A Research: Formulation and Evaluation of Nanoemulsion for Topical Drug Delivery System Using Model Drug.

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Abstract:

Nanoemulsion is an advanced mode of drug delivery system has been formulated and developed to overcome the major drawbacks associated with conventional drug delivery systems. These are transparent and thermodynamically stable isotropic system in which two immiscible liquids are mixed to form a single phase by means of an emulsifying agent, surfactant and co-surfactant. The droplet size of nanoemulsion is in the range 10–1000 nm. The main difference between emulsion and nanoemulsion lies in the size and shape of particles dispersed in the continuous phase. In this formulation Miconazole Nitrate and Oleic acid act as an oil phase and Tween 80, Propylene glycol and Water act as an aqueous phase. As per Placket Burman DoE 5 Formulations were Developed using independent variables concentration of oils, surfactant and co-surfactant. Formulations F1 to F5 were formulated using Miconazole Nitrate, Tween 80, Oleic acid and propylene glycol. Nanoemulsion was characterized for various parameters like, viscosity, Density, pH, Drug content, Centrifugation, Freeze thaw cycle, Particle size determination, and drug diffusion release study. The optimized formulation F5 showed 100.78 % drug release in 5 hrs. This outcome signified its potential suitability as a carrier for effectively administration of Miconazole Nitrate through topical delivery. Viscosity and Density F5 50 cps and F5 1.05 g/cc respectively.

Key words: Nanoemulsion, Oil, Surfactant, Co-surfactant.

1. INTRODUCTION:

Nanoemulsions have gained popularity in recent times for their widespread usability in pharmaceuticals, pesticides, cosmetics, food, paint, and environmental applications. Nanoemulsions are kinetically stable systems exhibiting multiphase colloidal dispersion with longer shelf life. Due to their small size, they enhance penetration, spreading, and uniform distribution in the targeted area. It is a mixture of two immiscible liquids stabilized by an emulsifier, soluble in the continuous phase

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The adoptability of the o/w or w/o type depends upon the use of nanoemulsion in the area of specific application. The emulsifier used is generally a surfactant, effective in the preparation of nanoemulsions. Surfactants play a major role in the deformation and breakup of droplets and prevent coalescence during emulsification. Surfactants are classified on the basis of hydrophilic-lipophilic balance. When dispersed oil droplets coated with surfactants come close to one another, then a thin film of water forms between the droplets. The similar charges of surfactant layers on the oil droplets repel each other. This phenomenon stabilizes the film rupturing of the oil droplet and does not allow the droplets to coalesce. The most effective surfactants are non-ionic surfactants used to emulsify o/w or w/o.

A transparent, thermodynamically stable mixture of two non-soluble liquids, such as oil and water, stabilised by an interfacial surfactant coating is referred to as a nanoemulsion. Using an emulsified oil and water system with a mean droplet size that spans from 50 to 1000 nanometers (nm), nanoemulsions are a revolutionary medication delivery technology. Submicron-sized colloidal particle systems called nanoemulsions are composed of two immiscible liquids, such water and oil, and are stabilized by an interfacial film formed of the right co-surfactant and surfactant to form a single phase. [1]

For the formulation of nanoemulsions, high energy consumption is the major constraint during methods such as microfluidization, high-pressure homogenization, and ultrasonication. Conversely, low-energy methods, i.e., phase transition temperature, phase inversion composition, microemulsion dilution, and phase emulsification method, consume significantly less energy for the formulation of nanoemulsions. The property of the formulated nanoemulsion is determined by various characterization techniques. These characterization methods analyze the droplet size and shape, rheology, and system stabilizing factors, i.e., conductivity, pH, and zeta potential. Though nanoemulsions are kinetically stable, destabilization mechanism such as flocculation, coalescence, ostwald ripening and creaming might lead to phase separation.

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2. AIM, OBJECTIVE AND NEED OF STUDY:

The aim of the study Formulation and evaluation of nanoemulsion for topical drug delivery system using model drug.

OBJECTIVES –

1. To increase the solubility of a drug by nanonization.
2. To increase therapeutic effect at targeted site.
3. To enhance skin penetration and permeation for topical application.
4. To improve patient compliance

3. DRUG PROFILE

IUPAC name: (RS)-1-(2-(2,4-Dichlorobenzyloxy)-2-(2,4-dichloro phenyl) ethyl)-1H imidazole

Brand name: Aloe Vesta 2-N-1 Antifungal.

Chemical name: 1-[(1RS)-2-(Dimethyl amino)-1-(4- hydroxyphenyl) ethyl] cyclohexanol succinate monohydrate

Molecular formula: $C_{18}H_{14}Cl_4N_2C.\ HNO_3$

Molecular weight: 416.129 g/mol

Physical Properties: A white or almost white, Crystalline, or micro-crystalline powder

Melting point: 184-185 °C

Pharmacokinetics:

After application to the skin, miconazole can be measured in the skin for up to four days, but less than 1% is absorbed into the bloodstream. When applied to the oral mucosa (and possibly also for vaginal use), it is significantly absorbed. In the bloodstream, 88.2% are bound to plasma proteins and 10.6% to blood cells. The substance is partly metabolized via the liver enzyme CYP3A4 and mainly eliminated via the faeces.

Uses:

Miconazole topical (for the skin) is used to treat skin infections such as athlete's foot, jock itch, ringworm, tinea versicolor (a fungus that discolors the skin), and yeast infections of the skin.

4. EXCIPIENTS PROFILE:

Table no:1 Excipients profile

Excipient	Use
Oleic acid	Oil
Tween 80	Surfactant
Propylene Glycol	Cosurfactant
Methyl Paraben	Preservative
Methyl Cellulose	Thickening agent

5. MATERIALS AND METHOD:

5.1 Analytical chacterization of drug sample:

The drug solution (2, 4, 6,8,10µg/ml) in Phosphate buffer of pH 7.4 was taken. From the stock solution 0.2ml solution was pipetted out in 100ml calibrated volumetric flask and final volume was made up to 100ml with phosphate buffer 7.4 to obtain stock solution of 2µg/ml concentration, from this solution 0.2ml, 0.4ml, 0.6ml, 8ml, 10 ml was pipetted out in different 100ml volumetric flask respectively and final volume as made up to 100ml with phosphate buffer of pH 7.4 to obtain concentration 2µg/ml concentration, and its concentration is determined by UV-spectrophotometer at

274 nm phosphate buffer pH 7.4 as blank by UV spectrophotometric method. A graph is plotted by using concentration at X-axis Vs absorbance at Y-axis.

5.2 FT-IR SPECTROSCOPY:

Drug Excipient Interaction Study was carried out to check the interaction between the drug and mixture of nanoemulsion by using FT-IR spectrophotometer. The mixtures of Miconazole Nitrate nanoemulsion and plane drug Miconazole Nitrate were placed separately on the sampling plate of FT-IR spectrophotometer.

5.3 Preparation of Nanoemulsion:

Miconazole Nitrate used as an API, Propylene Glycol as co-surfactant, Tween 80 as surfactant, Methyl Paraben as preservative, Methyl Cellulose as a thickening agent

Table No.02: List of Materials used for formulation

Ingredients	Use
Miconazole Nitrate	Drug
Oleic acid	Oil
Tween 80	Surfactant
Propylene glycol	Co-surfactant
Methyl cellulose	Thickening agent
Methyl paraben	Preservative
Distilled water	-

Table No.3: Composition of Nanoemulsion according to Plackett Bhurman

Sr.no	Formulation	Miconazole Nitrate (mg)	Tween 80 (ml)	Propylene Glycol (ml)	Oleic oil (ml)	Distilled water (ml)
1	NE-1	100	18 +1	6 +1	8 0	100
2	NE-2	100	15 0	5 0	8 0	100
3	NE-3	100	18 +	5 0	8 0	100
4	NE-4	100	15 0	6 +1	8 0	100
5	NE-5	100	21 +1	6 +1	8 0	100

Method:

High-Pressure Homogenization:

Nanoemulsion preparation required high pressure homogenization. In this method high-pressure homogenizer/ piston homogenizer is used to produce nanoemulsions of extremely low particle size (up to 1 nm). During this process, several forces, such as hydraulic shear, intense turbulence, and cavitation, act together to yield nanoemulsions with extremely small droplet size.[7]

Preparation of Nanoemulsion:

1. Oil phase: oil (oleic acid) and drug (Miconazole Nitrate).
2. Aqueous phase: Water.
3. Emulsifying agent: Surfactant (Tween 80) and cosurfactant (Propylene glycol)

Make the oil phase by adding the Miconazole Nitrate drug into oleic acid as an oil, and this is stirred with a magnetic stirrer to get a homogenous mixture, and then mild heating is done. Make an aqueous

phase by taking water into a suitable beaker, then mild heating the water. Make an emulsifying agent by taking Tween 80 as a surfactant and propylene glycol as a cosurfactant in a suitable beaker, making them homogenous in a magnetic stirrer, and then mild heating is done.

Next, the oil phase is added dropwise to the aqueous phase, then an emulsifying agent is added dropwise, and all this mixture is homogenized under high-pressure homogenization at 17000 RPM for 1 hr. until a transparent nanoemulsion is obtained.

5.4 Characterization of Nanoemulsion:

Measurement of Droplet Size:

The particle size of nanoemulsion was measured by photon correlation spectroscopy using a Zetasizer. Samples were diluted appropriately with the aqueous phase of the formulation to get optimum kilo counts per second (Kcps).

Drug Content:

Accurately weighed quantities of nanoemulsion were mixed with phosphate buffer using suitable solvent. The filtrate was analysed spectrophotometrically at 274 nm for drug content. Corresponding drug concentrations in the samples were calculated from the calibration plot generated by regression of the data. Drug content was calculated as detected amount of Naproxen with respect to theoretical amount of drug used for the preparation of Nano emulsion. Each determination was carried out.

In-vitro Drug Diffusion:

In vitro percent drug release studies were carried out by using franz diffusion cell. Cellophane membrane was used as filtration purpose. The Membrane was soaked in phosphate buffer for 12 hours before mounting it on cell. Miconazole Nitrate formulation was placed in the donor compartment and recipient compartment was filled with diffusion medium phosphate buffer pH 7.4. The content of the cell was stirred with the help of magnetic stirrer at 37ºC. Sampling was performed after 1, 2, 3, 4, 5h. Fresh phosphate buffer was placed at receptor compartment to maintain constant volume. Samples were analysed by spectrophotometrically at 274 nm.

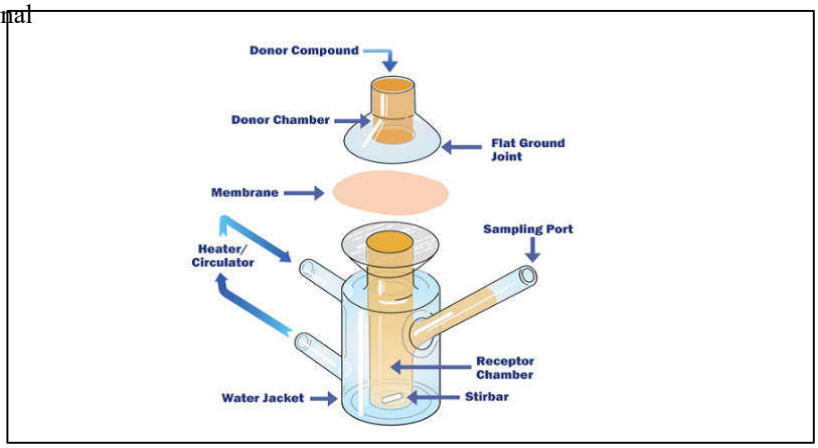

Fig No. 1: Franz Diffusion cell

6. RESULTS AND DISCUSSION:

6.1 Preparation of standard calibration curve of Miconazole Nitrate in buffer of pH 7.4:

Sr.no	Concentration (ug/ml)	Absorbance at 274 nm
1	10	0.104
2	20	0.198
3	30	0.301
4	40	0.391
5	50	0.492

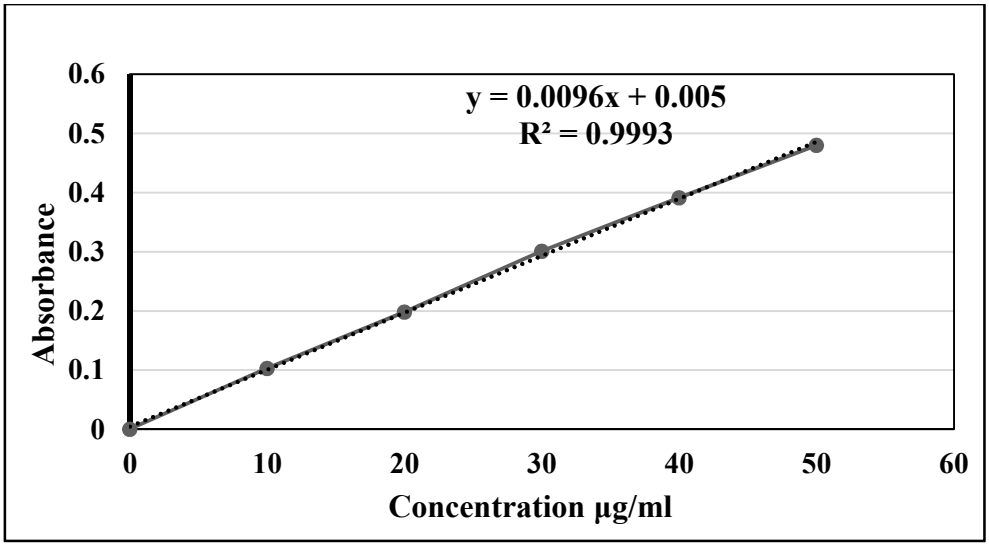

Figure No.2: Standard calibration curves of Miconazole Nitrate

6.2 Drug – Excipient Interaction Study:

Drug Excipients Interaction Study was carried out to check the interaction between the drug and excipients by using FT-IR spectrophotometer. Accurately weigh 10 mg of Miconazole Nitrate. The mixtures of Miconazole Nitrate Microemulsion and plane drug Miconazole Nitrate were placed separately on the sampling plate of FT-IR spectrophotometer. Then scanning of the sample was performed and IR spectra were obtained as shown in fig no. 3 & 4.

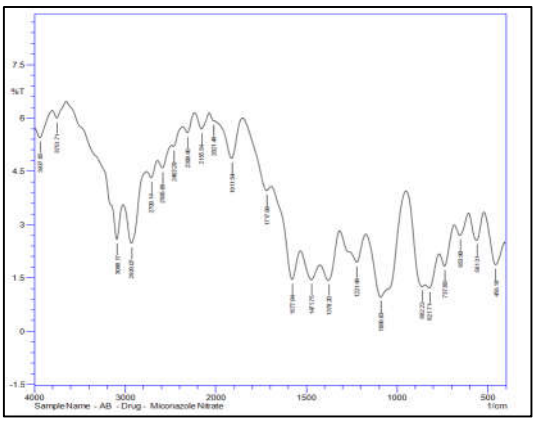

Fig No. 3: FTIR of Miconazole Nitrate

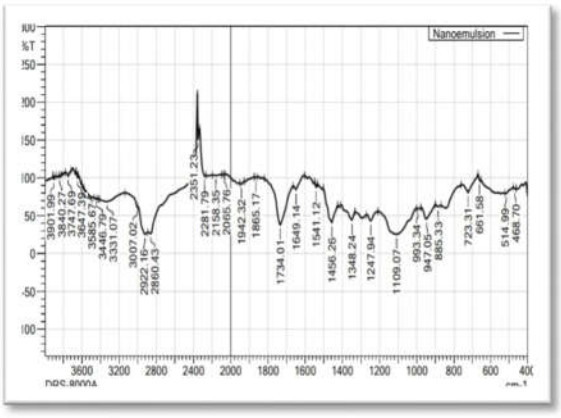

Fig No.4 : FTIR of Miconazole Nitrate Nanoemulsion

6.3 Evaluation of Miconazole Nitrate Nanoemulsion:

6.4.1 Droplet Size Measurements:

The mean droplet size was calculated from intensity, volume and bimodal distribution assuming spherical particles. Nanoemulsion had various average droplet diameters between 50 to 1000 nm. A small droplet sizes are very much required for drug delivery.

Table No.4: Particle Size of Prepared Formulations:

Formulations	Particle Size (nm)
F1	811.1 nm
F2	905.6 nm
F3	937.0 nm
F4	919.7 nm
F5	[i]258.8 nm

6.4.2 pH measurement:

Table No. 5: pH of Prepared Formulations

Formulation code	pH
F1	6.93
F2	6.94
F3	6.97
F4	6.87
F5	6.88

6.4.3 Density measurement (g/cc):

Table No. 6: Density of Prepared Formulations

Formulation code	Density (g/cc)

F1	1.03
F2	1.03
F3	1.03
F4	1.04
F5	1.05

6.4.4 Viscosity (cps) measurement:

Table No .7: Viscosity of Prepared Formulations

Formulation code	Viscosity (cps)
F1	40
F2	10.5
F3	30.1
F4	20.1
F5	50

6.4.5 Drug content (%) measurement:

Table No. 8: Drug content of Prepared Formulations

Formulation code	Drug content (%)
F1	52.5
F2	10
F3	29
F4	37.5
F5	70

6.4.6 In-vitro Drug Diffusion study:

In vitro percent drug diffusion studies were carried out. In- vitro percent drug release studies were performed for different formulations, which shows the controlled release of formulation F1, F2, F3,

F4, F5 and F1 and F5 shows higher rate of cumulative percent drug release of 75.52% and 100.78% in 5 hrs. The in-vitro release profile of Miconazole Nitrate nanoemulsion was represented in the table.

Table No.9: In-Vitro Cumulative Drug Diffusion study of Miconazole Nitrate Nanoemulsion of formulation F1-F5

Time(hr.)	0	1	2	3	4	5
F1 (%CDD)	0	35.59	51.22	66.49	69.97	75.52
F2 (%CDD)	0	26.69	44.53	46.22	46.88	49.22
F3 (%CDD)	0	32.45	33.85	37.86	41.07	56.09
F4 (%CDD)	0	19.13	37.50	38.44	50.86	56.02
F5 (%CDD)	0	65.63	75.00	82.97	91.41	100.78

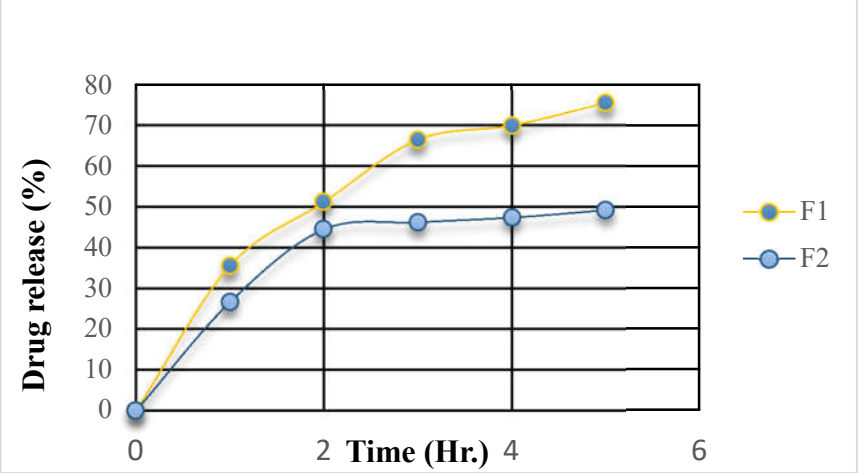

Figure No.5: Drug diffusion profile of nanoemulsion formulation F1 and F2

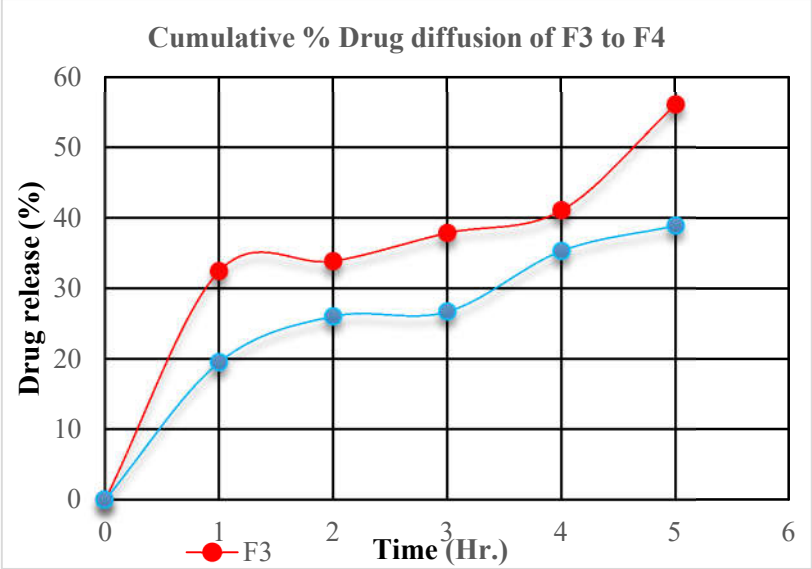

Figure No.6: Drug diffusion profile of nanoemulsion formulation F3 and F4

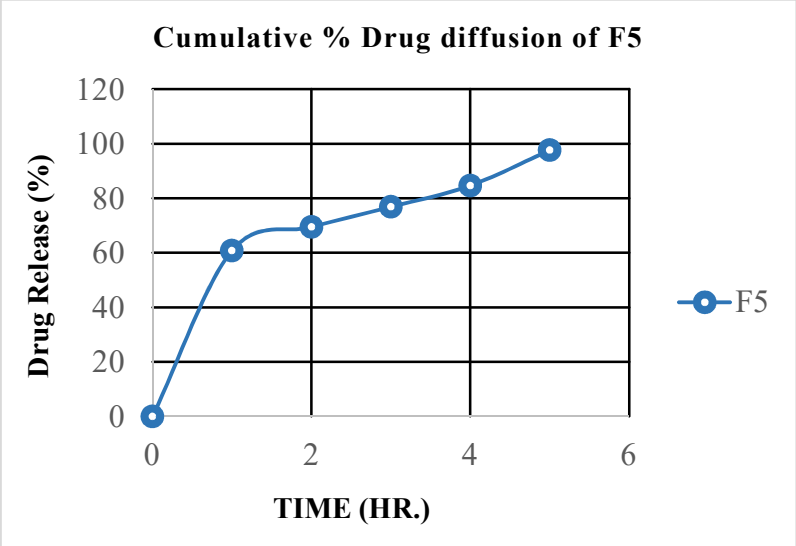

Figure No.7: Drug diffusion profile of nanoemulsion formulation F5

Conclusion:

The Lipid-based nanoemulsion was formulated to enhance the bioavailability by enhancing drug solubility. The current study showed that Miconazole Nitrate nanoemulsion formulation can be manufactured by using oleic acid, tween 80, propylene glycol methyl paraben, methyl cellulose. From the above obtained results and it was concluded that formulations prepared by the lipid were in nano range and can be formulated. The tests carried out shows that the mean droplet size was in the nanometer range and having good uniformity of diameter. The best formulation among all was found to be F5 on the basis of particle size of F5 (258.6 nm) and percent cumulative release of F5 (100.78%) having r^2 value 0.9993, therefore Miconazole Nitrate nanoemulsion using a lipid can be formulated.

ACKNOWLEDGEMENT:

We wish to acknowledge the support of Pataldhamal Wadhwani College of Pharmacy Yavatmal.

CONFLICT OF INTEREST: The authors have no conflict of interest.

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