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DEVELOPMENT AND EVALUATION OF FLUOCINOLONE ACETONIDE AND NEOMYCIN SULPHATE NANOMIEMGEL FOR TOPICAL DRUG DELIVERY SYSTEM

Salman J. Latif*[1] and Dr. Shubhangi C. Daswadkar[2]

[1]M.Pharmacy (Quality Assurance Technique), Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune-44, Maharashtra, India.

[2]Department of Chemistry, Dr.D.Y.Patil College of Pharmacy, Akurdi, Pune-44, Maharashtra, India.

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***Corresponding Author**
Salman J. Latif
M.Pharmacy (Quality Assurance Technique), Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune-44, Maharashtra, India.

ABSTRACT

Objective: The skin enacts as the effective barrier which prevents permeation of numerous drug through it. Nanomiemgel is a combination of two novel drug delivery systems i.e. nano-micelles and nano-emulsions. This combination provides synergistic approach providing the benefit of prolonging the duration of action, increased incidence on skin thereby increasing the contact time, maintaining steady state concentration, improving solubility of poorly soluble drugs and decreasing the toxicity. **Method**: Firstly the nano-emulsion is formed by sonication method with the aid of surfactant mixture of tween 80 and oleic acid. Further the nano-micelles are formed by solvent evaporation method. The gel was formed by using carbopol and triethanolamine in which both the nano-emulsion and nano -micelles are incorporated. **Results:** The nano-emulsion, nano-micelles and nanomiemgel were evaluated for physical appearance, pH and viscosity was found to be within critical limits. The in-vitro release for the nanomiemgel was found to be 98.7%. The globule size for nano-emulsion and nano-micelle were 92.95nm and 70.79nm respectively. **Conclusion:** by formulating the nanomiemgel the incidence of the drug on the skin increases as well as the controlled release of the drug is achieved. The stability of the both the preparations is increased and toxicity is also decreased.

KEYWORDS: Nano-emulsion, nano-micelles, nanomiemgel, fluocinolone acetonide, neomycin sulphate.

INTRODUCTION[6,12,13]

Recent remedies for the cure of skin related inflammation are not wholly efficient and could be characteristic to the types of topical delivery systems used. Hence there is a demand to develop a controlled-release drug delivery system that would efficiently transport different agents to decrease pain as well as disease progression and prohibit the adverse reactions.

The skin is an extraordinary efficient barrier as well as it limits the permeation of a number of the drugs which are used for therapeutic functions. Not many drugs have the proficiency to permeate in desirable amounts through the skin. A number of the topical dosage forms accessible in the recent market possess poor penetration, which is followed by poor therapeutic benefit. Therefore a delivery system that causes the skin to be more permeable as well as penetrates the skin via multiple mechanisms to increase the topical drug delivery is of huge formulation interest.

In current years, dermal drug delivery has developed as an enticing as well as substitute approach to oral drug delivery system for localized drug deposition followed by systemic absorption. Skin drug delivery system comprises of mainly of two types, namely topical (dermal) and transdermal drug delivery. Topical delivery involves drug transport at the skin surface or transport to the dermal layer of skin for localized drug action, whereby transdermal delivery is the delivery of drug across skin layers for the aim of systemic drug absorption. The major obstacles in skin delivery, though topical or transdermal, is the existence of the outermost sublayer of epidemis called as the stratum corneum (SC). It provides an obstacle for scientists to conquer this inherent barrier for drug permeation.

The first strategy is to improve drug permeation through the stratum corneum with the aid of chemical permeation enhancers like ethanol, terpenes, glycol, as well as azones. Chemical permeation enhancers cause dermal drug deposition with the aid of partially fluidizing SC lipids.

A second strategy for skin permeation enhancement is achieved with the aid of physical methods like sonophoresis, iontophoresis, electroporation, microneedles, etc. Physical

methods are usually painful, as well as there is less of patient compliance, while the chemical enhancers can produce skin irritation.

Nanotechnology has developed as the third approach which has opened chances for skin drug delivery with the use of Nano system-like nanoparticles, nano-emulsion, liposomes, ethosomes, lipid-based nanoparticles, dendrimers, etc. The size of Nano systems for topical and transdermal delivery usually falls in the range from 1 to 1000 nm. The skin permeation is improved by increasing drug solubilisation, partitioning of drug into the skin layers, as well as fluidizing the SC lipids.

Mechanism of action of nanomiemgel[1,6,7]

Nanomiemgel through an innovative formulation technique that uses the "**Multi Absorption Mechanism**" concept and has a broad applicability. Nanomiemgel consists of two different matrices; 1 and 2. Matrix 1 contains the nano-emulsion and matrix 2 is comprised of the nano-micelles. The theory of the present study is that every nano drug delivery system is distinct and its rate and mechanism of absorption depend on the size, charge and composition of the nano drug delivery system. So, when a combination of completely different drug delivery systems is utilized for the delivery of a drug, the absorption of the combined system would be better than either of the individual drug delivery systems due to the usage of the maximum possible paths of absorption accessible for that particular drug.

Dermal drug delivery offers several advantages[1,7, 9]

a. convenience,
b. pain free,
c. avoidance of frequent dosing,
d. constant drug plasma concentration,
e. enhanced patient compliance,
f. improved bioavailability of poorly oral bioavailable drugs

Need of work[1,7,10,12]

1. Conventional products such as creams gives a highly concentrated layer which releases active ingredient rapidly when applied on the skin and results into rash, irritation, itching, redness, allergic reaction, etc.
2. Also topical preparation possess problem such as greasiness, stickiness, lack of patient compliance, etc.

3. The major requirement is to provide a system that will release the drug at a steady constant rate and therefore maintaining the concentration at a steady level for prolonged period of time.
4. Alternative need was to formulate the preparation in such a way so that it does not get washed away readily and remains at the site of action for a prolonged period of time.
5. The nanomiemgel also avoids the problems with the respect to insoluble as well as fairly soluble drugs.
6. Nanomiemgel helps to decrease the dose of drug as well as the unnecessary exposure to whole body.

DRUG PROFILE

1. Fluocinolone acetonide

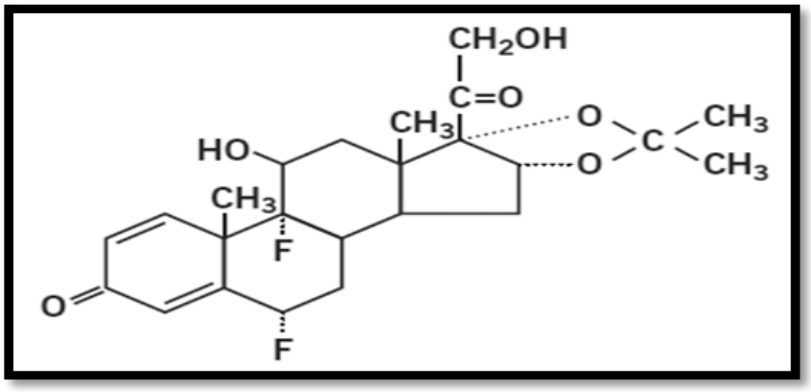

Fig 1: Structure of Fluocinolone Acetonide.

Molecular formula: $C_{24}H_{30}F_20_6$

Molecular weight: 452.5 g/mol

IUPAC name: 6α, 9α-difluoro-11β, 21-dihydroxy-16α, 17α-Isopropylidenedioxypregna-1, 4-diene-3, 20-dione.

Category: adrenocortical steroid.

State: solid crystalline powder.

Colour: white or almost white.

Odour: odourless

Taste: bitter

Melting point: 266°C-268°C

Solubility: soluble in water, ethanol, methanol, chloroform etc.

2. Neomycin sulphate

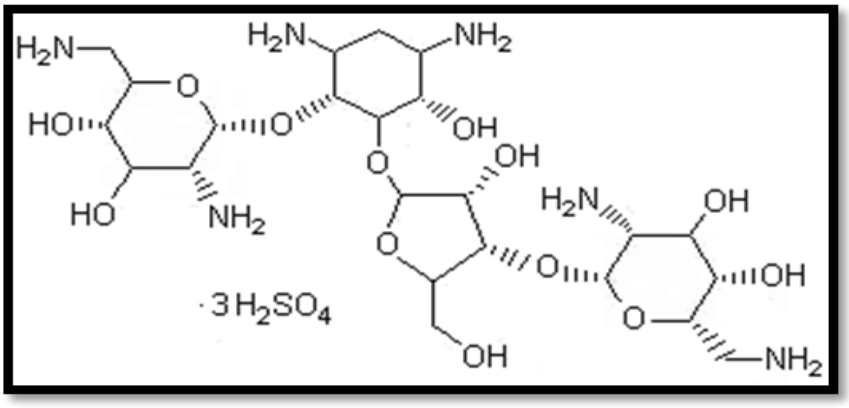

Fig 2: Structure of Neomycin Sulphate.

Molecular formula: $C_{23}H_{46}N_60_{13}$

Molecular weight: 615 g/mol

Source: *Streptomyces fradiae*

IUPAC name: (2*R*, 3S, 4R, 5R, 6R)-5-amino-2-(amino methyl)-6-[(1*R*, 2R, 3S, 4R, 6S)-4 Diamino-2-[(2*S*, 3R, 4S, 5R)-4-[(2*R*, 3R, 4R, 5S, 6S)-3-amino-6-(aminomethyl)-4,5 dihydroxyoxan-2-yl] oxy-3-hydroxy-5-(hydroxymethyl) oxolan-2-yl] oxy-3-hydroxycyclohexyl]oxyoxane-3,4-diol

Category: Anti-bacterial.

State: Solid crystalline powder.

Colour: Yellow or cream colour.

Odour: Odourless

Taste: Bitter

pH: 5.0-7.5

Melting point: 265°C-266°C

Solubility: soluble in water, ethanol, methanol, chloroform.

MATERIALS AND METHODS

A. Drug:

1. Fluocinolone acetonide.
2. Neomycin sulphate.

B. Chemicals

Table No 1: List of all the chemicals needed for formulation of nanomiemgel.

Dicholoromethane	Polyvinyl alcohol
Polyethylene glycol 400	Acetonitrile
Carbopol	Olive oil
Pluronics F-127	Lanolin
Glycerine	Oleic acid
Acetone	Distilled water
EDTA	Triethanolamine

C. Equipment

1. Lab stirrer
2. Magnetic stirrer
3. Electronic balance
4. Probe sonicator
5. Ultra sonicator
6. UV spectrophotometer
7. Franz diffusion cell
8. pH meter

- **METHODOLOGY**

A. Formulation of nano-emulsion[2,3,12]

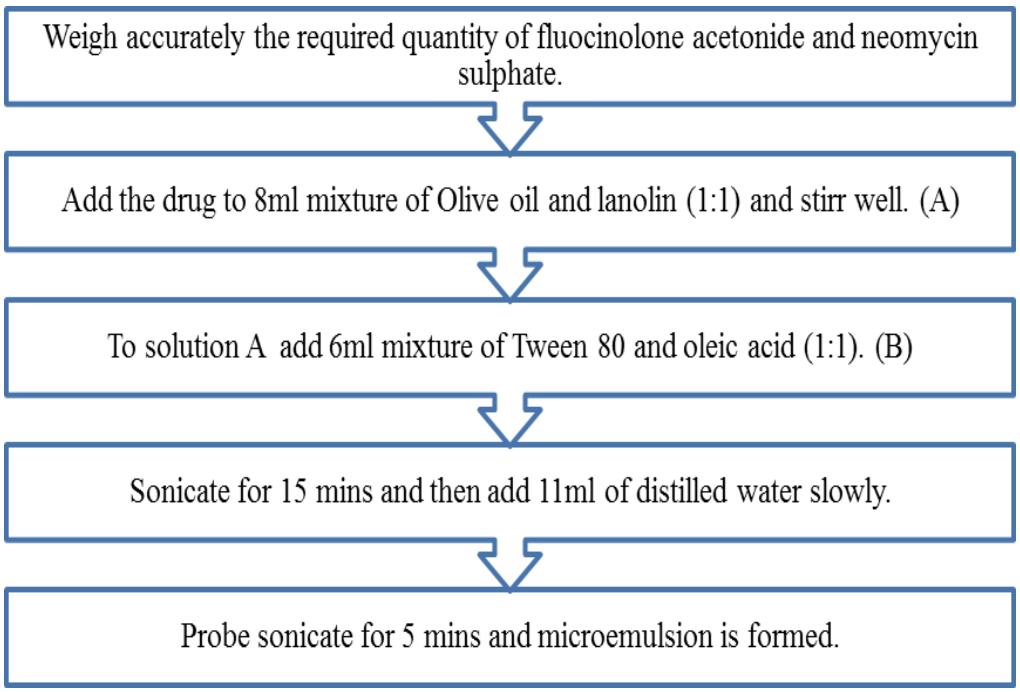

Fig 3: Procedure for Preparation of Nana-Emulsion.

Table No 2: Formula for Preparation of Nano-Emulsion.

Sr. No.	Ingredients	F1	F2
1	Fluocinolone acetonide	2.5 mg	2.5 mg
2	Neomycin sulphate	5 mg	5 mg
3	Olive oil	4 ml	4 ml
4	Lanolin	4 ml	4 ml
5	Polysorbate 80	3 ml	3 ml
6	Oleic acid	3 ml	-
7	Glycerine	-	3 ml
8	Distilled water	11 ml	11 ml

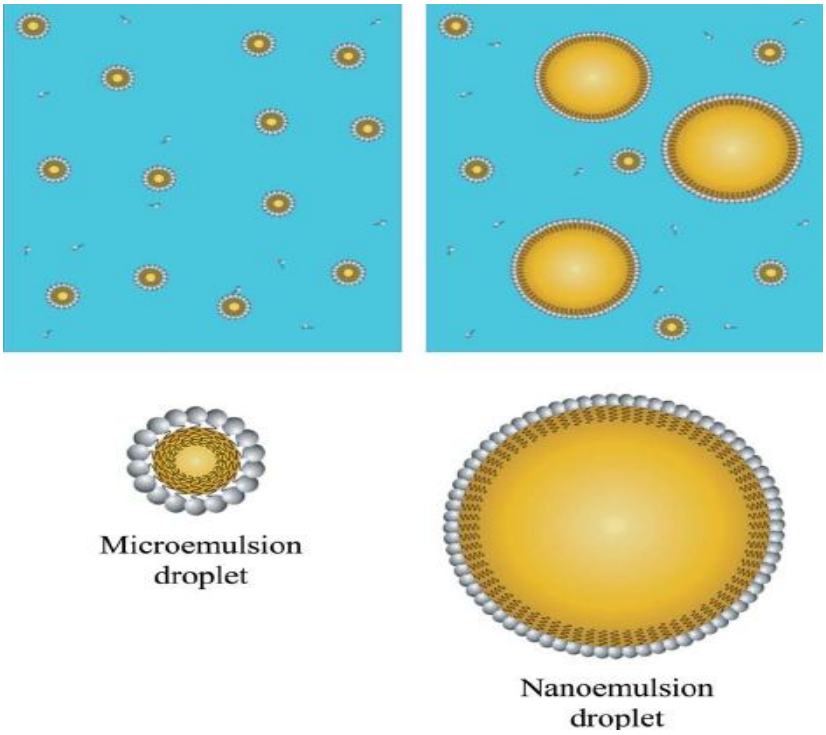

Fig 4: distinction between Micro-emulsion and Nana-Emulsion.

B. Formulation of nano-micelle: (solvent evaporation method)[4,5,6]

1. Weigh accurately the required quantity of drug viz. Fluocinolone acetonide and neomycin sulphate and take them in a beaker.
2. Add PEG/SLS to the beaker and shake well.
3. Add acetone 2 ml to the beaker and stir.
4. After sometime clear solution is obtained.
5. Add 25 ml of distilled water to the solution and keep aside.
6. Remove the organic solvent gradually through evaporation.
7. Micelles are formed and are precipitated.

Table No 3: Formula for Preparation of nano-micelle.

Sr. No.	Ingredients	F1	F2
1	Fluocinolone acetonide	2.5 mg	2.5 mg
2	Neomycin sulphate	5 mg	5 mg
3	Peg	6 mg	-
4	Sodium lauryl sulphate	-	6 mg
5	Acetone	2 ml	2 ml
6	Distilled water	25 ml	25 ml

C. Preparation of nanomiemgel[1,2]

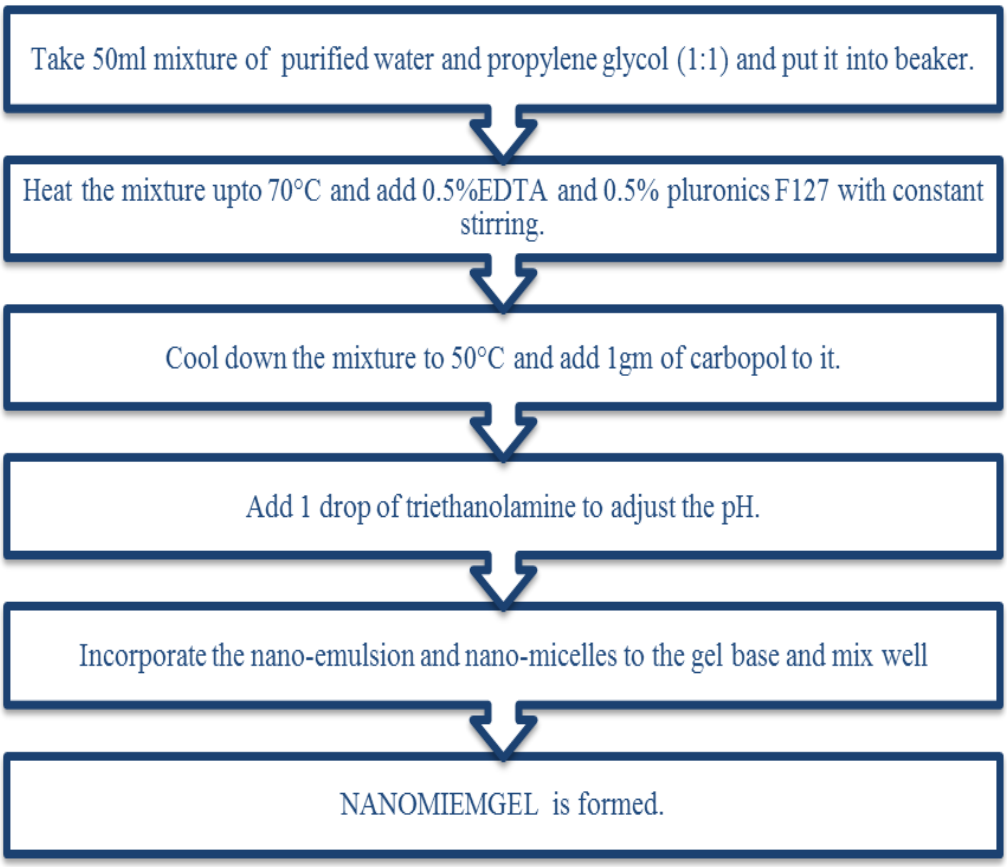

Fig 5: procedure for formulation of nanomiemgel.

EVALUATION PARAMETERS

A. Physical appearance

The formulations were observed visually for their

1. Colour,
2. Homogeneity and consistency,
3. Presence of any clog and
4. Change in viscosity.

B. pH

The formulation's pH was measured with the help of a digital pH meter. The pH of gel is also required to measure because change in pH may affect the zeta potential and finally affect the stability of products. The calibration of the pH meter was done each time before checking the pH of the formulation and the pH meter was calibration with the help of buffer solutions of pH 4 and 7. The electrode was immersed in gels and readings were recorded on pH meter. The measurements were done at ideal room temperature and in triplicate.

C. Rheological study

Rheology is an important parameter as it affects the Spreadability and adherence of the transdermal formulations to the skin surface. The rheogram of gel was obtained at 25°C with a Brookfield Digital viscometer. Spindle S-64 was used for measuring the viscosity.

D. Extrudability test (tube test)

Extrudability test is based upon the determination of weight required to extrude 0.5 cm ribbon of gel in 10 sec. from lacquered collapsible aluminium tube. The Extrudability value was calculated using following formula:

Extrudability = Weight applied to extrude gel from tube (gm.) / Area (cm2)

E. In-vitro diffusion study

In-vitro diffusion was performed by modified Franz diffusion cell. A glass cylinder having both ends open, 3.7 cm outer diameter, 3.1 cm inner diameter and 10 cm height was used as diffusion cell. A cellophane membrane was heated in the beaker containing water and removed with forceps. It was fixed to one end of the cylinder with the aid of an adhesive. About 1gm of gel was taken in the cell (donor compartment) and cell was immersed in a beaker containing 500 ml of phosphate buffer (pH 6.8) as receptor compartment. The entire surface of the cell was in contact with the receptor compartment which was agitated using magnetic stirrer and a temperature of 37°C was maintained. Sample of 5ml of the receptor compartment was removed at required interval of time over a period with same amount replaced to maintain sink condition. The sample was analysed using UV Spectrophotometer. Amount of drug released at various time intervals was calculated with the help of calibration curve with phosphate buffer (pH 6.8) and plotted against time.

F. Globule size

As visual observation is not sufficiently capable of studying most instability mechanisms as well as droplets smaller than 100 μm, microscopy is used to observe the droplets that cannot be viewed by unaided eyes and to examine the factors that influence the stability of the emulsion system. For example, using microscopy, one could easily observe the distribution and dimensions of droplets, and thus obtain information on the cause of the emulsion system's instability. That is, the emulsion is no flocculated if the droplets are homogenously distributed in the image with a relatively small size. By contrast, a flocculated emulsion can be identified when the equally larger-sized droplets gather close to one another without merging into bigger ones. The emulsion may undergo coalescence or Ostwald ripening if there is presence of small and big droplets present at the same time.

RESULTS AND DISCUSSION

A. Physical appearance

- Colour : Milky white
- Odour : Odourless
- Appearance : Translucent
- Consistency : Smooth
- Grittiness : Non- gritty
- Clogs : Absent

B. pH

- **For nano-emulsion**

Table No 4: pH of nano-emulsion.

Formulation no	pH
F1	6.73
F2	6.46

- **For nano-micelles**

Table No 5: pH of nano-micelles.

Formulation	pH
F1	7.21
F2	6.86

- **For nanomiemgel**

Table No 6: pH of nanomiemgel.

Formulation	pH
F1	6.86
F2	6.94

C. Rheological study:(viscosity)

➢ **For nano-emulsion**

1. 570 cp
2. 630 cp
3. 597 cp

$$\text{Mean} = \frac{\Sigma X}{N} = \frac{1797}{3} = 599 \text{ cp}$$

➢ **For nano-micelles**

1. 260 cp
2. 280 cp
3. 274 cp

$$\text{Mean} = \frac{\Sigma X}{N} = \frac{814}{3} = 271.33 \text{ cp}$$

➢ **For nanomiemgel**

1. 3080 cp
2. 3165 cp
3. 3121 cp

$$\text{Mean} = \frac{\Sigma X}{N} = \frac{9366}{3} = 3122 \text{ cp}$$

D. Extrudability study

Table No 7: Extrudability studies of nanomiemgel.

Sr. No.	Formulation no.	Extrudability
1	F1	++++
2	F2	+++

E. In-vitro diffusion study

1. For nanomiemgel

Table No 8: Drug release from nanomiemgel.

Time	% release
0	0
10	12.5
20	29.86
30	42.43
40	60.64
50	73.52
60	80.83
120	91.1
180	97.32
240	98.33
300	99.64

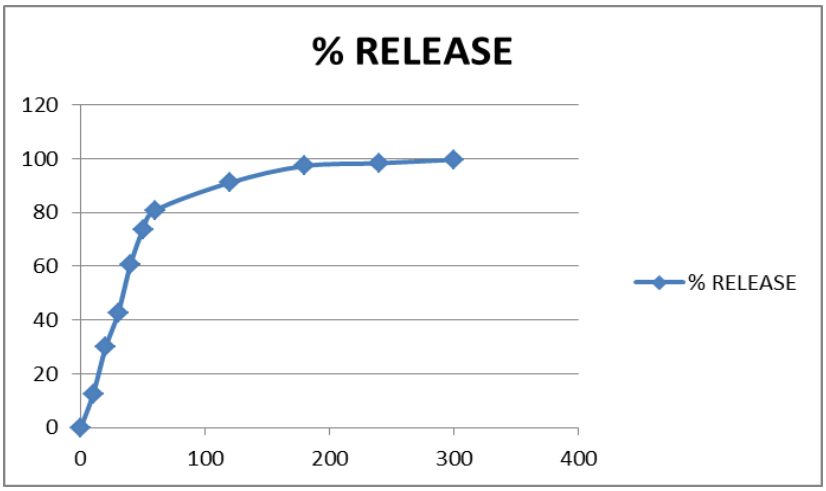

Fig 5: Graph showing drug release pattern.

F. Globule size analysis

I. Nano-emulsion

Table No 9: Globule size detection of nano-emulsion.

Globule no.	Globule size(nm)	Globule no.	Globule size(nm)
1	63.22	**11**	79.94
2	74.11	**12**	113.23
3	57.32	**13**	124.90
4	38.96	**14**	70.12
5	67.23	**15**	130.89
6	76.54	**16**	140.74
7	85.96	**17**	142.65
8	32.12	**18**	145.03
9	101.19	**19**	123.55
10	110.03	**20**	80.92

$$\text{Mean} = \frac{\Sigma X}{N} = \frac{1859.09}{20} = 92.95 \text{ nm}$$

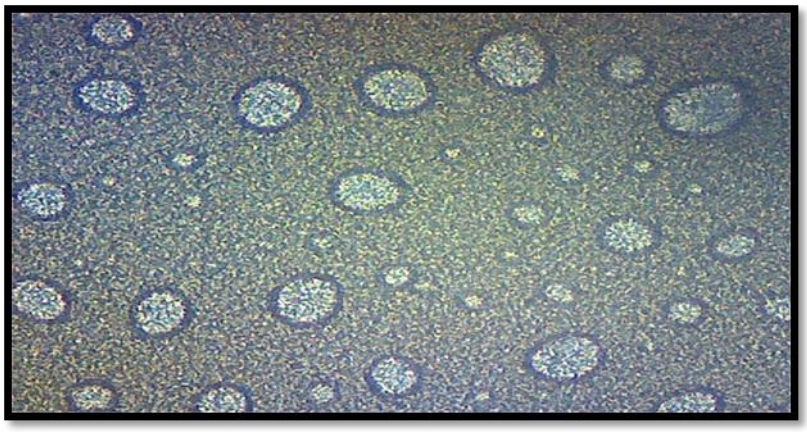

Fig 6: Globules of nano-emulsion.

II. Nano-micelle

Table No 10: Globule size detection of nano- micelle

Globule no.	Globule size(nm)	Globule no.	Globule size(nm)
1	63.22	**11**	79.94
2	74.11	**12**	116.23
3	57.32	**13**	28.90
4	138.96	**14**	54.12
5	67.23	**15**	10.89
6	76.54	**16**	20.74
7	85.96	**17**	32.65
8	132.12	**18**	41.03
9	101.19	**19**	123.55
10	110.03	**20**	180.92

$$\text{Mean} = \frac{\Sigma X}{N} = \frac{1595.92}{20} = 79.796 \text{ nm}$$

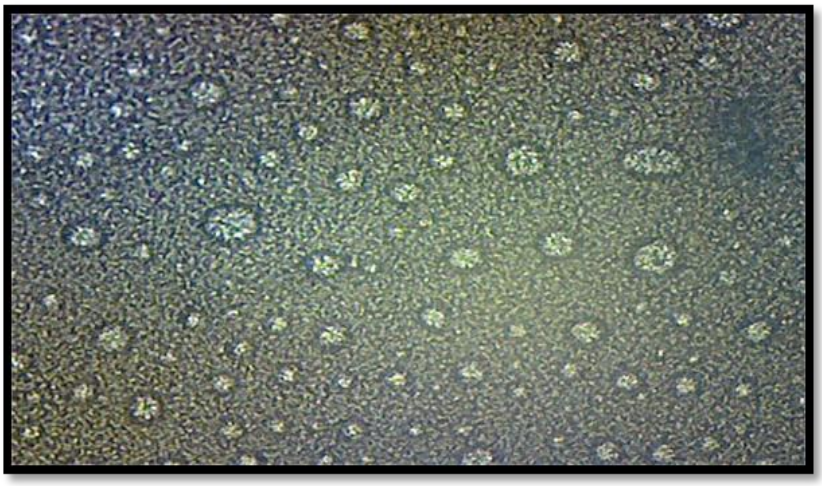

Fig 7: Globules of nano-micelles.

CONCLUSION

Using a new combination of two different drug delivery systems (NEM+NMI), the absorption of the combined system (NMG) was found to be better than either of the individual drug delivery systems owing to the utilization of the almost all the paths of absorption available for that particular drug.

Conventional topical formulations are not able to provide prolonged drug release and also associated with many side effects like gastric irritation, nausea, vomiting, bleeding etc. the Nanomiemgel comprising. Nano emulsion and Nano micelle enhanced the skin permeation by Trans locating the nanoparticles across the deeper skin layers by improving the skin contact time and it forms a thin layer on the skin surface. It remains adhered to the effected part for a longer period without getting rubbing and it's provide sustained drug release and improve the patient compliance.

The in-vitro diffusion profile gives shear evidence that the release of nanomiemgel is between nano-emulsion and nano-micelles and the duration of release is been enhanced to a drastic level.

REFERENCES

1. Jaganmohan Somagoni, Cedar H. A. Boakye, Nanomiemgel- A Novel Drug Delivery System for Topical Application, PLOS- ONE, 9(12): e 115952.
2. Deepak Singh and Dr. Prashant Upadhyay; NANOEMULSION: A NOVEL APPROACH; World Journal of Pharmacy and Pharmaceutical Sciences, 5(12): 1586-1592.
3. Pande VV and Sanklecha VM. Review on NANO- EMULSION: A Novel Drug Delivery System. Austin Pharmacol Pharm, 2018; 3(1): 1013.
4. Nazia Khanam, Md. Irshad Alam, Anupam K Sachan1, Sudhir S Gangwar, Ranjana Sharma4; RECENT TRENDS IN DRUG DELIVERY BY NANO-MICELLE : A REVIEW; Asian Journal of Pharmaceutical Research and Development, May–June 2013; 1(3): 115-122.
5. Rampal Rajera, Kalpana Nagpal, Shailendra Kumar Singh, and Dina Nath Mishra; NANO-MICELLE: A CONTROLLED AND NOVEL DRUG DELIVERY SYSTEM; Biological & Pharmaceutical Bulletin, July, 2011; 34(7): 945—953.
6. Vyas S. P., Khar R. K., "TARGETED AND CONTROL DRUG DELIVERY," 1st ed., Chap. 6, CBS Publishers and Distributors, New Delhi, 2002; 249—276.

7. Gandhi Arijit, Sen Suma Oomen, Paul Abhijit.; CURRENT TRENDS IN NANO-MICELLE DRUG DELIVERY SYSTEM; Asian Journal of Pharmacy and Life Science, July-Sept, 2012; 2(2).
8. Tangri Pranshu and Khuran Shaffi; NANO-MICELLE: FORMULATION AND EVALUATION.; International Journal of Biopharmaceutics. 2011; 2(1): 47-53.
9. Das Krishnagopal and Ram Alpana; NANO-MICELLE AS A NOVEL DRUG DELIVERY SYSTEM: A REVIEW; International Journal of Applied Pharmaceutics, 2013; 6(1): 1-7.
10. Kaur Harsimran, Dhiman Sonia, Sandeep Arora; NANO- EMULSION: A NOVEL DRUG DELIVERY SYSTEM; International. Journal of Pharmaceutical Sciences. Rev. Res., 2012; 15(1): 22, 113-120.
11. Chandu V. Pola, Arunachalam A, Jeganath S, Yamini K, Tharangin K, Chaitanya; NANO-EMULSION: A NOVEL DRUG DELIVERY SYSTEM; International Journal Of Novel Trends In Pharmaceutical Science;, Feb, 2012; 2(1): 25-31.
12. Verma Navneet Kumar and Roshan Asha; NANO- EMULSION AND ITS APPLICATION-A REVIEW; International Journal of Research in Pharmacy And Life Sciences, 2014; 2(1): 182-184.
13. Arul Jothy M, Shanmuganathan S, Nagalakshmi; AN OVERVIEW ON NANO-EMULSION AS CARRIER INDERMAL DRUG DELIVERY; Journal of Pharmaceutical Sciences And Research, 2015; 7(11): 923-927.