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Design, Development and Evaluation of Nano-formulations for a New Class of Antifungals

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Abstract

The main objective of the study was to develop and evaluate nanoemulgel of Eberconazole for topical delivery in treating fungal infections. Nanoemulgel was prepared by nanoemulsion. For screening of nanoemulsion components, solubility of Eberconazole in various oils, surfactants and co-surfactants were done for their ability to nanoemulsify the selected oily phase. Of all the oils tested almond oil was chosen as suitable oil phase as it showed good solubilising capacity and excellent drug penetration. Drug loaded nanoemulsion was prepared using Span 20 as surfactant, PEG 400 as co-surfactant, Almond oil as oil phase and distilled water as aqueous phase by ultrasonic emulsification method. The formulations were evaluated for mean particle size, polydispersibility index, zeta potential by changing the process parameters. Nanoemulsion composed of oil (1%), surfactant (0.6%), co-surfactant (0.2%) and water (0.4%) was finally selected as optimized nanoemulsion. The optimized formulation had small average globule diameter of 387.3nmwith polydispersibility index of 0.492 and zeta potential of -29.5. This formulation was incorporated into gel. Prepared nanoemulgel was further studied for drug content, in-vitro drug release using Franz diffusion cell. The drug release from the formulation was found to be 15.29±0.20% at the end of 6 hrs. These results suggest that nanoemulgel can be used as potential vehicle for improved topical delivery of Eberconazole.

Keywords: Nanoemulsions, Eberconazole, Pseudo phase ternary diagram, Transdermal delivery, Penetration Enhancers, rheological property,

Introduction

Skin is the part of body with a large surface area and is prone for infection. Bacteria and fungi are the main causative agents for superficial skin infections. Once the skin is infected superficially, it progresses if the immune system is weak. Skin is the most easily accessible organ of human body. Superficial fungal infection is most common in tropical countries (1). An effective antimycotic agent is need of the hour to treat and cure fungal infections that has arise due to decrease in immunity power, changes in socio-economic states. Transdermal route helps to overcome disadvantages associated with oral and I.V routes (2). Nanoemulsions are stable and clear dispersions having droplet size between 20- 500nm. It consists of 2 immiscible liquids such as oil and water stabilised by interfacial film of surfactant and co-surfactant

molecules (3). It is considered as the one of the most promising drug delivery systems for drugs that has poor aqueous solubility in order to enhance its bioavailability, also it acts as a carrier for both hydrophilic and lipophilic drugs. As an ideal vehicle it offers high solubilization property, long shelf life, ease in preparation, low viscosity and smaller droplet size (<150nm) that delivers the drug in a more controlled manner (4).

Components of Nano-emulsion (5)

Oil phase

Viscosity, permeability, stability of nanoemulsion depends on selection of appropriate oil. Investigation has shown that vegetable oils form unstable nanoemulsion due to its poor emulsification ability but when oil with less hydrophobic property was used it had better emulsification property. Therefore, selection of appropriate oil is a necessary step in formulation development.

Surfactants

They act by enhancing the penetration of drugs through skin by reversibly binding to keratin filaments leading to disruption of corneocytes thereby altering diffusion co-efficient of stratum corneum. They are classified as non-ionic, anionic and cationic or zwitter ionic surfactants. Non-ionic surfactant has low toxicity and minimizes interference. Therefore, they are commonly used in transdermal nanoemulsions. They enhance drug absorption by first entering intercellular lipid region of stratum corneum, fluidizing, solubilizing and extracting the lipid components. Following this it penetrates intercellular matrix, interacting and binding with keratin filament resulting in disruption of corneocytes (6). Anionic surfactants enhance skin penetration of target molecules due to more powerful interaction with keratin and lipids. Cationic surfactant interacts with keratin fibrils and disrupts the cell lipid matrix**.** They interact with anionic components and alter the electronic properties of SC, enhancing the transfer of anionic drugs through the skin.

Co-surfactants

Chain length of co-surfactants affects the stability of nanoemulsion (7). Optimal selection of multiple co-surfactants improves the overall flux of drug without the necessity to use penetration enhancer. Medium chain alcohol forms stable oil droplets with less signs of phase separation whereas use of heptanol and hexanol having long chain alcohol in their structure results in separation of closed water domain inside a continuum of a hydrocarbon layer leading to less uniform and less organized micelle system. Co-surfactants act by reducing the interfacial tension and increasing the fluidity of the liquid-liquid interface by decreasing the bending stress. Density and viscosity of the nanoemulsion is highly influenced by the use of alcohol as a co-surfactant. Ethanol when mixed with wide range of surfactants increases the dissolving power of active compounds (8). The increased concentration of co-surfactant increases the interfacial tension and decreases continuously until a minimum above which it increases again.

Techniques for preparation of nanoemulsion (9).

High energy methods include High pressure homogenization., Microfluidisation and Ultrasonication. Low energy methods include Phase inversion emulsification method. Transitional Phase Inversion (TPI), Phase Inversion Temperature (PIT), Phase Inversion Composition (PIC), Catastrophic Phase Inversion (CPI), Emulsion Inversion Point. The self-nano-emulsification method.

Materials and Methods

Determination of λ_{max} of drug

A dilute solution of Eberconazole in ethanol: phospahte buffer (pH 6.8) was prepared and scanned for absorption maxima against blank between 200-400 nm using UV-visible spectrophotometer (UV-1601, Shimadzu, Japan). The maximum absorbance was found to be 212 nm.

Table1: List of materials used

SL. NO.	MATERIALS	SOURCE
1	Eberconazole	GlenmarkPharmaceuticals, India
2	Span20	SDfinechemicals,Mumbai, India
3	PEG 400	SDfinechemicals,Mumbai, India
4	Carbopol 934LR	HiMediaLab,Mumbai, India.
5	Almondoil	DaburIndiaLtd,Ghaziabad, India.

Calibration curve of eberconazole

Accurately weighed Eberconazole (25 mg) was transferred into a 25 ml volumetric flask, dissolved and adjusted the volume up to 25ml with ethanol to get stock solution A. From the stock solution A, 1 ml was pipetted out into a 50 ml volumetric flask and volume was made up to mark with ethanol to get stock solution B. From the stock solution B, known volume were pipetted out and made up to 10 ml with phosphate buffer (pH 6.8) in 10 ml volumetric flask to get 0.5-5 µg/ml concentration solutions and absorbance was recorded at 212 nm by UV-visible spectrophotometer (UV-1601, Shimadzu, Japan).

Table 2: Calibration curve of Eberconazole in ethanol

Sl. No.	Concentration (µg/ml)	Absorbance (at212nm)
1	0	0
2	0.5	0.111
3	1	0.214
4	1.5	0.298
5	2	0.401
6	2.5	0.48
7	3	0.589
8	3.5	0.683
9	4	0.783
10	4.5	0.88
11	5	0.998

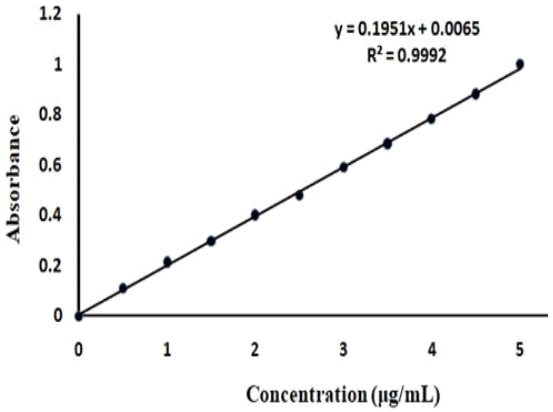

Figure1: Calibration Curve of Eberconazole in ethanol: phosphate buffer pH (6.8).

Preparation of drug solution

Drug solution was prepared by dissolving 100mg of drug in 10 ml alcohol and volume made up to 50 ml using phosphate buffer (pH 6.8).

Screening of oils

The screening of oils was performed by evaluating solubility of Eberconazole. Various oils like Castor, Almond, Eucalyptus, Coconut, Liquid paraffin, Olive and Mustard were selected for screening. 2ml of drug solution was added to 2ml of selected oils taken in separate volumetric flasks respectively. These flasks were kept in rotary shaker for 48 hrs for partitioning of drug between oil and water. Later the aqueous phase was removed, diluted with phosphate buffer (pH6.8) and absorbance was noted at 212 nm. The aqueous layer of oil that showed minimum drug content was selected as suitable oil for further studies.

Screening of oils

Table 3: Amount of free drug in aqueous phase obtained during screening of oils.

S. No	Oils	Amount of drug in aqueous phase (µg/ml)
1	Liquidparaffin	55.21±9.36
2	Almond oil	51.84±3.34
3	Castor oil	60.09±10.83
4	Mustardoil	61.74±6.30
5	Olive oil	63.45±5.26
6	Coconut oil	53.02±4.33
7	Eucalyptusoil	53.74±8.46
8	Groundnutoil	74.37±7.28

Screening of surfactants
Determination of absorbance

To 2 ml of selected oil, 2 ml of drug solution was added. To this, 2ml of various surfactants like Tween 20, 40, 80, Span 20 and 80 were added taken in separate volumetric flasks respectively. They were kept under shaking for48hrs in rotary shaker at120rpm. After 48hrs the supernatant aqueous phase was taken, diluted with phosphate buffer (pH 6.8) and absorbance determined at 212 nm using UV-Visible Spectrophotometer. The aqueous layer that showed minimum absorbance was selected as suitable surfactant.

Determination of %transmittance

The aqueous layer of surfactant was checked for percent transparency by diluting it with distilled water at 638nm against double distilled water as blank and the aqueous layer that showed maximum % transparency was selected as suitable surfactant for further screening.

Screening of co-surfactants
Determination of absorbance

To2ml of selected oil, 2ml of selected surfactant, 2ml of various co-surfactants like PEG200, PEG 400, ethanol, benzyl alcohol was added in volumetric flasks respectively. The flask was kept under shaking for 48 hrs at 120 rpm for complete solubilization of drug in the oil. The supernatant aqueous phase was diluted with phosphate buffer (pH 6.8) and absorbance was noted at 212 nm. The aqueous phase that showed minimum absorbance in aqueous phase was selected as suitable co-surfactant for preparation of nanoemulsion.

Screening of surfactants

Table 4: Concentration of drug in aqueous layer while screening of surfactants

S. No	Surfactants	Amount of drug in aqueous layer(µg/ml)
1	Tween20	55.74±6.83
2	Tween80	118.64±9.95
3	Tween40	76.96±8.92
4	Span20	51.61±5.02
5	Span80	65.47±10.97

Table 5: Percent transmittance against distilled water as blank at212nm

S. No	Surfactants	% Transmittance of surfactants
1	Tween20	67.23±3.40
2	Tween80	64.06±8.64
3	Tween40	65.83±7.35
4	Span20	71.73±2.04
5	Span80	63.66±5.50

Determination of percent transmittance

The aqueous layer was diluted with distilled water and examined for % transmittance at 638nm. The layer that showed maximum % transmittance was selected as suitable co- surfactant for optimization (26).

Optimization of selected components

Preparation of solutions

Preparation of 5% oil solution: 5ml of almond oil was diluted to 100ml using distilled water. Preparation of surfactant solution: 1, 2, 3, 4 and 5ml of span 20 was diluted with distilled water up to 100 ml taken in separate volumetric flask to get 1, 2, 3, 4 and 5% v/v solutions respectively.

Preparation of co-surfactant solution: 1, 2, 3 and 4 ml of PEG 400 was taken in 100 ml volumetric flask and volume made upto 100 ml with distilled water to get 1, 2, 3, 4% w/v solutions respectively.

Screening of co-surfactants

Absorbance of aqueous layer while screening of co- surfactants

Table 6: Determination of Amount of drug in aqueous layer(µg/ml)

S. No	Co-surfactants	Amount of drug in aqueous layer(µg/ml)
1	PEG 200	87.67±9.80
2	PEG 400	32.93±2.48
3	Benzyl alcohol	99.56±11.89
4	Ethanol	84.10±6.03
5	Propylene glycol	55.71±7.96

Table 7: Estimation of drug content in aqueous layer of prepared S_{mix}

S. No	S_{mix} (%)	Amount of drug content aqueous layer(µg/ml)
S1	0.4 :0.2	20.47±0.91
S2	0.6:0.2	4.06±0.68
S3	0.8:0.6	12.54±0.77
S4	1:0.6	9.46±1.20

Preparation of S_{mix}

Various S_{mix}were prepared having surfactant and co-surfactant in the ratio of (0. 8:0.6,0.8:0.4,0.8:0.6,0.8:0.2,0.6:0.4,0.4:0.2, 0.6:0.2,1:0.8,1:0.4,1:0.2,1:0.8, 1:0.6) % w/w. To this oil (1% w/w) and water (1% w/w) were added. The mixtures were kept under magnetic stirring for several hours. The obtained mixtures were centrifuged at 1200rpm for 15 min and kept aside for several days for sedimentation of oil droplets. The S_{mix} that showed no signs of separation were selected for determination of maximum drug content in oil phase.

Table 8: Preliminary studies of nano emulsion

S. No	Surfactant: Co-surfactant (%)	Oil (%)	Drug solution (%)	Water (%)
S1	0.4 :0.2	1	20	0.4
S2	0.6:0.2	1	20	0.4
S3	0.8:0.6	1	20	0.4
S4	1:0.6	1	20	0.4

Determination of %transmittance

The aqueous layer of surfactant was checked for percent transparency by diluting it with distilled water at 638nm against double distilled water as blank and the aqueous layer that showed maximum % transparency was selected as suitable surfactant for further screening.

Estimation of drug content in S_{mix}

The upper aqueous layer collected from various S_{mix} was checked for absorbance by diluting it with phosphate buffer (pH 6.8) using UV-Visible Spectrophotometer at 212 nm. The S_{mix} that showed minimum absorbance in aqueous phase and maximum drug content in oil phase was selected as suitable S_{mix} for formulation development.

Development of nano emulsion

The nanoemulsion was developed by varying volume of S_{mix} components. These emulsions were subjected to magnetic stirring for several hours and the nano emulsion that had no phase separation or sedimentation of oil droplets was selected to carry out effect of rheological properties.

Characterization of nanoemulsion

Particle size and Poly dispersity index (PdI) of the Nanoemulsion were measured by dynamic light scattering technique using Malvern Zetasizer Nano ZS (Malvern Instruments, UK) at 25°C. Zeta potential (ZP) of the nanoemulsion was also measured by the same instrument. Before measurement, then a noemulsion was appropriately diluted to yield asuitablescattering intensity with ultra-pure water. For Particle size (PS) and Polydispersity index (PdI) measurements, the diluted nanoemulsion was poured into the disposable sizing cuvette which was then placed in the cuvette holder of the instrument and analyzed using the zetasizer software (DTS v 7.11, Malvern Instruments, UK). For zeta potential measurement, disposable folded capillary cuvette was used

Stability of prepared nanoemulsions

The nanoemulsion that passed the evaluation test were subjected to stability studies. The prepared formulations were maintained for 1 month at various temperatures like 25±1ºC and 40±1ºC and the formulations that were stable having no sign of phase separation, creaming or cracking were taken for gel preparation.

Preparation of nanoemulgel (10)

Topical nanoemulgel was prepared using carbopol 934 LR as gelling agent. TheF6 (5ml) was added for 10g of topical nanogel and pH of all nanoemulgel was adjusted to 7.4 using 1N sodium hydroxide i.e pH near to skin. The batches were prepared by changing concentration of gelling agent. The concentration of carbopol 934LR as 1%, 2%, 3%, 4% and 5% was used in formulation batches. The obtained topical nanogel was then evaluated for pH, moisture content and spread ability. The nanogel that had good spreading capacity and minimum loss of moisture was taken for drug content determination and in vitro drug release study.

Characterization of prepared nanoemulgel Determination of pH

pH was measured by using digital pH meter (Elico Ltd, Bangalore). One gram of topical nanogel was transferred to 20 ml purified water. The electrode of pH meter was dipped into topical nanogel and pH was noted.

Spread ability

The spread ability of topical nanogel was measured by using 2 glass slides (15×10 cm^2). One-gram topical nanogel of each batch were placed between 2 slides and left for 1 minute by applying a weight of 250g. Diameter of spread circle of topical nanogel measured and compared with each other.

Moisture content determination

Before carrying out the study, the initial weight of empty petri plates was noted. To this one gram of prepared nanoemulgel (3 and 4 and 5%) was added taken in separate petri plates respectively. The initial weight of petri plate with nanoemulgel was noted. It was kept aside for a period of 5 days and again the weight of petri plates was rechecked. The % of moisture content was determined by applying suitable formula the gel that had maximum % of moisture content in it was selected for further studies.

%Moisture content=(W_2-W_3/W_2-W_1) ×100
Where, W_1 = weight of empty petri plates. W_2=initial weight of petri plates with gel, W_3= weight of petri plates with gel after period of 5 days.

Table 9: Effect of ultrasonication time and energy on particle size, poly dispersibility index and zeta potential.

Formulation	Globule size (nm)	Poly dispersibility Index (PDI)	Zeta potential (mV)
F1	1112	0.363	-41.3
F2	2329	0.124	-44.5
F3	3903	1.000	-43.0
F4	192.4	0.234	-8.16
F5	258.5	0.241	-0.785
F6	387.3	0.492	-29.5
F7	546.7	0.459	-25.6
F8	414.4	0.401	-26.2

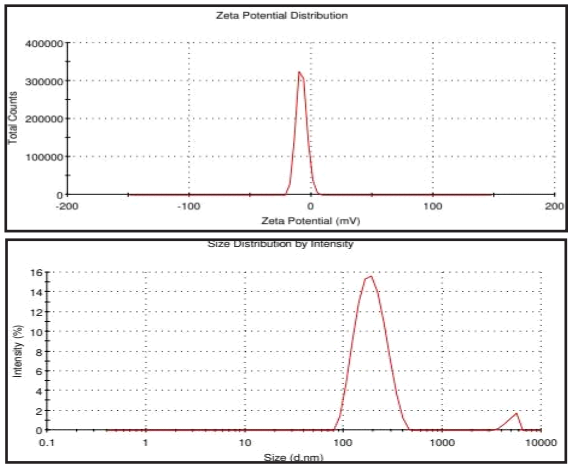

Figure 2: Characterization of optimized nano-emulsion formulations F2 and F5(XRD)

Figure 3: Images of prepared nano-emulsion formulations F2 and F5.

In-vitro drug release study:

Preparation of phosphate buffer saline(pH6.8):

Accurately weighed 22.8 g of disodium hydrogen phosphate, 11.4 of potassium dihydrogen phosphate were dissolved in 1000ml of distilled water in a volumetric flask (34).

Diffusion study

The analysis carried out using Franz diffusion cell assembled with a semipermeable membrane. The cells were filled with the release media 7ml of phosphate buffer saline(pH6.8) having 1% of tween 80. Tween 80 a surfactant, was added to the media to increase the solubility of the drug. Formulations like nanoemulgel (1g), nanoemulsion (1ml) and drug solution (1ml) were placed in donor compartment respectively and receptor compartment was filled with phosphate buffer media (pH 6.8). A diffusion membrane was placed between two compartments and the whole setup was tightened with a clamp. The diffusion studies were performed at 37±1ºC agitated at 300rpm. The samples were collected at predetermined time intervals 0.5,1,2,3,4,5 and 6 hrs and replaced with the fresh media. The volume of obtained samples were made upto 10ml using phosphate buffer (pH 6.8). Then the samples were analyzed by UV-Visible spectroscopy at 212 nm for the estimation of Eberconazole.

Drug content determination

Topical nanogel (1 g) was weighed and dissolved into 10 ml ethanol. It was sonicated for 15 min to dissolve the Eberconazole completely into ethanol. The solution was filtered through whatmann filter paper and 1ml of resultant filtrate was diluted with phosphate buffer (pH 6.8) upto 10ml. The aliquot subjected for estimation of drug at wavelength 212 nm using UV- Visible spectrophotometer and drug content was calculated.

Table 10: In-vitro drug diffusion studies for various formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	0.43±0.21	0.49±0.34	0.51±0.58	1.29±0.47	1.89±0.57	2.30±0.38	2.17±0.31	2.23±0.73
1	2.82±0.34	2.89±0.14	3.81±0.53	4.29±0.54	4.98±0.78	5.58±0.45	5.3±0.47	5.2±0.87
2	4.45±0.42	4.87±1.24	5.47±0.83	6.39±0.04	6.78±0.48	8.07±0.48	7.89±0.71	8.04±0.39

3	5.49±1.24	6.18±1.84	7.25±0.91	7.58±1.83	9.08±1.68	11.54±1.49	10.59±0.96	11.05±0.87
4	7.87±2.65	8.28±0.91	9.03±0.78	9.87±1.59	11.84±1.54	14.54±2.19	13.59±0.57	13.98±0.54
5	8.59±0.64	10.12±0.27	11.57±0.35	13.87±1.53	15.49±2.04	18.49±5.17	17.84±0.18	17.59±0.39
6	9.45±1.40	12.54±0.71	13.58±1.48	15.56±1.85	18.49±0.97	24.03±482	21.59±1.81	21.87±0.84

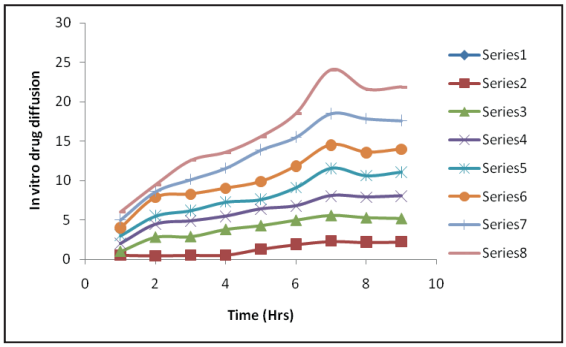

Figure 4: Cumulative % drug release of various formulations

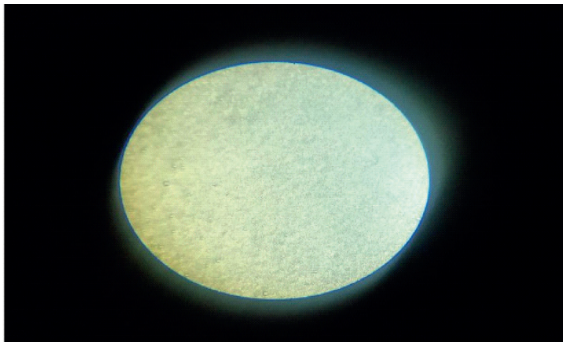

Figure 5: Image of droplet size of nano-emulsion when observed under 40X after 1 cycle of ultrasonication

Table 11: pH, %Moisture content and spreadability of Nanoemulgels

S. No	Formulations	pH of the formulation	%Moisture content	Spreadability (cm)of Formulation
1	NG1	7.23±0.2	178.93±0.13	5.41±0.15
2	NG2	6.91±0.1	116.54±0.26	4.33±0.1
3	NG3	6.96±0.15	109.2±0.32	3.76±0.17

Table12: Table Determination of drug content

S. No	Formulation	Drugcontent (µg/g)
1	Nanoemulgel (3%)	102.42±1.34

Table 13: Amount of drug diffused from different formulations

Time (hrs)	% Cumulative drug release		
	Nano-emulgel	Drug solution	Nano-emulsion
0	0	0	0
0.5	1.29±0.08	0.53±0.14	2.30±0.38
1	2.84±0.09	0.89±0.47	5.58±1.45
2	4.68±0.06	2.37±0.38	8.07±1.46
3	6.86±0.03	3.53±0.45	11.54±2.19
4	9.38±0.01	4.85±0.66	14.55±3.86
5	12.25±0.06	6.67±1.05	18.49±5.17
6	15.29±0.20	8.92±1.58	24.03±4.82

Mechanism and kinetics of nanoemulgel.

Table 14: Mechanism and kinetics of *in-vitro* drug release study of nanoemul gel

Mechanism and kinetics of *in-vitro* drug release study of Nano-emulgel.			
Regression co-efficient(R^2)			**Korsmeyer- Peppa's equation (n)**
Zeroorder	**Firstorder**	**Higuchi**	
0.996	0.903	0.906	0.928

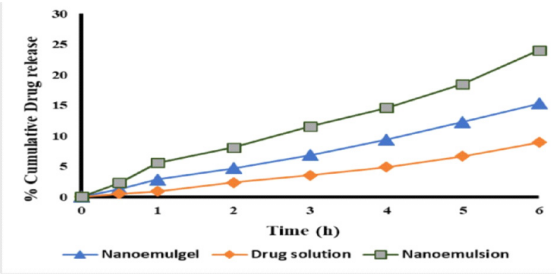

Figure 6: Cumulative % drug of various formulations.

Results and Discussion:

The aim of the current study was to develop the Eberconazole nano emulgel for the topical application to treat fungal infections. Components like oils, surfactants and co-surfactants were screened before preparing nanoemulsion. The selected components were optimized to prepare suitable emulsion with no signs of phase separation. Later, the nanoemulsion was developed by ultrasonic emulsification method. Prepared nanoemulsion was subjected to change in process parameters. The effect of these parameters was noted on prepared nanoemulsion. The nanoemulsion was converted to gel using suitable gelling agent and the prepared gel was subjected to evaluation tests.

Standard plot of Eberconazole was constucted plotted using mixture of ethanol and phosphate buffer (pH 6.8) as solvents it satisfies the Beers lamberts law with the regression coefficient value 0.9989. Maximum solubility was observed in the selected surfactants and cosurfactants with their screening methods at its ratios selected. Various S_{mix} were prepared by changing the percent ratio of surfactant and co- surfactant. Out of all S_{mix} the emulsion containing surfactant and co-surfactant in the percentage ratio of (0.4:0.2, 0.6:0.2, 0.8:0.6 and 1:0.6) were found to be stable. The S_{mix} that showed minimum drug content in aqueous phase and maximum drug content in oil phase was selected for formulation development. Formulation development was carried out by varying volume of selected S_{mix} ie by changing the volume of different components. Preparation of nanoemulsion was carried out by adding aqueous phase containing surfactant and co-surfactant in distilled water to oil phase to prepare o/w nanoemulsion.

Effect of various process parameters were carried out i.e effect of time and effect of energy on prepared nanoemulsion was carried out to determine effect of these parameters on particle size, polydispersibility index and zeta potential. The optimized nanoemulsion was converted to gel using suitable gelling agent. The prepared nanoemulgel was characterized for pH, drug content, moisture content, spread ability and in-vitro drug release. The gel that showed good in-vitro drug release and had good drug content required for topical application was considered as final formulation.

Conclusions

The present investigation demonstrated that optimsed nanoemulsion drug delivery system of Eberconazole can be prepared from almond oil (oil), tween 20 (surfactant) and PEG400 (co-surfactant). The formulations showed excellent physicochemical properties and the effect of process variables were also

evaluated. Optimized nanoemulsion formulae were incorporated in carbopol based gel. In vitro diffusion study results revealed that nanoemulsion based carbopol gel formula which consisted 40% Eberconazole, 3% carbopol gel, 0.4% water, 1% oil and 0.6:0.2% S_{mix} exhibited the required permeability of nanoemulsion based gel formulae and also had maximum drug content. These results indicated that nanoemulgel can be used as promising drug delivery to treat fungal infections. The aim of the current study was to develop the Eberconazole nanoemulgel for the topical application to treat fungal infections. Components like oils, surfactants and co-surfactants were screened before preparing nanoemulsion. The selected components were optimised to prepare suitable emulsion with no signs of phase separation. Later, the nanoemulsion was developed by ultrasonic emulsification method. Prepared nanoemulsion was subjected to change in process parameters. The effect of these parameters was noted on prepared nanoemulsion. They converted to gel using suitable gelling agent and the prepared gel was subjected to evaluation tests. the results showed proof of the aim.

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