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FORMULATION AND EVALUATION OF BIFONAZOLE NANOEMULGEL FOR TOPICAL DELIVERY

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ABSTRACT

Emulgels are emulsions, either of the oil-in-water or water in-oil type, which are gelled by mixing with a gelling agent. This study is to investigate the potential of Nanoemulgel formulation to improve the controlled release of Bifonazole (BIF). Bifonazole is an antifungal drug used to treat various fungal infections like Tenia pedis etc. Nanoemulsion were formulated by highspeed homogenization technique by using oleic acid as oil, Tween 80 as surfactant, Isopropyl Alcohol as co-surfactant. The resultant Nanoemulsion were characterized by Particle size, Zetapotential, Drug content, In-vitro drug release. Best formulation F2 showed particle size of 33.37nm, Zeta potential of -21.2mV and a maximum drug release of 79.17% in 7 hours. The best formulation F2 was choosen based on the particle size and drug release, which is then incorporated to carbopol 934 gel for the proper feasibile application to the skin. The prepared gel was evaluated for its parameters like Physical apearene, pH, drug content, spreadablity, viscocity, Invitro diffusion studies and kinetic studies. Result revealed that the formulation F2 having 90.98% of drug content, cumulative drug release of 82.55% with a spreadability of 19.03. The results obtained suggest that the Nanoemulgel could be an efficient carrier for topical application in the treatment of fungal infection like Tinea pedis etc.

KEYWORDS: Emulgel, Topical drug delivery, Emulsion based gel formulation and Evaluation.

INTRODUCTION

Novel drug delivery systems (NDDS) are crucial in pharmaceutical R&D due to their lower development costs and timeframes compared to new chemical entities. NDDS development typically costs $20-50 million and takes 3-4 years, whereas new chemical entities can cost $500 million and take 10-20 years. NDDS focus on designing systems for new and established drugs, enhancing commercial viability. Significant advancements have occurred in NDDS over the past three decades. Controlled and sustained drug delivery systems, like emulsions and gels, play major roles.

Emulsions facilitate controlled drug release by transferring drug particles from internal to external phases, acting as reservoirs. Gels, with their cross-linked networks, provide controlled drug release and extended skin contact. However, gels face limitations in delivering hydrophobic drugs, addressed by novel formulations like emulgels.[2]

Nanoemulgels combine the properties of emulsions and gels by gelling water-in-oil or oil-in-water emulsions with a gelling agent. This dual-control release system enhances stability and allows for thixotropic, biofriendly, easily removable, spreadable, non-staining, and transparent formulations. With emollient qualities, long shelf life, and anti-inflammatory effects, they utilize nanoparticles for pharmaceutical delivery, particularly via topical routes.

Nanoemulgels offer advantages over vesicular and conventional systems, finding extensive applications in dermal health and cosmetic formulations.[6]

Emulgels combine gel and emulsion, utilizing both types for delivering medications to the skin. Their properties include thixotropy, ease of spreading and removal, emollience, and longer shelf life.[7]

Topical drug delivery is the simplest and easiest route of delivery of drugs through localized action, by different routes such as rectal, vaginal, ophthalmic and skin. Through topical delivery, drug absorption is enhanced through skin when the drug is in solution form and if it has suitable water partition coefficient. Topical formulations vary in their physicochemical nature, from solid to semisolid to liquid. Semi-solid formulations, in all of their variations, dominate the topical distribution mechanism.[8]

These topical formulations can also be used as barriers for the skin such as sun screening agents which protect the skin from harmful ultraviolet radiation and many emollient preparations which restore the liability to a desiccated horny layer. Since There are many steps which are involved in percutaneous absorption which mainly include the establishment of a concentration gradient which is the main driving force for the drug movement across the skin, drug diffusion across the layers of the skin (diffusion coefficient) and release of drug from the vehicle (partition coefficient). The topical drugs need to have ideally low molecular mass (600Da), adequate solubility in oil and water, and a high partition coefficient. But there are a few molecules which do not penetrate the stratum corneum such as very small particles, water soluble ions and polar molecules.[9]

Drug absorption through the skin is augmented if we have the drug substance in the solution form or if the lipid/water partition coefficient is favourable and the last criteria could be that it is a non- electrolyte. Antiseptics, antifungal agents, skin emollients and protectant are some of the type of drugs which are used for their localized actions. There are many advantages of topical drug delivery systems such as avoidance of first pass metabolism and gastrointestinal incompatibility.[10]

MATERIALS AND METHODS

Materials: Bifonazole, Tween80, Span80, Tween20, Isopropyl alcohol, poly ethylene glycol 400, oleic acid, caproyl oil, carbopol 934, HPMC K100M, Methyl paraben.

Methods

Preformulation Studies

A. **Evaluation test for emulsion containing Bifonazole**[11]

1. Physical examination:

The prepared nanoemulsion formulation were visually examined for their appearance, phase separation, grittiness, homogenity and consistency.

2. Centrifugation stability study

Nanoemulsion were diluted with purified distilled water. Then nanoemulsion were centrifuged at 1000 rpm for 15 minute at 30°C and observed for any change in homogenecity of nanoemulsions.

3. Zetapotential

Measurement of zetapotential of the emulsion was done by using Malvern nano zeta sizer instrument. Measurements were performed on the samples prepared for size analysis. Zetapoetntial indicates the degree of repulsion between adjacent, similarly charged particles in dispersion system.

4. Measurement of pH

The pH of nanoemulsion formulation were determined by using digital pH meter. 1 ml of nanoemulsion was dissolved in 100 ml of distilled water and pH was determined.

5. Drug content determination

The drug content of emulsion was measured using UV-Visible spectroscopic method. The 2µg/ml of aliquot was prepared using nanoemulsion formulation using methanol. The sampl at ƛmax were measured. Results were taken in triplicate.

6. Globule size determination

The globule size of the nanoemulsion was measured by Malvernzeta sizer. The nanoemulsion (1-1.5 ml) was transferred to a disposable polystyrene cuvette with the help of plastic syringe or micropipette and the droplet size of the nanoemulsion wasdetermined.

7. *In-vitro* drug diffusion study of emulsion

The franz diffusion cell (with effective diffusion area 3.14 cm2 and 110 ml cell volume) is used for the drug release studies. Nanoemulsion (5ml) was taken in cellophane membrane. The cellophane membrane was clamped between donor and receptor chamber of diffusion cell. The receptor chamber was filled with mixture of freshly prepared 25 ml phosphate buffer (pH 7.4) and methanol (80:20) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples is collected at suitable time interval and sample was analyzed for drug content by UV visible spectrophotometer at λ_{max} after appropriate dilutions.

FORMULATION OF GEL CONTAINING EMULSION

Based on the results, the emulsion with best particle size and *invitro* diffusion rate choosen for converting in to gel. Carbopol 934 forms very good consistency transparent gel at low concentration. 1% carbopol gel base was prepared by dispersing the required amount of carbopol934 in 5 ml hot distilled water. The mixture was stirred until thickening occurred and then neutralized by the drop wise addition of 0.5 ml triethanolamine to achieve a transparent gel. Added the prepared gel to the selected nanoemulsion formulation to get the Nanoemulgel.[12]

B.CHARACTERIZATION OF EMULGEL

1. Measurement of pH: The pH of nanoemulgel formulation was determined by using digital pH meter.1 gm of gel was dissolved in 100 ml of distilled water, it was placed for 2 hr and pH was determined.

2. Rheology study: The viscosity of the formulated batches was determined using a Brookedfield Viscometer with spindle 64. The formulation whose viscosity was to be determined was added to the beaker. Spindle was lowered perpendicular in to the centre of nanoemulgel taking care that spindle does not touch bottom of the adapter and rotated at a speed between 100 rpm for 10 min.

3. Spreadability: The spreadability of the gel formulation was determined by taking two glass slides (14*5cm) of equal length. On one glass slide, 1gm gel was applied. To the other slide, weights (125g) are added and the time taken for the second glass slide to slip off from the first glass slide was determined. A shorter interval indicates better spreadability.[13]
Spreadability was calculated byusing the formula, **S=M*L/T**

Where, S = spreadability, M = Weight kept on upper slide, L = Length of glass slides, T = Time taken to slip off the slides completely from each other.

4. Drug content: The drug content of emulsion was measured using UV-Visible spectroscopic method. The 1 g of emulgel is dissolved in 100 ml methanol, from this 1 ml was makeup to 10 ml using methanol The sampl at λmax were measured. Results were taken in triplicate.
Amount of drug = concentration from the standard graph/1000× DF

5. In-vitro diffusion study: *In vitro* diffusion studies were performed by using a franze diffusion cell with a receptor compartment capacity of 50ml. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated gel of 1gm was placed over the drug release membrane (In the donor compartment) and the receptor compartment of the diffusion cell was filled with 25 ml of phosphate buffer pH 7.4 and methanol (80:20). The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37 ± 0.50C by surrounding water in jacket. The samples of 1ml were withdrawn at time interval of 1, 2, 3, 4, 6, 8 and 8 hours and analyzed for drug content UV. Spectrophotometrically at 254.5nm against blank.[14]

6. Kinetic studies: To analyze the mechanism of drug release from the topical gel, the release data were fitted to Following equations.

a. Zero order kinetics: Drug dissolution from pharmaceutical dosage forms that release the drug slowly, assuming that The area does not change and no equilibrium conditions and are represented by the equation: $Qt = Q_0 + K_0 t$ Where Qt is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution K_0 is the zero order release constant.

b. First order model: The application of this model to the drug dissolution studies used to describe absorption and/or elimination of drugs. To study the first order rate kinetics the release rate data were fitted into the following equation. $Log\ QT = \log Q_0 - K_1 t / 2.303$ Where Qt is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution, K_1 is the first order rate constant.

RESULTS AND DISCUSSION

PREFORMULATION STUDUES OF BIFONAZOLE

1. Organoleptic characteristics: Organoleptic characteristics like general description, colour was determined. It was found that Bifonazole is White crystaline powder and the results obtained were shown in table No. 5.

2. Melting point: The study was carried out and found that the drug melted at 146˚C which is within the reported range of 145-150˚C and indicating that the drug is pure. The results obtained were shown in table No. 5.

3. Solubility: Bifonazole was found to be insoluble in water, soluble in phosphate buffer pH 7.4 (1.9123gm/ml) and methanol (2.035mg/ml). Solubility of bifonazole in all the solvents was within the reported literature limits. The results obtained were shown in table No.5.

4. Determination of λmax: The absorption spectrum of pure Bifonazole was scanned between 200-400nm. The λmax of pure Bifonazole was found to be 254.5 nm by using Methanol and phosphate buffer pH 7.4. The curves obtained were shown in figure No.6.

5. Standard calibration curve of Bifonazole Table No. 6 shows the absorbance of Bifonazole at concentration ranging from 2- 10µg/ml in phosphate buffer pH 7.4. Figure No. 7 shows the standard calibration curve of Bifonazole in phosphate buffer, which was found to be linear with values 0.2012,0.3589,0.5311,0.6893,0.8437 and 0.0838 as slope and regression value 0.9983 for phosphate buffer pH 7.4 respectively.

6. Compatibilty studies The IR spectra of the Bifonazole was compared with the mixture of drug and polymer and the characteristic peaks associated with specific functional groups and bonds of the molecule and their presence/ absence were noted in table No. 7 and the overlay of pure drug and mixture was shown in figure No. 8 & 9. The prominent peaks associated with C=C stretch (1620--1680), Aromatic C-H stretch (3000-3100), Aliphatic C=H stretch (2850-3000), C-H deformation (1350- 1480) were analysed. The range of peak values were found to be the same indicating that there were no interaction of Bifonazole with polymer conforming the stability of drug in the formulation.

7.Pseudo Ternary Phase study Pseudo-ternary phase diagram were constructed using water titration method .Selected surfactant and co-surfactant was mixed in different volume ratios(1:1).Oil and surfactant/co-surfactant(Smix)is mixed thoroughly in different volume ratios(1:9,2:8,3:7,4:6,5:5,6:4,7:3,8:2,9:1)Titrated with water by drop wise addition under gentle agitation. 1:1Ratio found as a ratio for Nanoemulsion, and 5 clear nanoemulsion region were found in Table No: 8. Experiment method is given in Fig No: 11.Pseudo-

ternary phase diagram was constructed using Microsoft excel in Fig No: 10.

2. EVALUATION OF BIFONAZOLE NANOEMULSION

1 Physical Examination: Appearance of the 5 formulation was shown as light yellow colour (F1-F5). No phase separation was found in all formulation. F2 showing excellent homogeneity while F1, F3, F4, F5 are in good homogeneity shown in Table No: 9.

2. Average particle size Particle size analysis of Emulsion was determined using Malvern zeta sizer instrument. The results showed that emulsion which is undergone more homogenization, then the particle size decreases. The table no: 10 shows that the particle size of formulation F1-F5 that is 35.89nm, 33.37nm, 35.94nm, 78.12 and 112.15 nm, from which F2 (33.37) was lesser than other formulation. Fig.No.12 shows that the average particle size of selected F2 was approximately 33.37nm.

3. Zeta potential: Zeta potential of the Bifonazole Nanoemulsion F2 was determined by Malvern nano zeta sizer instrument. It was found that zeta potential of all formulation was negative i.e -21.2mV Negative potential indicates that the particles have no charge as a whole system is stable.

4. Centrifugation study, pH, Drug content: After centrifugation study five formulation (F1-F5) was found with no phase separation and pH was found in the range of 6.09-6.30. Drug content of each formulation was found to be F1 (75.12) F2 (93.22) F3 (82.5) F4 (86.12) F5 (78.46) in table No: 12.

5. In-vitro drug release from Emulsion: In-vitro drug dissolution profiles of Emulsion were observed by Franz diffusion method. The results obtained for all formulations (F1 –F5) were shown in table No.13 and fig.No.14. The cumulative percent drug release after 12 hours were found to be 76.11±0.93, 79.71±0.49, 75.99±0.9, 76.01±0.78, 74.16±0.82 respectively.

Formulation F5 showed least percentage cumulative drug release value 74% at 7 hrs and formulation F2 showed highest percentage of drug release value 79.71% at 7 hrs. As expected all formulations (F1 –F5) were shows controlled drug release for 7 hours.

3. EVALUATION OF EMULGEL

1. Physical examination: The prepared Emulgel formulations were light yellow colour preparation with a smooth and homogeneous appearance and there was no phase separation in any of formulation. Physical examination results were shown in the table No 14.

2. Measurement of pH: pH of the formulations is shown in the table No.14. The pH values of the prepared formulation was 6.5±0.05, which are considered acceptable to avoid the risk of irritation upon application to the skin because adult skin pH is 5.5.

3. Viscosity Study: Viscosities of the formulations were evaluated by using Brookfield viscometer at 27oC using spindle no.64 at 6-60 rpm. The viscosity of the Emulgel was found to be 2465 cps shown in table No:1.

4. Spreadability: The values of spreadability were shown in table No. 14. The Emulgel formulation showed 19.03±0.103g cm/ sec. The results indicate that the polymers used gave gels better spreadability and the spreadability of the emulgel decreases with the time.

5. In vitro diffusion study of Emulgel: The invitro release profile of the drug is given fig no 15. The emulgel formulation with 1:1 polymer ratio showed 82.55 within 8 hours. This observation indicates that the polymer is important for the release of drug. As the concentration of polymer is increased, the release concentration of the drug is increased. When the formulation is incorporated in the gel, it will shows higher drug release.

6. Kinetic study: In order to study the exact mechanism of drug release from emulgel loaded with Bifonazole, drug release data were fit into various mathematical models, zero order firstorde, higuchi matrix and peppas and were shown in fig no 17(a),17(b),17(c)17d) Based on the highest regression values (r), the best fit model for the emulgel formulation was found to be zero order. The data were processed for regression analysis using MS –EXCEL. The results of kinetics analysis of the invitro drug release data for all formulation are given in table No16.

7. Stability studies: Stability study of the emulsion is the major determinant for the stability of the formulations. The study was carried to evaluate physical appearance, drug content and Invitro diffusion studies at accelerated condition [(25±20 c at (60±5%RH]. According to the data obtained, formulations stored at accelerated condition showing better stability. The results of stability study of the formulation were depicted in table No 18.

Table No. 1: Pseudoternaryphase study.

Sl No	MLof Oil	Smix(ml)	Water (ml)	Type of emulsion/ observation
1	1	9	8.1	Clear
2	2	8	12.5	Clear
3	3	7	14.9	Clear
4	4	6	19.2	Clear
5	5	5	25	Clear

6	6	4	29.1	Viscous
7	7	3	30.6	Turbid
8	8	2	31.7	Turbid
9	9	1	32.9	Turbid /gel

Table No. 2: Centrifugation, pH, Drug content.

Formulatio n	Centrifugatio n study	pH	Drug content
F1	No phase separation	6.30±0.01	75.12±0.03
F2	No phase separation	6.26±0.01	93.22±0.02
F3	No phase separation	6.21±0.01	82.5±0.05
F4	No phase separation	6.12±0.01	86.12±0.02
F5	No phase separation	6.09±0.01	78.46±0.06

*****Dataexpressed asa mean±SD, n=3

Table No. 3: *In-vitro*drugreleasedataof formulations(F1-F5).

Time (hour s)	%cumulativedrugrelease				
	F1	F2	F3	F4	F5
0	-	-	-	-	-
0.25	17.67±0.04	20.20±0.01	10.66±0.04	21.85±0.09	17.86±0.02
0.5	22.41±0.04	24.58±0.05	15.78±0.03	24.51±0.07	20.20±0.01
1	23.73±0.01	28.63±0.07	25.47±0.01	27.69±0.02	24.89±0.02
2	33.89±0.05	38.95±0.02	36±0.06	34.59±0.02	32.12±0.02
3	41.91± 0.01	45.68±0.08	43.58±0.09	41.62±0.08	42.72±0.08
4	52.96 ±0.08	59.78±0.07	56.70±0.07	51.57±0.03	52.14±0.05
5	64.72± 0.02	68.79±0.05	64.65±0.06	65.78±0.01	63.22±0.03
6	72.18±0.06	75.46±0.01	71.94±0.02	72.55±0.09	70.16±0.01
7	76.11±0.03	79.71±0.09	75.99±0.01	76.01±0.08	74.16±0.02

Table No. 4: Physicalcharacteristicsof Bifonazole Nanoemulgel.

Formul ation code	Appearane	pH	Spreadability (gms.cm/sec)	Drug content (%)	Viscosity Cps
F2	Light yellow colour	6.5±0.05	19.03±0.103	90.98%	2465

Table No 5: *In vitro*diffusion study of Emulgel.

Time(hr)	% Cumulativedrugrelease
0	0±0.00
1	16.33±0.01
2	19.99±0.04
3	27.78±0.021
4	36.67±0.052
5	49.67±0.231
6	62.27±0.015
8	82.55±0.032

*****Dataexpressedas amean±SD, n=3.

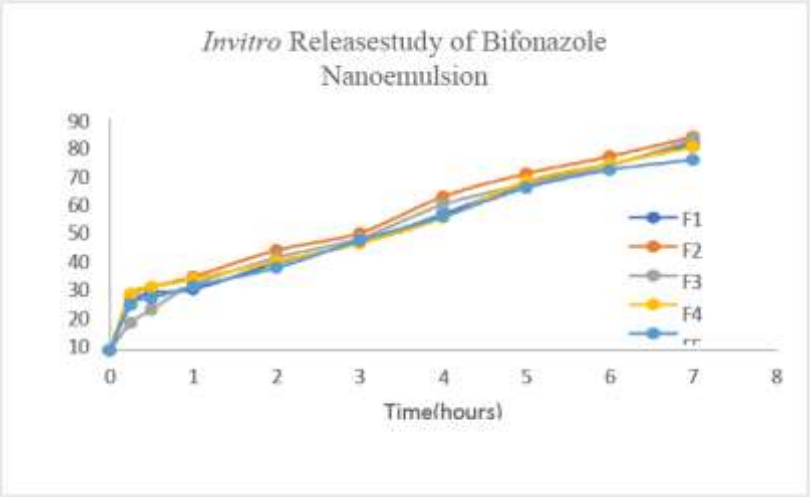

Figure No.1: *Invitro*drugreleaseprofile of Bifonazole Nanoemulsion (F1-F5).

Figure No. 2: Pseudoternaryphase Study.

Figure No 3: Bifonazole Nanoemulgel.

CONCLUSION

The present study has been a satisfactory attempt to formulate Nano emulgel for the controlled delivery of Bifonazole using suitable oil (oleic acid) and smix (IPA, Tween 80). From the reproducible results of the executed experiments, it can be concluded that: Preformulation studies of Bifonazole comply with the reported literature limits. The particle size determination of formulated emulsion shows that the particles in all formulations were in nano range. From result F2 showed the smallest

paricle size that is 33.37nm. The cumulative drug release from formulation F2 with oil and Smix ratio of 1:1 showed the desired release rate, compared to other formulations. Showed desired drug release of about 79.71 % after 7 hours. The F2 formulartion was selected as best formulation and conveniently incorporated into carbopol 934 gel (1%). *In vitro* release studies of Emulgel showed that the drug release is maximum at 8 hr that is 82.55%. The Nanoemulgels were shown to be stable and to release Bifonazole effectively. The current investigation shown that carbopol 934 may be used to successfully produce Bifonazole nanoemulgel formulations. Nanoemulgels appear to be a reliable approach for topical administration of hydrophobic medicines in water soluble gel bases.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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