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Development and Characterization of a Nano-Emulgel: A New Approach for Permeability Enhancement

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ABSTRACT:
The object behind this research work was to improve the solubility and bioavability of lipophilic drugs by using nanoemulgel technique. Nano-emulgel drug delivery system is an innovative tool and play an highly important role in drug delivery as they can reduce toxicity and modify pharmacokinetic and bioavailability. Luliconazole used as topical antifungal drug. Antifungal agents used in many skin diseases, used to treat candidiasis such as athlete foot, ringworm and mycosis. Topically applied nanoemulgel can increase the residence time of drugs in the upper layers of skin (stratum corneum and epidermis), while reducing the systemic absorption of the drug. This drug is used in patient with tinea pedis, tinea cruris and tinea corporis. Foot fungal skin infections (tinea pedis, also called athlete's foot) is the most common fungal infection in the general population. Nanoemulgel containing Luliconazole was prepared by high-speed homogenization technique using different concentration of Coconut oil, and non-ionic surfactants (Tween80, Span 80). Six nanoemulgel formulations were prepared (B1-B6) and evaluated for physical appearances, pH, Viscosity, Drug Content and FTIR studies. As, nanoemulgel has topically a high degree of skin permeation and prolongs maintenance of drug by increasing the residence time in the target area at a therapeutic level thereby decreasing the frequency of administration and increasing patient compliance. The synergistic effect of Luliconazole and Coconut oil help to recover the fungal wound infection. Topical Nano-emulgel was homogeneous, transparent and free from particulate matter containing a high concentration of surfactant and co-surfactant.

Key words: Nano-emulgel, Luliconazole,lipophilic drugs, etc.

I. INTRODUCTION:

Topical administration of drug is simplest and easiest route of localized drugdelivery system anywhere in the body as compare to other routes such as ophthalmic, rectal, vaginal and skin. These are applied as wide spectrum of preparations in case of both cosmetic and dermatological fields, to the healthy or diseased skin.[1-5]

A topical drug delivery system is a way to deliver the Active Pharmaceuticals Ingredient that is applied onto a particular part of the body, generally the skin, to obtain the localizing effect of drug.[5-8] Topical drug delivery system has many advantages over other drug delivery system such as the capability of formulation to

NANO-EMULGEL:

Nano-Emulgels are nano-emulsions, either of the oil-in-water or water in oil type, which are gelled by mixing with a gelling agent. Emulsified gel is stable one and superior vehicle for hydrophobic or poorly water soluble drugs. In short nanoemulgels are the combination of nano-emulsion and gel. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So, to overcome this limitation an emulsion based approach is being used, so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. In recent years, there has been great interest in the use of novel polymers which can function as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase.[9-15]

Composition of Nano-Emulgel:

- Nano-Emulsion
- Gel

Emulsion: A mixture of two or more liquids in which one is present as droplets, of microscopic or ultramicroscopic size, distributed throughout the other.

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Gel: [16-17]

The term "gel" represents a physical state with properties intermediate between those of solids and liquids. A gel consists of a polymer which swells in the presence of fluid and perhaps it within its structure. These gels are wet and soft and look like a solid material. These are capable of undergoing large deformation in their physical state i.e. from solid to liquid. The USP defines gels (sometimes called jellies) as semisolid systems containing either suspensions made up of small inorganic particles, or large organic molecules interpenetrated by a liquid.[18]

Method of Preparation of Nano emulsion:

Formulation of Nano emulsion can be carried out by both high energy and low energy methods depends on the nature and concentration of components used [19].

High-pressure Homogenization:

In the homogenization technique, a very high pressure near about 500-20,000 psi is applied along with the continuous impact, attrition, turbulence and hydraulic shear, during the process of emulsification. Various types of forces such as shear forces, hydraulic forces and cavitations forces act simultaneously to convert macro sized emulsion into the coarse emulsion and then the formed product is subjected to the same process to obtain the droplets of desired size (nano) and polydispersity index(PDI) [20]

Formulation of Nano-emulsion:

- **Using S-mix (1:1)**

Percent of oil	Percent of S-mix (1:1)	Percent of Water
1.01	9.09091	89.899
3.38	9.5234	88.09
4.26	11.111	84.127
8.01	10.52	82.47
11.9	11.9	76.19
21.27	18.181	54.54
40.72	21.73	27.53
91.42	17.85	10.98
63.33	9.25	7.4

- **Using S-mix (1:2)**

Percent of oil	Percent of S-mix (1:2)	Percent of Water
1.01	9.09091	89.899
2.38	9.5234	88.09
4.76	11.111	84.127
7.01	10.52	82.47
11.9	11.9	76.19
27.27	18.1818	54.54
50.72	21.73	27.53
71.42	17.85	10.98
83.33	9.25	7.4

Method of Preparation of Gel:

Different formulations were prepared using varying amount of gelling agent. The method only differed in process of making gel in different formulation. The preparation of emulsion was same in all the formulations. The gel bases were prepared by dispersing Carbopol 934 and in distilled water separately with constant stirring at a moderate speed using mechanical shaker. Formulations B1 and B2 were prepared by using Xanthan Gum as a gelling agent with different concentration and formulation B3 and B4 were prepared by using carbopol 934 as a gelling agent with different concentration and formulation B5 and B6 were prepared by using Guar gum with different concentration. The gel were prepared by dispersing

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the gelling agent in heated distilled water (75°C) and the dispersion was cooled and left overnight. Then Luliconazole was added to oil phase. The obtained nano-emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the nano-emulgel.[21,22]

	Ingredients	B1	B2	B3	B4	B5	B6
Nano-Emulsion	Distilled Water	14mg	14mg	14mg	14mg	14mg	14mg
	Tween 80	4mg	4mg	4mg	4mg	4mg	4mg
	Virgin Coconut Oil	3.5 mg	3.5 mg	3.5 mg	3.5 mg	3.5 mg	3.5 mg
	Span 80	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
	Luliconazole	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg
Gel base	Polymer	Xanthan gum (1%)	Xanthan gum (1.5%)	Carbapol (1%)	Carbapol (1.5%)	Gaur Gum (1%)	Gaur gum (1.5%)
	Water	24.5 mg	24.5 mg	24.5 mg	24.5 mg	24.5 mg	24.5 mg

Composition of nano-emulgel formulations

II. RESULTS AND DISCUSSION:

a) Solubility of Luliconazole:

Table 1. Detection of solubility

Solvents	Solubility
Distilled water	Insoluble
Coconut oil	Soluble
Pam Oil	Soluble

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Methanol	Soluble
Acetone	Soluble
Ethanol	Soluble

The solubility of pure drug in 10mg/ml of solvent was carried out and it reveals that it is soluble in Coconut oil, methanol; acetone and insoluble in distilled water.

b) Physical appearance & Melting point determination:

Table 2. Physical appearance & Melting point determination

Properties	Observation
Colour	White
Odour	Slight
Appearance	Microcrystalline Powder
Melting Point	150-152℃

The physical characters was found to be as per standard drug, So drug used in formulation was found to be pure according to Indian Pharmacopeia specification. The melting point of pure luliconazole was found to be 150-152℃ so drug used in formulation was found to be pure according to Indian Pharmacopeia specification.

c) **FTIR study**

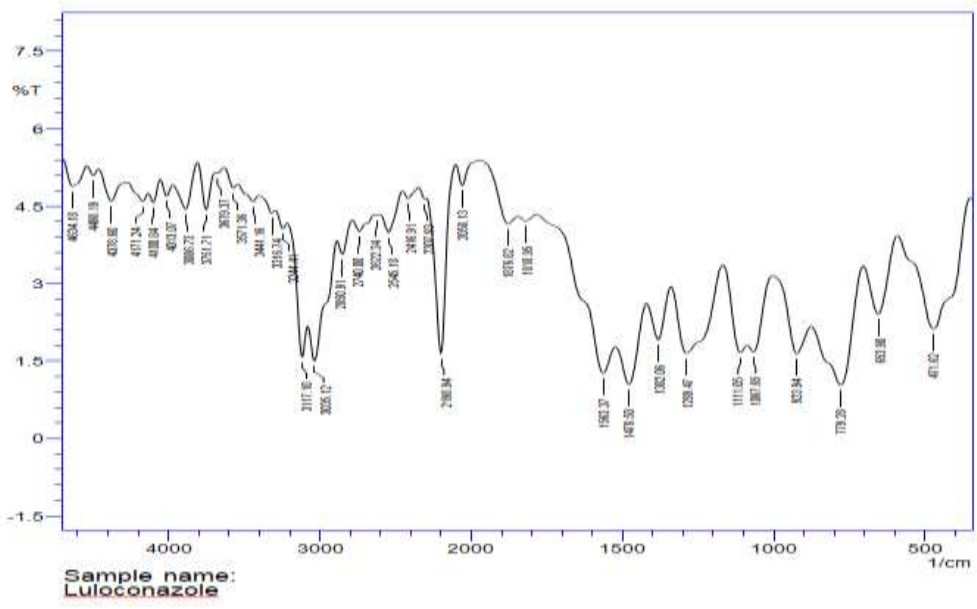

Fig. 2 FTIR of Drug(Luliconazole)

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Characteristics Peaks	Reported (cm^{-1})	Observed(cm^{-1})
C-H stretch	2850 – 3000	2979.43
C≡N Stretch	2100 – 2400	2198.82
C=C aromatic stretch	1450 – 1650	1554.35
C=C-C Aromatic ring stretch	1510 – 1450	1471.35
para C-H distribution	860 – 800	820.41
C-Cl stretch	600 – 800	759.46

Table.3 FTIR interpretation of luliconazole

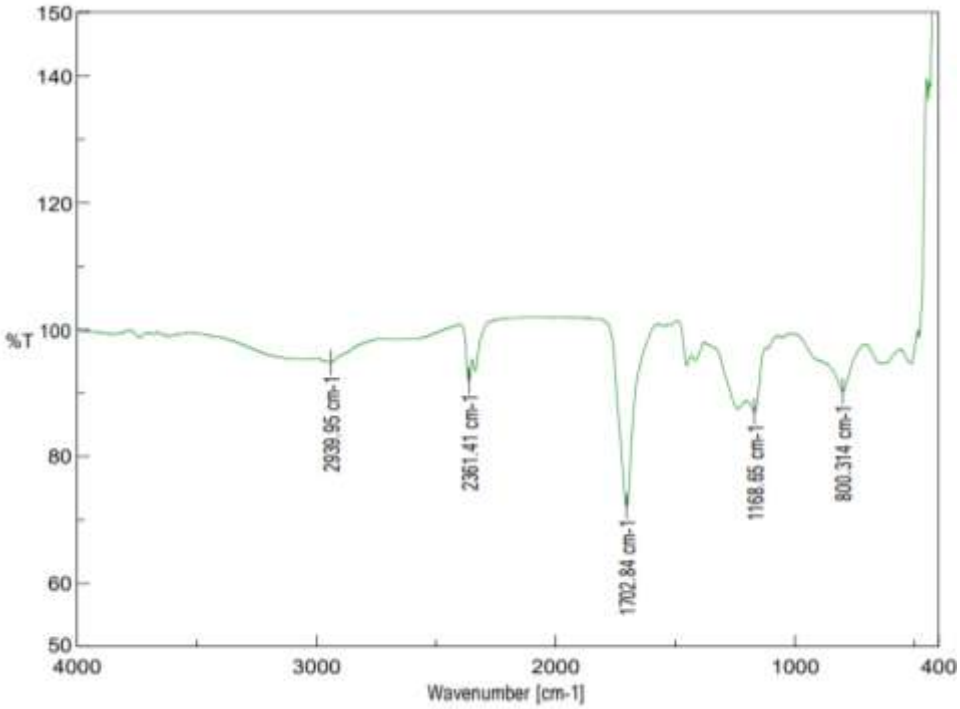

Fig. 4 FTIR of Carbapol

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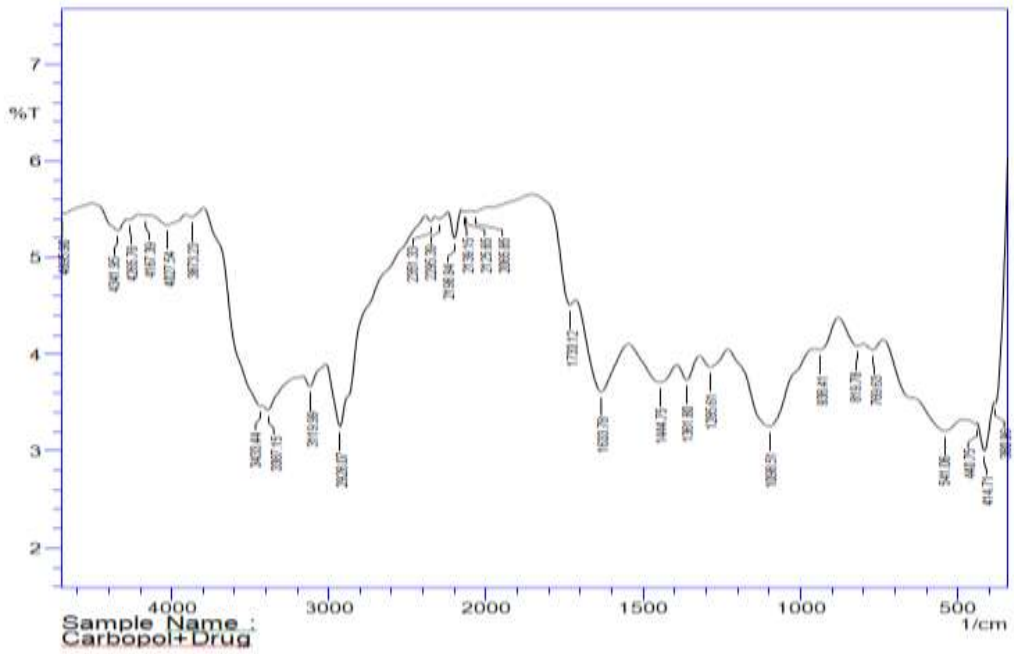

Fig. 5 FTIR of Drug and Carbopol

The FTIR analysis performed of luliconazole and Carbopol for better compatibility analysis of leading moiety before and after formulation. FTIR spectra of luliconazole is shown in above Figure; Table 6. principal IR absorption peaks of luliconazole at 2979.43 cm^{-1} (C-H stretch), 2198.82 cm^{-1} (C≡N stretch), 1554.35 cm^{-1} (C-H aromatics stretch), 1471.35 cm^{-1} (C=C-C aromatic ring stretch), 820.41 cm^{-1} (para C–H distribution) and 759.46cm^{-1} (C-Cl stretch) were all detected in spectra of luliconazole. These detected principal peaks confirmed purity and authenticity of luliconazole as similar to referenced report.

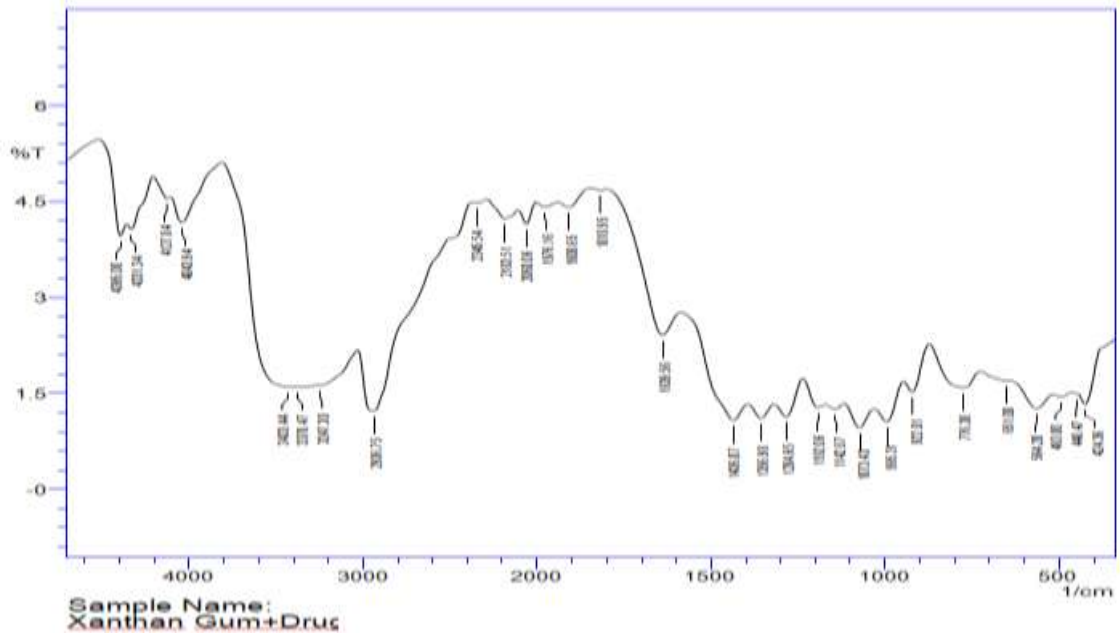

Fig. 6 FTIR of Drug and Xanthan Gum

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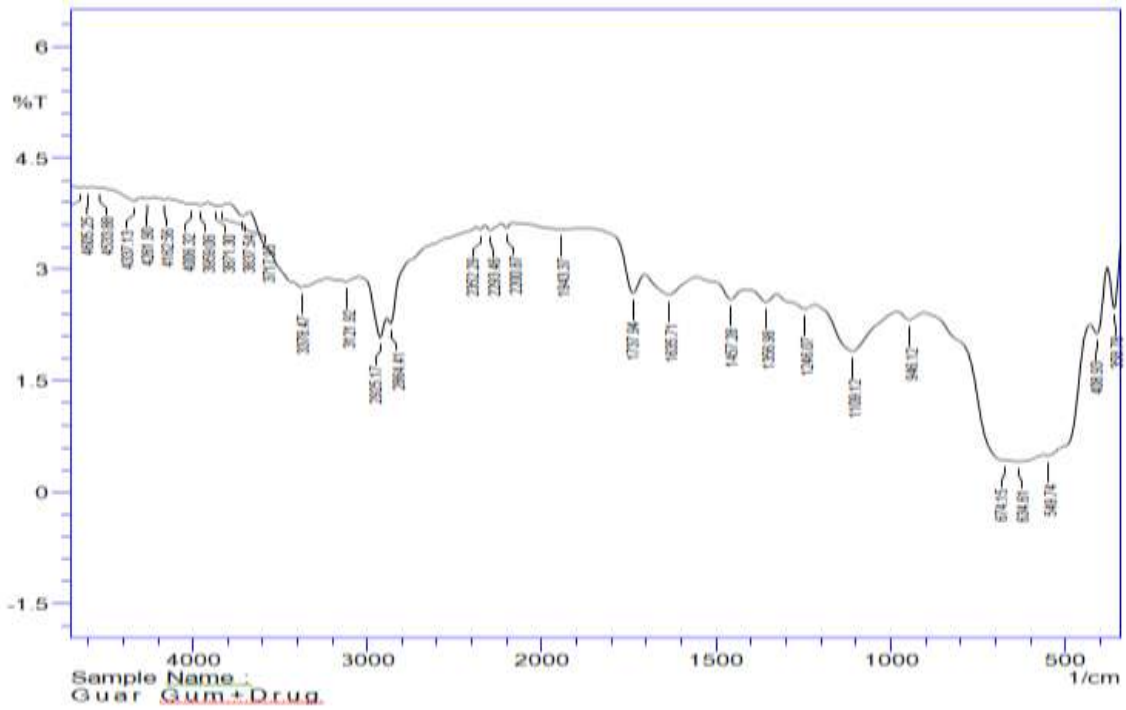

Fig. 7 FTIR of Drug and Gaur Gum

From the below results of FTIR spectra of both drug and excipients, it concluded that no interaction was found among drug and Excipients.

Luliconazole showed the maximum wavelength at 300 nm, which matches with the standard, Hence drug used in formulation, was found to be pure according to Indian Pharmacopeia specification.

d) Determination of Wavelength:

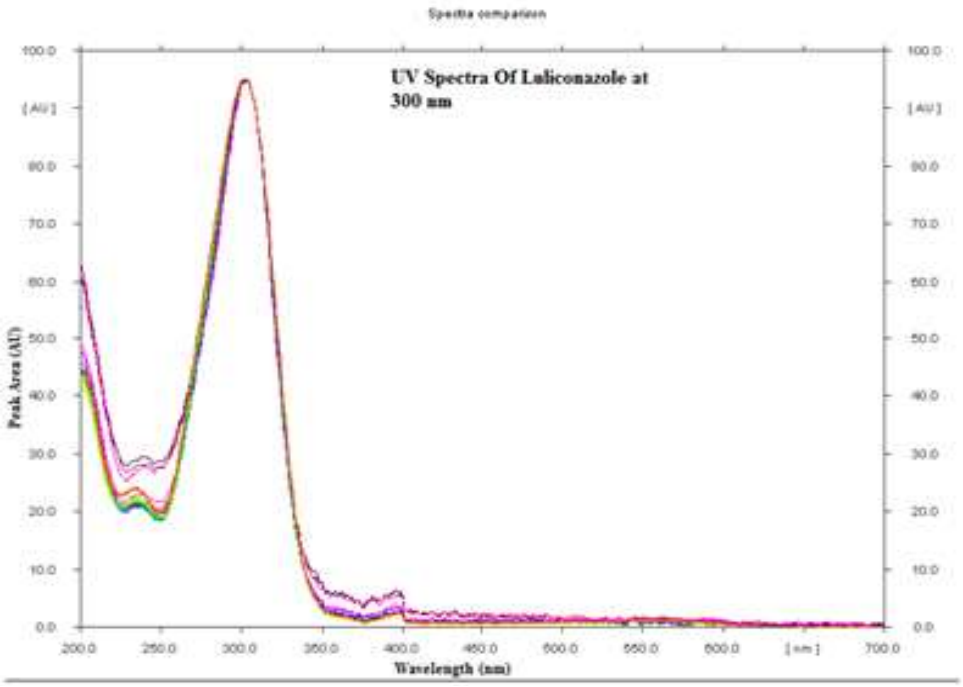

Fig. 8 Wave length of the Luliconazole

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e) Calibration Curve of Luliconazole:

Table 4: Calibration Curve of Luliconazole with Phosphate Buffer-5.5

Concentration(µg/ml)	Absorbance
2	0.0132
4	0.0231
6	0.0406
8	0.0539
10	0.0632

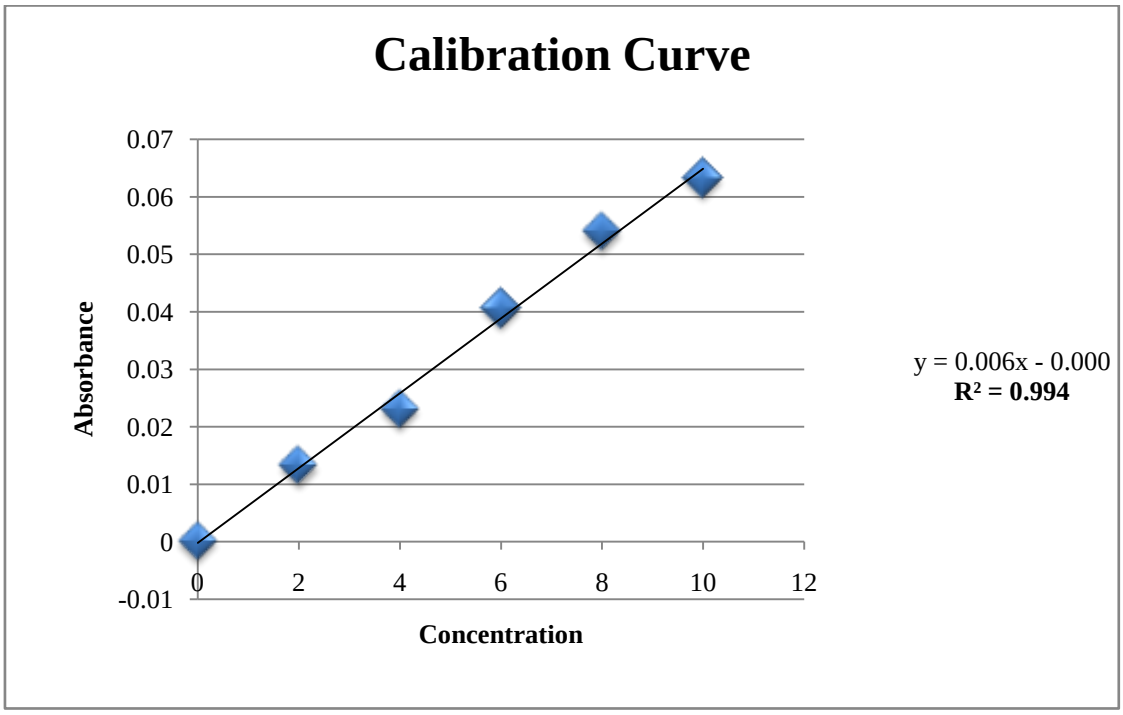

Fig 9: Calibration Curve

f) **Assay of Liliconazole:**

By titrimetric method the percent purity of Luliconazole was found to be 98% which is acceptable as per the IP standards.

g) Solubility of luliconazole in selected oils:

Luliconazole showed the maximum solubility in Coconut oil and Methanol among the selected oils, so it was considered as an oil phase for the preparation of emulsion.

h) Pseudo ternary phase diagram:

From following ternary phase diagrams i.e. 1:2 the ratio of S-Mix concentration showed stable Emulsion hence selected for formulation of nano-emulsion. A ternary phase diagram shows possible phases and their equilibrium according to the composition of a mixture of three components at constant temperature and pressure.

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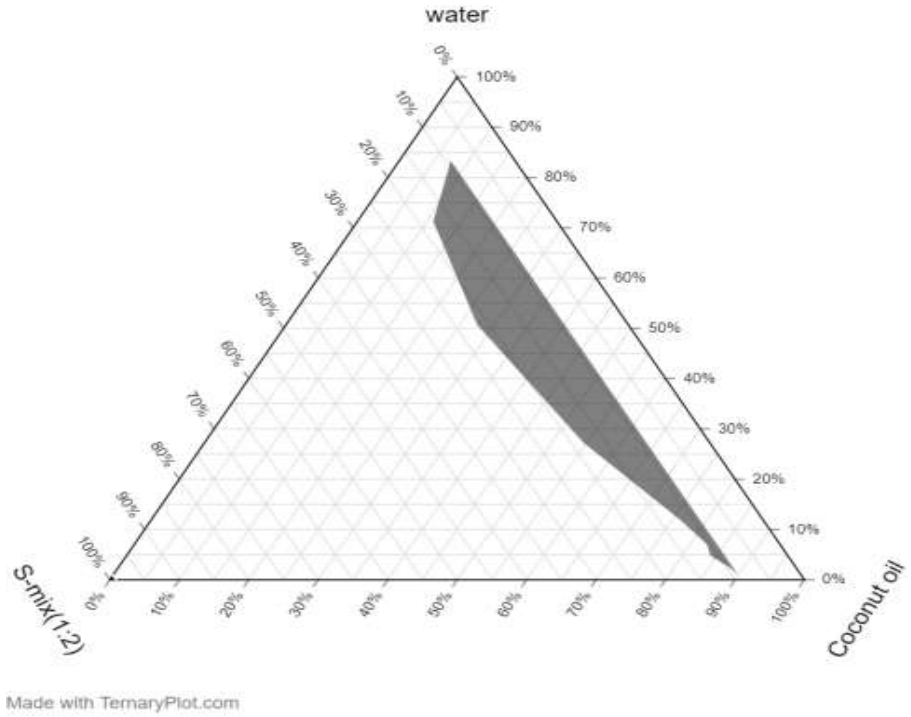

Fig.11 Ternary Phase Daigram

Evaluation of Nano-emulsion:

The Nano-emulgels were prepared by the procedure as mentioned in the experimental work under method of preparation.

a) Phase separation: Emulsion is thermodynamically unstable system, which may separate when subjected to physical stresses like centrifugation. Though nano-emulsions are homogeneous single phase system, they were subjected to centrifugation to confirm the absence of phase separation.

Evaluation of Nano-emugel:

Physical appearance of Nano-emulgel formulation:

The prepared Nano-emulgel was inspected visually for their color, homogeneity and consistency.

Fig.6 (a)Physical properties of formulated Nano-emulgels

Formulaton	Colour	Homogenicity	Consistency	Phase separation
F1	Milky white	Homogeneous	Cream like semisolid	No
F2	Milky white	Homogeneous	Cream like semisolid	No
F3	Milky white	Homogeneous	Cream like semisolid	No
F4	Yellowish creamy	Homogeneous	Cream like semisolid	No
F5	Milky white	Homogeneous	Cream like semisolid	No
F6	Milky white	Homogeneous	Cream like semisolid	No

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Determination of pH:

The pH of the topical formulations should be compatible with skin pH. Change in the pH may cause skin irritation or disruption. The pH of the all Nano-emulgels formulations was modified with the help of triethanolamine and when checked it was found in between the range 5 and 5.65, which is acceptable for skin preparations.

Fig. 6 (b) Physical properties of formulated Nano-emulgel

Formulation	pH (mean±SD)	Spreadability(gm./s) (mean±SD)	Extrudability
F1	5.58±0.07	40.52±0.57	Very good
F2	5.57±0.07	35.61±0.57	Excellent
F3	5.53±0.05	32.5±0.57	Excellent
F4	5.44±0.05	22.85±1.15	Very Good
F5	5.45±0.01	33.56±0.57	Very good
F6	5.65±0.01	31.98±0.57	Very good

Extrudability: - a) 90%-100%= Excellent, b) 80%-90%=Very good

Viscosity:

Rheological behavior of the Nano-emulgel formulations exhibited non-Newtonian shear thinning pseudo plastic type of flow, i.e. decreases in viscosity at increasing shear rates. As the shear stress is increased, the disarranged molecules of the gelling material are caused to align their long axis in the direction of flow. Viscosity for respective Nano-emulgel formulations was found to be in acceptable limit.

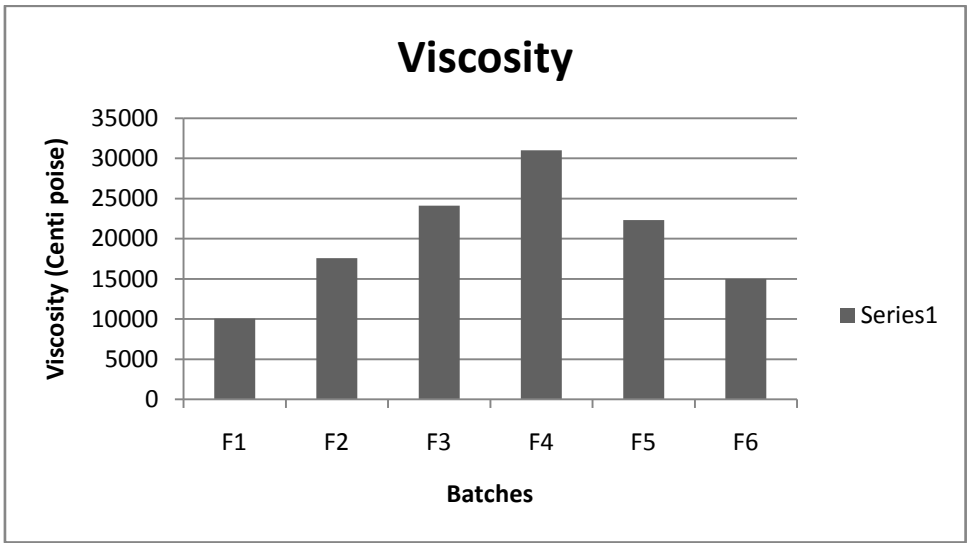

Fig. 11 Bar graph showing viscosity of formulated Nano-emulgel

Table. 7 Viscosity of formulated Nanoemulgels

Formulations	Viscosity (cps)
F1	10042
F2	17580
F3	24100
F4	31012
F5	22321
F6	15000

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Spreadability:

Spreadability is the term expressed to denote the extent of area to which the gel readily spreads on application to the skin. One of the essential criteria for an emulgel is that it should have good spreadability. It depends upon the type and concentrations of polymers used in the formulation. More viscous formulation would have poor spreadability. The formulation F2 showed more spreading coefficient, i.e.40.61, as compared to other formulations, this is because formulation contained optimum concentration of Carbopol 934, i.e. 1%

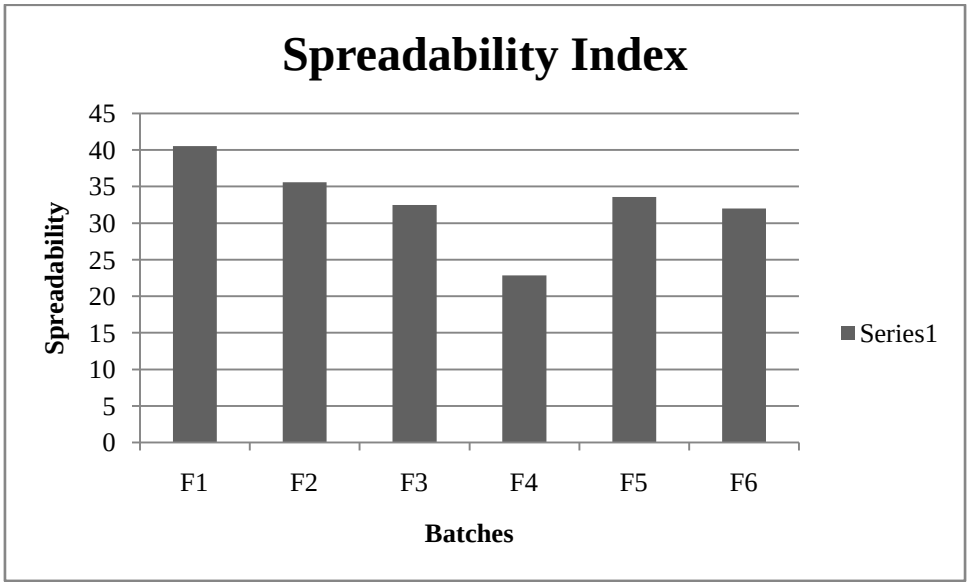

Fig. 12 Bar graph showing spreadability of Nano-emulgel

Drug content determination:

All formulations showed drug content in between the range of 90 % to 98%.The drug content of all formulations is tabulated as under:

Table.8 Drug content of formulated Nanoemulgel

Formulation	Drug Content (%) (mean ± SD), n=3
F1	91.70±0.32
F2	97.18±0.95
F3	95.30±2.46
F4	98.85±1.43
F5	90.75±0.25
F6	96.64±0.35

In-vitro drug release:

The release of active pharmaceutical ingredient (Luliconazole) from the nano-emulgel was varied according to polymer concentration. As the concentration of polymer increase the % drug release decreases. The cumulative % of drug release profile of all the formulated batches has been shown below

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Table. 9 In-vitro% cumulative drug release of formulations F1 to F6

Time (hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	26.72	22.54	28.73	22.22	28.35	16.55
2	31.34	25.98	42.33	27.73	37.95	29.6
3	40.21	36.85	57.85	39.15	48.13	42.55
4	57.1	50.85	77.95	57.23	58.23	58.88
5	79.16	75.95	90.3	74.97	78.17	70.17
6	95.16	87.98	97.98	94.76	93.17	90.3

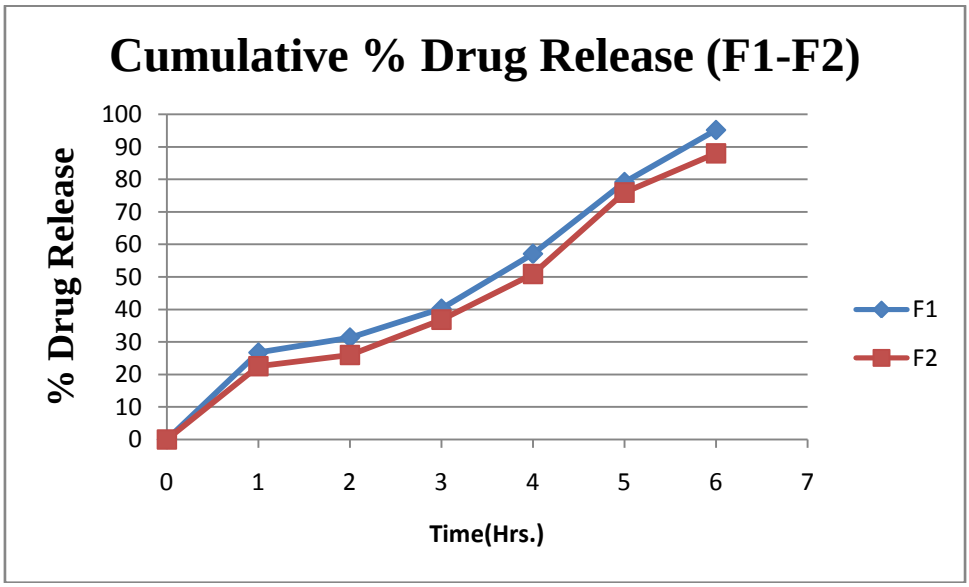

Fig. 13 (a) % Cumulative drug release of F1-F2

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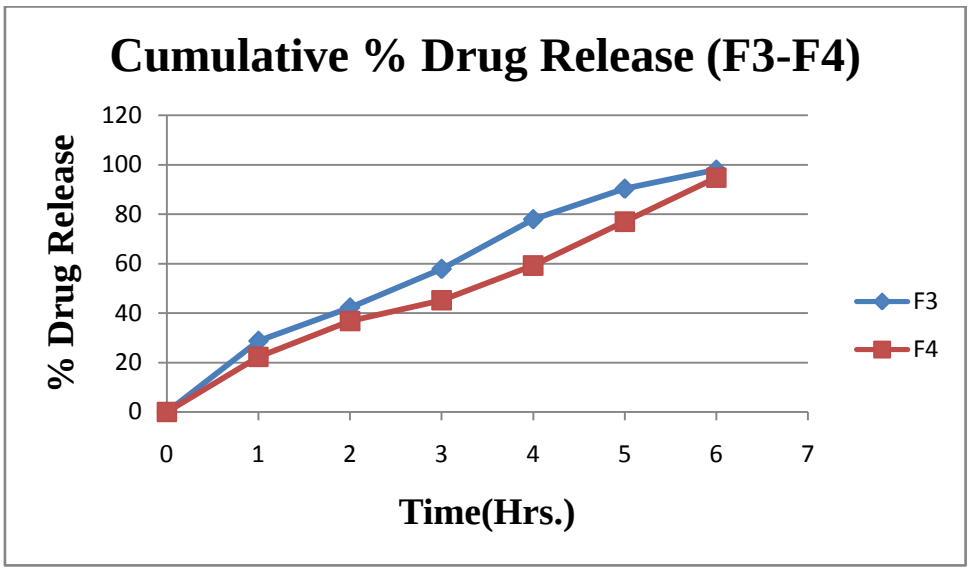

Fig. 13 (b) % Cumulative drug release of F3-F4

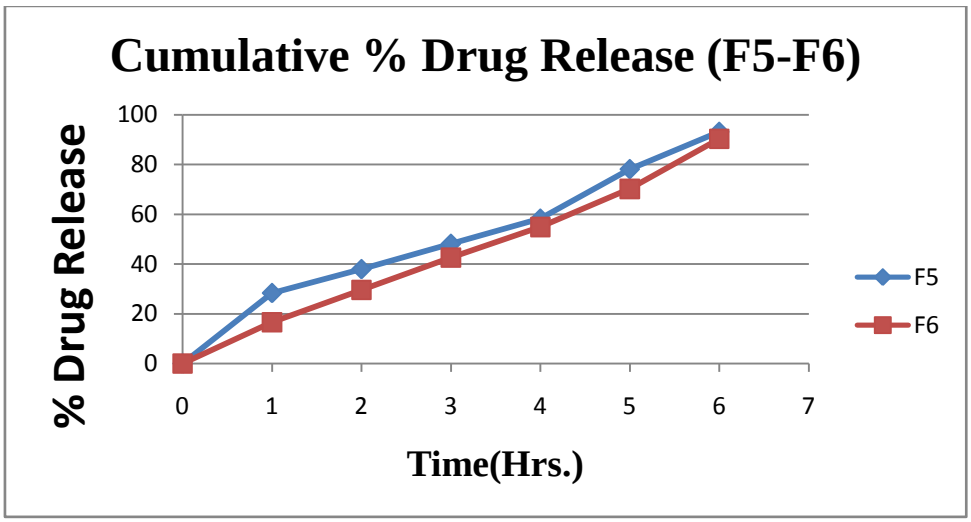

Fig. 13 (c) % Cumulative drug release of F5-F6

Stability study:

Optimized batch F3 taken for a 2-month stability study at 40°C and 75% RH. Initial results and after 2 month results were compared for any loss or change during stability. The results of the initial and after 2 month were recorded which was given in table. And all the parameter obtained is satisfactory.

Table.10 Stability Study at 40^0C

Parameter	Day 1	Day 60
Colour	Milky white	Milky white
Phase Separation	No change	No change
pH	5.53	No change
Viscosity(cps)	24100	23450
Spreadabiliy	32.5	31.1
Drug content (%)	95.30	94.20
Drug Release (%)	97.98	No Change

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