopropyl myristate (X_1) and concentration of carbopol 940 (X_2) and dependent variables were viscosity and in-vitro drug release. [5]

Table No1: Sertaconazole Nitrate Emulgel Composition

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sertaconazole nitrate (gm)	0.2								
Isopropyl myristate (gm)	0.5	0.5	0.5	1	1	1	1.5	1.5	1.5
Carbopol 940 (gm)	0.03	0.06	0.09	0.03	0.06	0.09	0.03	0.06	0.09
Tween 80 (gm)	0.3								
Glycerin (gm)	0.5								
Propylene glycol (gm)	0.5								
Methyl paraben (gm)	0.02								
Triethanolamine	q. s								
Water	q. s								
Total	10gm								

Evaluation of Emulgel

1. Physical Examination

Colour, odour, consistency and homogeneity were evaluated by visual inspection of the prepared formulations. [6]

2. pH Determination

A calibrated digital pH meter was utilised to measure pH of formulation by dispersing 1 g of emulgel in 10 mL of distilled water. [11]

3. Viscosity

The formulations' viscosities were measured at 25 ± 1°C using spindle No. 64 of Brookfield viscometer set at 50 rpm [6].

4. Spreadability Test

Slip and drag method was employed for determining the spreadability. Spreadability was determined based on the following formula: [8]

$$\text{Spreadability} = \frac{\text{Weight tied to upper slide} \times \text{Length moved by glass slide}}{\text{Time}}$$

5. Drug Content Uniformity

It was measured by spectrophotometry at 260 nm following methanol solubilisation and suitable dilution. Analysis of Drug Release in Vitro The Franz diffusion cell equipment with a cellophane membrane was used for in vitro drug diffusion research. A phosphate buffer by a pH of 6.8 was used as the receptor media, and a temperature of 37 ± 0.5 ℃ was maintained. Timely sample collection and spectrophotometric analysis at 260 nm were employed. [10,12,13]

6. Antifungal Activity

Candida albicans was chosen as the test fungus to determine the antifungal activity and Sabouraud dextrose agar medium was used. The zone of inhibition was determined after incubation. Stability Studies Accelerated stability studies of optimized batch were conceded out according to ICH rules at 40 ± 2°C & 75 ± 5% RH for 90 days.[14]

V. RESULT AND DISCUSSION

1. Drug Characterization:

Sertaconazole nitrate was observed with respect to its colour, odour and appearance. The colour is white, odour is odourless and the appearance was observed is fine powder.

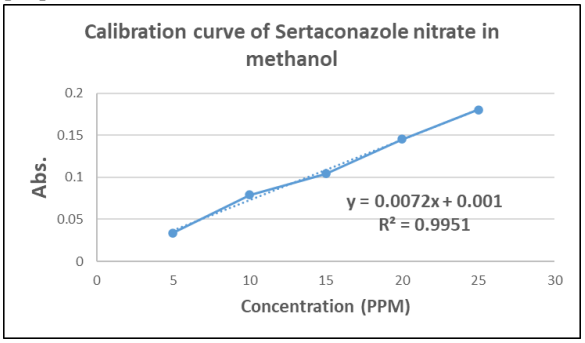
2. Determination of melting point:

The results show that sertaconazole nitrate has a melting point between 158 - 160 degrees Celsius, which is in agreement with the previously stated value.

3. Solubility study:

Different solvent systems were used to conduct a solubility study for sertaconazole nitrate. The sertaconazole nitrate is soluble in dimethyl sulfoxide, methanol, dimethyl formamide and insoluble in water. [23,24]

UV-visible spectrophotometric analysis:
The investigation was conducted using a V 550 Spectrophotometer from Jasco Corporation, Japan, and spectra manager software for UV-visible spectrophotometric data. While sertaconazole nitrate calibration curves are being prepared, the absorbance of various concentrations of sertaconazole nitrate in methanol was measured at 260 nm, and a calibration curve of the compound was subsequently constructed. From 5 to 25 µg/ml, the sertaconazole nitrate calibration curve followed Beer-Lambert's law and was linear. A very good degree of data linearity was specified by correlation coefficient values of 0.9951. [15]



Calibration curve for Sertaconazole nitrate

FT-IR of Sertaconazole nitrate:
A Fourier transform infrared spectrometer was used to record IR spectra. FTIR spectrum revealed the presence of distinct functional groups.

Table No 2: IR frequencies of Sertaconazole nitrate

Functional group	Reported Frequency	Observed Frequency
C=N stretching (Imidazole group)	1600 - 1500	1576.72
C-C stretching (Aromatic ring)	1500 - 1400	1458.07
N-O stretching (Nitrate group)	1342-1266	1327.83
C-O stretching (Aliphatic ether)	1150-1085	1086.04
C-Cl stretching (Chlorine substituents)	850-550	792.42

Drug excipient compatibility study:
There is no evidence of interaction among drug, polymer, and excipients based on FTIR spectra of both the pure form of sertaconazole nitrate and their physical mixture.[16]

VI. EVALUATION OF FORMULATED BATCHES:

1. Physical evaluation:
Some batches showed smooth and grease free appearance whereas, some were viscous in nature. Colour difference was not observed in between any batch as all were White. Additionally, all batches had a moderate scent, thus there was no discernible difference between them. [17]

2. Determination of pH
All batches were tested for pH determination and outcomes were found ranging from 6.00 – 6.14 which is within the limit as per literature. [11]

3. Determination of viscosity
The outcomes showed that viscosity increased in the order of the concentration of Carbopol used in the formulation as a gelling agent. In addition, isopropyl myristate only had minor effects on viscosity, by increasing the solubility of sertaconazole nitrate and slightly altering its spreadability, but it does not have such an effect as Carbopol 940. In general, the viscosity values for the different batches were found to be within acceptable limits. [6]

4. Spreadability test:
Testing the spreadability of each of the produced batches showed that it falls anywhere between 11.3 and 21.2 gm.cm/sec. The spreadability of the prepared emulgel decreases as the concentration of carbopol 940 increases due to the viscosity. [8]

5. Determination of Drug content:
Using UV-Visible spectrophotometry at 260 nm, the drug's presence was examined in all nine batches of the sertaconazole nitrate emulgel. All of the formulations had a drug concentration ranging from 98.45% to 101.35%, indicating that the medication was evenly distributed throughout the formulation. [10,12,13]

6. Determination of Drug release (Drug diffusion):
Using UV-Visible spectrophotometry at 260 nm, the drug's presence was examined in all nine batches of the sertaconazole nitrate emulgel. With time, the drug diffusion mechanism slowed down and showed prolonged effect as the formulation viscosity increased and the concentration of the penetration enhancer decreased. [18]

Table No 3: % drug diffusion

Time (Hrs.) ↓ / Batches →	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	12.18	13.47	14.6	14.9	14.5	13.67	12.6	11.67	11.57
2	21.54	21.96	22.41	23.43	24.43	22.96	20.43	19.63	20.96
3	35.48	35.9	36.35	37.37	38.37	36.9	34.37	33.57	34.9
4	50.88	51.3	51.75	52.77	53.77	52.3	49.77	48.97	50.3
6	78.63	79.05	79.5	80.52	81.52	80.05	77.52	76.72	78.05
8	89.92	85.79	82.32	91.54	88.19	85.51	95.09	92.35	88.94

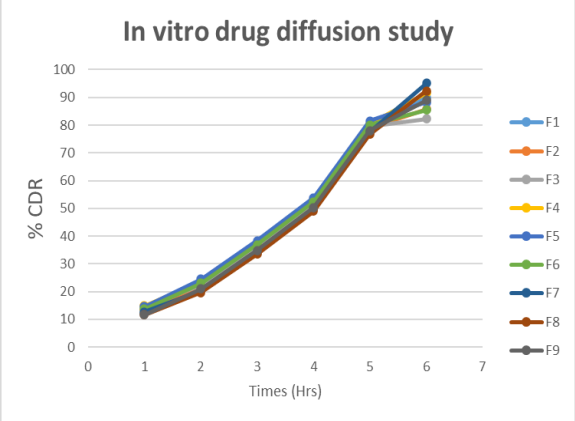


Fig No 1: % CDR vs Time for drug diffusion

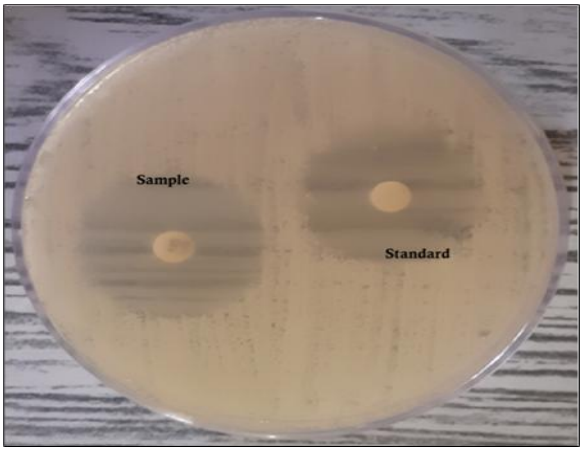


Fig No 2: Antifungal study results

7. Antifungal testing of optimized batch:
Antifungal study was performed as per the standard procedure mentioned under experimental work. For the optimized batch zone of inhibition was found as 27 mm. Based on antifungal results, it was proved that optimized batch of emulgel was having sufficient antifungal activity as zone of inhibition is 26 mm for the standard antifungal agent (Nystatin). [19, 20, 21, 25]

Table No 4: Antifungal study (zone of inhibition)

Sample	Zone of inhibition (mm)
Optimized batch (F7)	27
Standard agent for antifungal activity (Nystatin)	26

VII. CONCLUSION

In the present study the emulgel formulation of Sertaconazole nitrate with optimized formulation was successfully prepared and optimized in order to perform topical antifungal therapy. The physicochemical properties, spreadability, viscosity and uniformity of drug content of prepared emulgel formulations were satisfactory. Optimized batch (F7) had the highest release of drug and most effective antifungal activity against Candida albicans among all the formulations. The formulation was stable during stability test under accelerated conditions. Thus, the use of Sertaconazole nitrate Emulgel as a topical drug delivery system in fungal infections can be said to be promising and effective. [22]

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