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Nanostructured Lipid Carrier: An Approach for Topical Antifungal Drug Delivery

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ABSTRACT
Nanostructured lipid carriers are the advanced generation of lipid based nanoparticles made by blending of solid lipids with a certain proportion of liquid lipids resulting in less ordered lipid matrix that offer better stability delivery of the carrier molecule. Nanostructured lipid carriers were prepared by using seasame oil as a liquid lipid and piroctone olamine as a carrier. Optimization of nanocarrier was performed by design of experimentation, Box-Behnken design was used in optimization on the basis of three factors. Particle size of piroctone olamine loaded nanostructured lipid carriers was observed 155.7 nm. Optimized formulation was observed stable till the 12 months at room temperature conditions

Keywords: Nanostructured lipid carriers, Seasame oil, Piroctone olamine, Design of experimentation

1. INTRODUCTION

There are various routes of administration of drug to the human body. Namely oral, sublingual, rectal, parental, topical, inhalation etc. Topical drug delivery system is the localized administration which offer advantages of ease of delivery, high patient compliance as well as the avoidance of first-pass metabolism [1,2]. The specific challenge in designing a topical therapeutic system is lack, or reduced rate of absorption to achieve an optimal concentration of a certain drug at its site of action. One of the drawbacks is lack of cosmetic consideration for an appropriate duration [2,3]. Skin is the largest organ of the human body, which represents the outermost complex barrier between the body and the surrounding environment [4]. The skin consists of three layers, the epidermis, dermis and subcutaneous tissue. The subcutaneous layer is found beneath the dermis and is not considered part of the skin [5]. Epidermis act as a main barrier for topical drug delivery. Epidermis consists of keratinocytes layers in the following order: stratum basale (basal cell layer), stratum spinosum, stratum granulosum, and stratum corneum. Keratinocytes are protein-rich cells composed mostly of keratin and keratohyalin. Keratin provides structure and tensile strength by forming bundles of elastic fibrils that stretch across the cell [6,7]. Keratinocyte es from the stratum basale proliferate and move through the layers of the skin to eventually become anucleate, flattened cells called corneocytes, which are terminally differentiated cells in the stratum corneum [8]. The epidermal lipids act as a cement between cells of the stratum corneum that holds together the building blocks, corneocytes. The cornified envelope proteins and the covalently bound lipid envelope are important for the chemical resistance of the corneocytes [9].

Drug delivery systems ensure the delivery of drugs into the body where they are needed. This is directly concerned with the site of action and the desired effect of the preparation. Generally, topical preparations meant for systemic or local effects. Semi-solid formulations are more promising over solid and liquids considering its property to cling to surface of application for reasonable duration before they worn off [10]. Physicochemical properties, formulation composition and rheological properties provide a more scientific basis for the classification and distinction of topical dosage forms [11]. The vehicle plays a key role in the appearance, feel, and successful application of a topical drug. Therefore, the composition of a topical drug vehicle should be considered [12]. In search of safe and effective therapy, the development of new drugs has been the common practice historically. However, it involved numerous time, efforts, and huge cost. Alternate approach of drug delivery involved, carrier systems were used to deliver the molecules to specific receptor sites without afflicting the normal tissues and organs of the body [13]. The novel carriers have been exploited through almost all the routes of administration. In contrast to the conventional formulations, these novel dermatological systems are different in their composition and constructs including their exterior and interior design [13,14]

Nanostructured lipid carrier (NLC) is second generation smarter drug carrier system having solid matrix at room temperature. This carrier system is made up of physiological, biodegradable and biocompatible lipid materials and surfactants. NLC exhibit superior advantages over other colloidal carriers viz., nanoemulsions, polymeric nanoparticles, liposomes, SLN etc. The whole set of unique advantages such as enhanced drug loading capacity, prevention of drug expulsion, leads to more flexibility for modulation of drug release and makes NLC versatile delivery system for various routes of administration [15]. NLC's are made up of a binary mixture of solid-lipid and a liquid lipid (oil) as a hybrid carrier having an average size of 10-500 nm. The mixture NLC's is consist of long chain of liquid and lipid (oil) of ratio 99.9: 0.1 and having a short chain of solid and lipid having a ratio of 70:30. NLCs have three very specific features. These properties are based up on the location.

the drug is going to be integrated three different methods were adopted for a development and formulation of nanostructure NLCs [16]. NLC type I also called as imperfect crystal. NLC type I also called

imperfect crystal types have a badly structured solid matrix. The different fatty acids such as glycerides can be used to improve and modify the structure. The drug molecules lodges extra disorderly crystal as molecular form and amorphous clusters. To avoid this adding to a minor quantity of liquid lipid additional leans to increases the drug-loading [17]. Type II NLC`s are oil-in-lipid-in-water type they also called as multiple type. In type II NLC's, the solubility of oil is greater as compare to solubility of solid lipids. In type II NLC's high amount of oil are mixed with solid lipids. This kind of formulation permit controlled drug release and leakage of drug from lipid matrix [16, 18]. The III type of NLC's also called as amorphous type. In this technique of prepration of NLC's, the lipids are mixed in such a way that crystallizing can be prevented through mixing procedure. In type III lipid is in an amorphous state. The technique and method of crystallization often leads to drug expulsion [16, 19].

2. MATERIALS AND METHODS

Materials

Piroctone olamine was generously gifted. Seasame oil of RSG herbal house was purchased. Polyoxyethylene (20) oleyl ether, Ethanol and Polyethylene glycol 4000 was purchased from Sigma-Aldrich. Stearic alcohol (lanette 18) and Cetyl alcohol (lanette 16) was gifted by Sunshine India. Monosterol and Capryol 90 was gifted by Gattefosse. Glycerol monostearate was purchased by Loba chemie. Polysorbate 80 was purchased by Spectrochem Pvt. Ltd.. Phosphste buffer was purchased from Himedia. Captex was purchased from Abitec corporation. All the reagents were utilized in the experimentation were of analytical grade.

Methods

Formulation Development of Nanostructured Lipid Carriers

Screening of lipids for the formulation development of nanostructured lipid carriers

Selection of lipid was performed on the basis of solubility of API. Different types of lipids were choosen for the solubility analysis of piroctone olamine.

Table 1: Solubility study of piroctone olamine was performed in the following lipids

Sr. No.	Lipids
1	Seasame oil
2	Stearic alcohol (lanette 18)
3	Cetyl alcohol (lanette 16)
4	Captex
5	Polyethylene glycol 4000
6	Monosterol
7	Glycerol monostearate

The solubility of API in different solid lipids was determined by dissolving increasing amounts of individual API in a fixed amount of lipid and evaluation of the melt was performed visually. An evaluation of the solubility of the drug in lipids was initiated by mixing 5mg of piroctone olamine with a lipid. This mixture was then melted at 85°C and agitated at 100 rpm using a shaker water bath for 24 h. The solubility of piroctone olamine in the lipid was assessed visually. Followed by addition of 5mg of piroctone olamine to the dissolved lipid medium. The concentration of the drug in the lipid was increased by addition of 5mg of piroctone olamine in every step, until piroctone olamine failed to dissolve in the lipid after shaking for 24 h.

Screening of surfactants for the formulation development of nanostructured lipid carriers

The surfactants were screened based on their emulsification capacity which was assessed by size and PDI. As per the rHLB value concept every solid lipid and oil has a specific HLB value. If a surfactant combination reaches that HLB value, the optimum size of the formulation will be achieved. The formulations were prepared using different combination of surfactant and analysed for particle size and PDI by using zeta sizer. The combination which provides the minimum particle size and PDI was selected.

Preparation of nanostructured lipid carriers

Nanostructured lipid carriers were prepared by hot homogenization technique. Temperatures higher than the melting point of the lipids was selected for this process. Lipidic phase having mixture of oil, solid lipid, surfactant and piroctone olamine was heated. Similarly, at the same temperature aqueous phase of the formulation was heated. Aqueous phase (water and polysorbate 80) was added dropwise to the lipid phase. High shear homogenizer was used to prepare a hot emulsion. Mixture was homogenized for 15 minutes at 15000 rpm using high shear homogenizer resulting in an emulsion of oil in water type. Then, the product is left for cooling, and this leads to the initiation of solidification of lipidic part and then the formation of NLCs. Finally, cooling of the nanoemulsion to room temperature is done, and prepared formulation was analyzed for particle size and PDI of nanostructured lipid carriers.

Optimization of nanostructured lipid carriers

Formulation was optimized on the basis of homogenization speed and homogenization time. Further optimization of the formulation was carried out by using experimental design methods. The experiments are designed to allow us to estimate interaction and quadratic effects, and therefore they give an idea of responses. Optimization of formulation by Design of experiment (DoE) was performed by using response surface design. It helps in making the formulation robust and troubleshoots problems and weak points. Formulation was optimized on the basis of three factors by using Box-Behnken design. Box-Behnken design was selected over the designs because in this design the treatment combinations are at the midpoints of edges of the process space and at the center. These designs are rotatable and require 3 levels of each factor. The geometry of this design suggests a sphere within the process space. These designs require fewer treatment combinations than other designs in cases involving 3 or 4 factors [20]. Concentration of brij O20 (Polyoxyethylene (20) oleyl ether), glycerol monostearate and polysorbate 80 was considered as independent variables. Whereas, vesicle size and PDI was selected as dependent variables. Design expert software was used for the optimization studies. The responses of all the 17 runs were fitted in different model and relationship among the independent variables were generated by using design expert software.

Characterization of nanostructured lipid carriers

Particle size and zeta potential

Piroctone olamine loaded nanostructured lipid carriers were analyzed using malvern zetasizer. Sample was diluted and analyzed at 25°C and average of three measurement was observed. The PDI was determined as a measurement of the homogeneity of suspension.

Entrapment efficiency

The entrapment efficiency of nanostructured lipid carriers was determined by using centrifugation method. Dispersion of drug loaded nanoparticle was centrifuged at 20000 rpm for 45 minutes in a refrigerated centrifuge. After centrifugation the supernatant liquid was collected and filtered to measure the free drug concentration of drug. The filtered liquid was diluted and absorbance was measured by using UV spectrophotometer.

Entrapment efficiency= Weight of the drug incorporated/Weight of the drug initially taken*100

Morphology of nanostructured lipid carriers

The morphology and particle size of nanostructured lipid carriers were observed by using transmission electron microscopy (TEM). Briefly, a drop of vesicular formulation was placed on the carbon coated copper grid and stained with phosphotungistic acid (1% w/v) and excess was drained off with filter paper. The grid was air dried and viewed under the transmission electron microscope at different magnifications.

Stability of nanostructured lipid carriers

Stability of nanostructured lipid carriers was carried out at room temperature condition. Suspension of nanostructured lipid carriers was kept at room temperature at every time point suspension was analysed for their particle size and PDI. Suspension was analysed at 15 days, 1M, 2M, 3M, 6M, 9M, 12M and 15M time points.

3. RESULTS

Formulation Development of Nanostructured lipid carriers

Screening of lipids for the formulation development of nanostructured lipid carriers

Solubility of piroctone olamine was performed in different lipids. Solubility in lipids was observed until piroctone olamine was failed to dissolve. Maximum solubility of piroctone olamine was observed in Glycerol monostearate and minimum solubility was observed in captex. Glycerol monostearate was selected as solid lipid for the further formulation optimization process.

Solubility observed: Captex<seasame oil<Polyethylene glycol 4000<monosterol<lanette 18=lanette 16< Glycerol monostearate

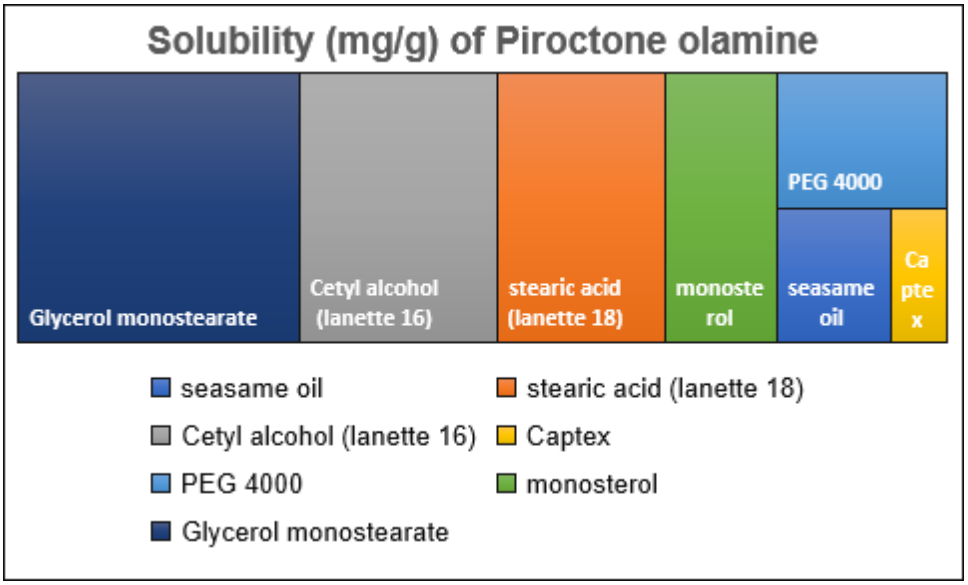


Figure 1: Solubility of piroctone olamine

Screening of surfactants for the formulation development of nanostructured lipid carriers

The surfactants were screened based on their emulsification capacity. As per the rHLB value concept emulsification of lipids was assessed by size and PDI. Polysorbate 80 was selected as surfactant for aqueous phase. Non aqueous phase was emulsified with aqueous phase by using Brij O20 (Polyoxyethylene (20) oleyl ether), Capryol 90 and Emuledge as a surfactant of lipidic phase. Results were analysed on the basis of particle size and PDI.

Table 1: Formulation 1 composition and results

Sr. No.	**Ingredients**	**Concentration (%w/w)**
1	Piroctone olamine	0.05
2	Glycerol monostearate	0.7
3	Seasame oil	0.2
4	Capryol 90	0.1
5	Polysorbate 80	0.05
6	Water	q.s.
	Results	
	Particle Size	230.9 nm
	PDI	0.359

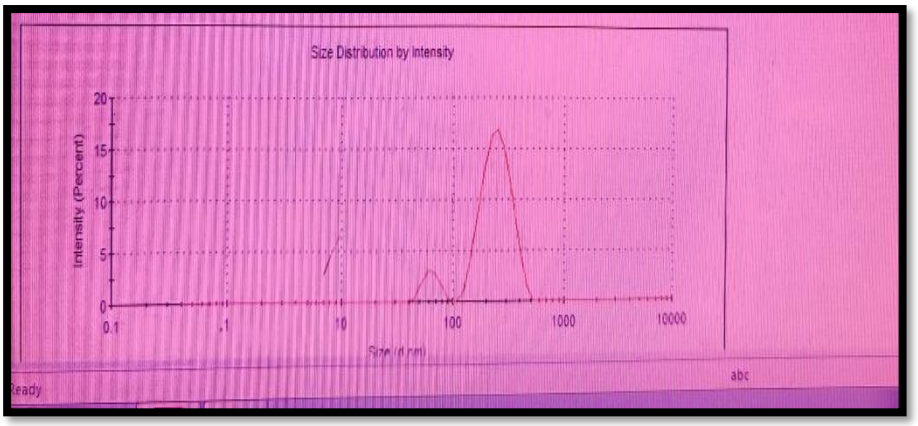


Figure 2: Particle size and PDI result of formulation 1

Table 2: Formulation 2 composition and results

Sr. No.	**Ingredients**	**Concentration (%w/w)**
1	Piroctone olamine	0.05
2	Glycerol monostearate	0.7
3	Seasame oil	0.2
4	Brij O20 (Polyoxyethylene (20) oleyl ether)	0.1
5	Polysorbate 80	0.05
6	Water	q.s.
	Results	
	Particle Size	108.3 nm
	PDI	0.286

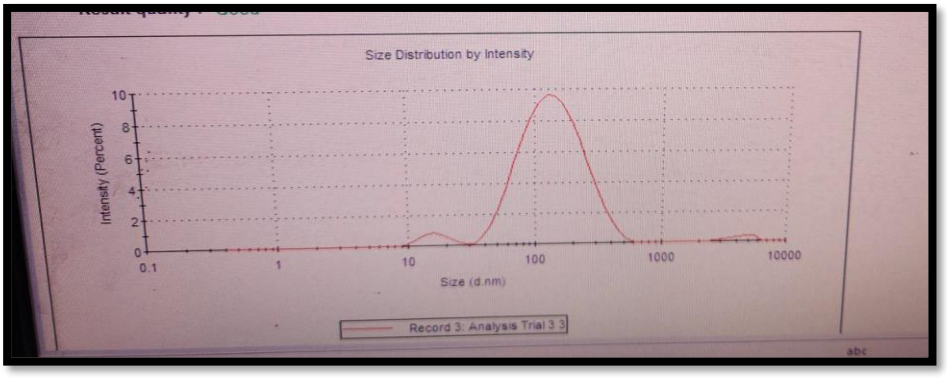


Figure 3: Particle size and PDI result of formulation 2

Table 3: Formulation 3 composition and results

Sr. No.	Ingredients	Concentration (%w/w)
1	Piroctone olamine	0.05
2	Glycerol monostearate	0.7
3	Seasame oil	0.2
4	Emuledge	0.1
5	Polysorbate 80	0.05
6	Water	q.s.
	Results	
	Particle Size	948.3 nm
	PDI	0.729

Figure 4: Particle size and PDI result of formulation 3

Preparation of nanostructured lipid carriers

Nanostructured lipid carriers were prepared by hot homogenization technique. Temperatures 75°C was selected for the process which is higher than the melting point of the glycerol monostearate which is 65°C. Lipidic phase having mixture of oil, solid lipid, surfactant and piroctone olamine was heated at 75°C. Similarly, at the same temperature aqueous phase of the formulation was heated. Aqueous phase was added dropwise to the lipid phase. Mixture was homogenized for 5,10 and 15 minutes by using high shear homogenizer. Homogenizer rpm range was selected for optimization. Formulation was prepared at 10000, 12000 and 15000 rpm using high shear homogenizer resulting in an emulsion of oil in water type. Then, the product is left for cooling for 15 minutes. Optimization of homogenization time and speed was performed. Homogenization speed at 15000 rpm and homogenization time 15 minutes was optimized for the formulation development of nanostructured lipid carriers on the basis of particle size and PDI.

Optimization of nanostructured lipid carriers

Formulation was optimized on the basis of homogenization speed and homogenization time. Further optimization of the formulation was carried out by using experimental design methods. Optimization of formulation by Design of experiment (DoE) was performed by using response surface design. Formulation was optimized on the basis of three factors by using Box-Behnken design. Concentration of brij O20 (Polyoxyethylene (20) oleyl ether), glycerol monostearate and polysorbate 80 was considered as independent variables. Whereas, vesicle size and PDI was selected as dependent variables. The responses of all the 17 runs were fitted in different model and relationship among the independent variables were generated by using design expert software.

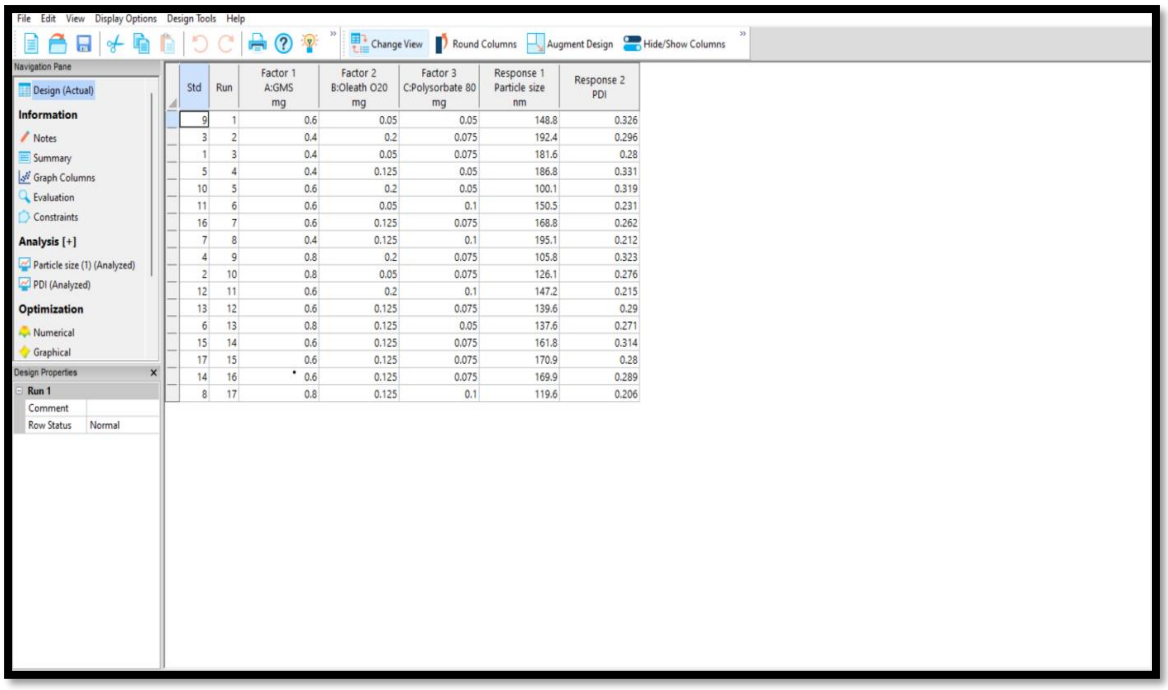


Figure 5: Nanostructured lipid carriers optimization trials as per Box-Behnken design

Limits of independent variables were selected on the basis of literature available. Summary of different factors and responses was observed satisfactory. Summary of factors and responses were summarized in figure 6 and 7 respectively.

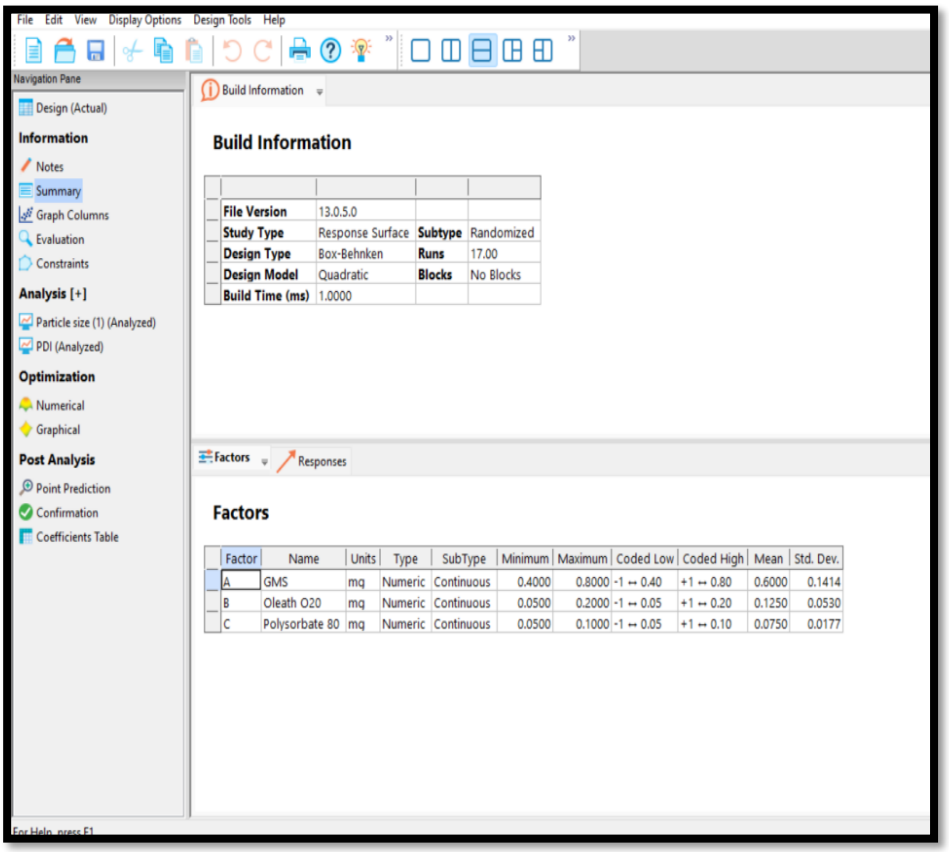


Figure 6: Summary of factors

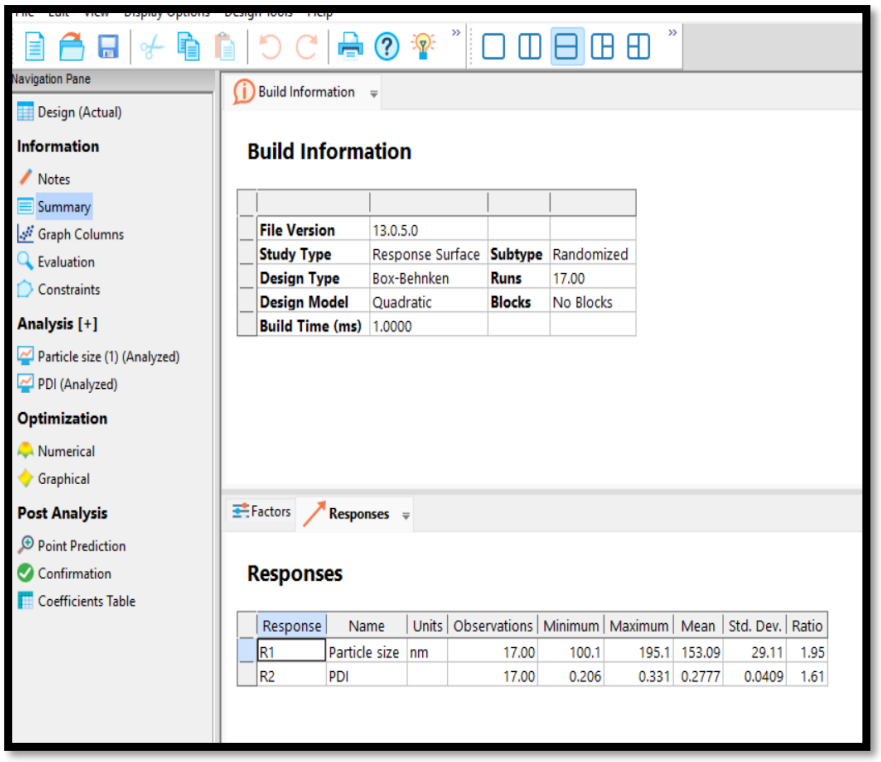


Figure 7: Summary of responses

Analysis of particle size an PDI by ANNOVA was performed F and P values indicates that model terms are significant. Predicted R^2 value is in reasonable agreement with adjusted R^2 .

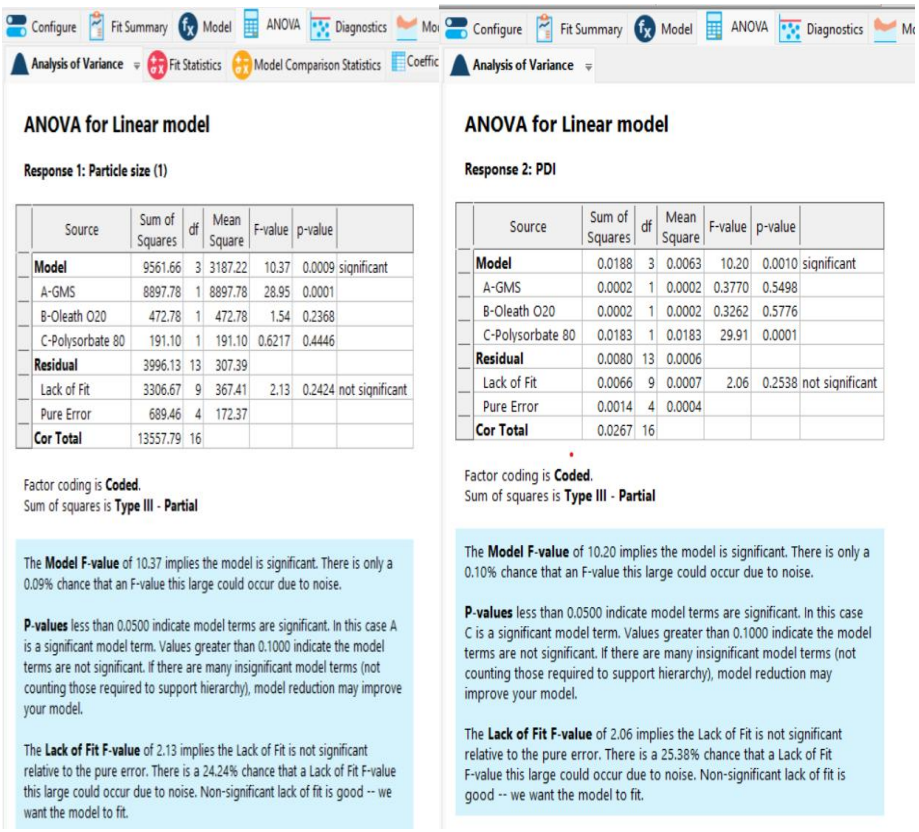


Figure 8. ANOVA results of responses particle size and PDI.

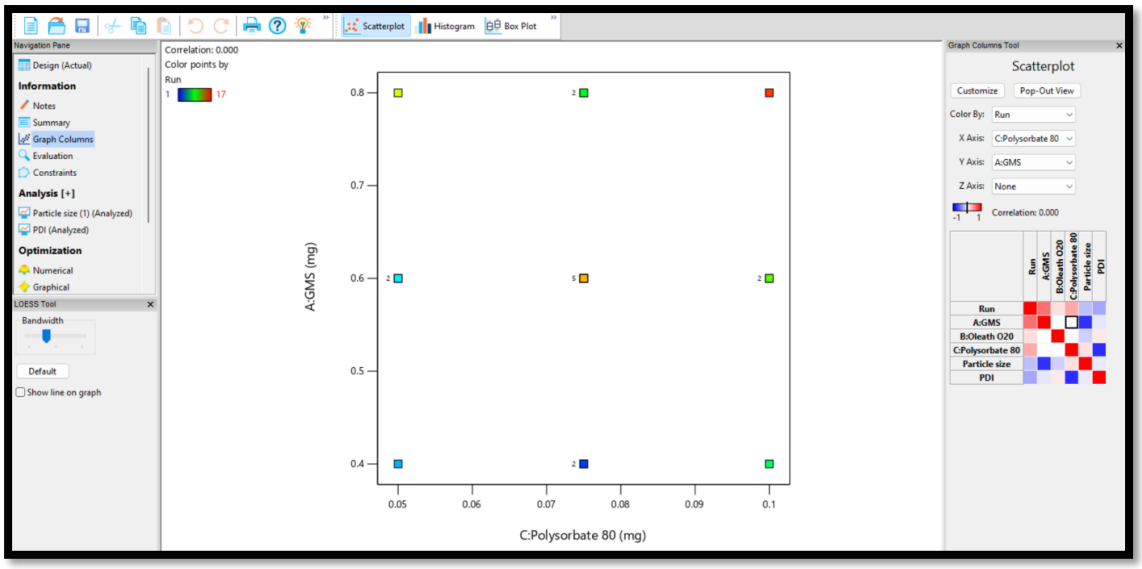


Figure 9. Relationship between independent variables

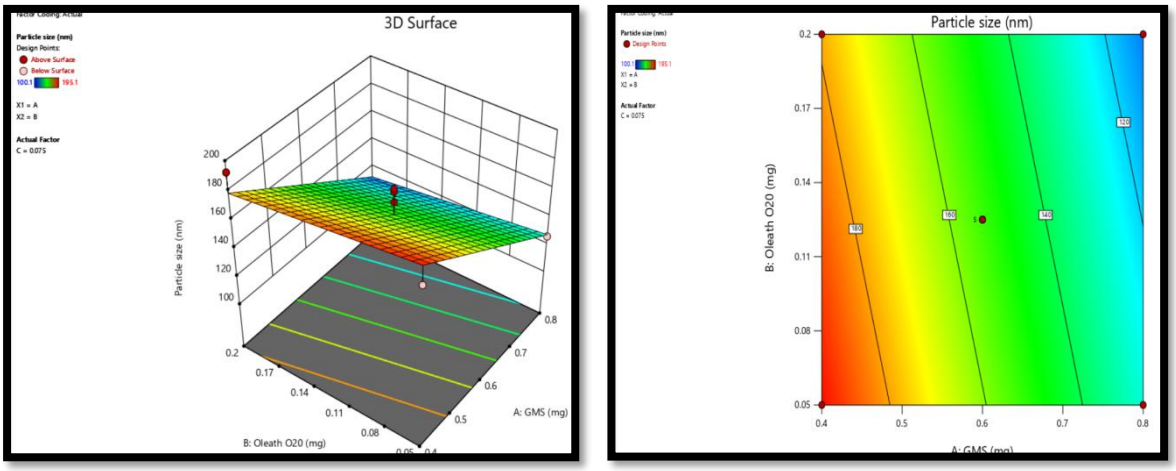


Figure 10. Contour plot and 3D surface plot for particle size

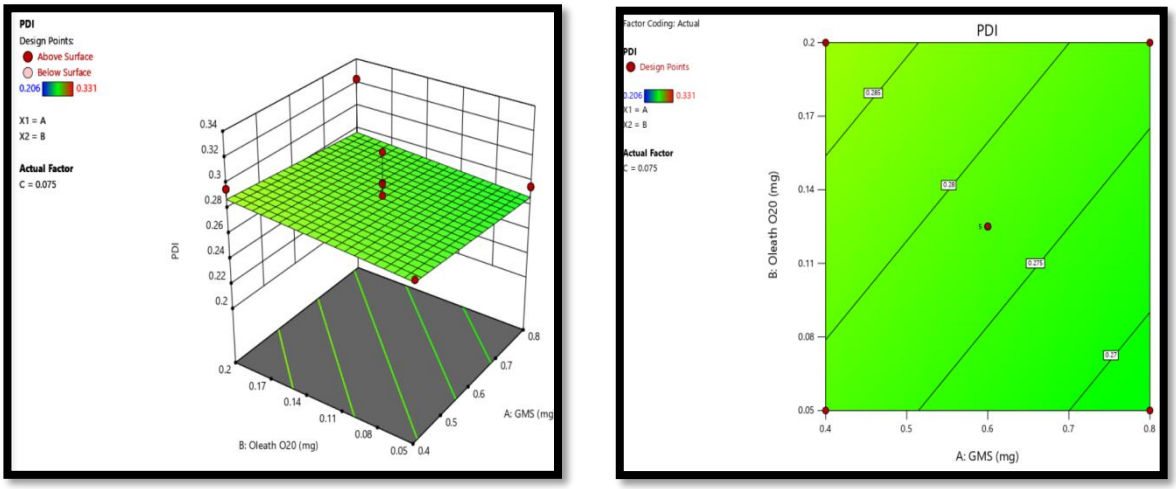


Figure 11. Contour plot and 3D surface plot for PDI

Table 4 Analysis of optimized formulation

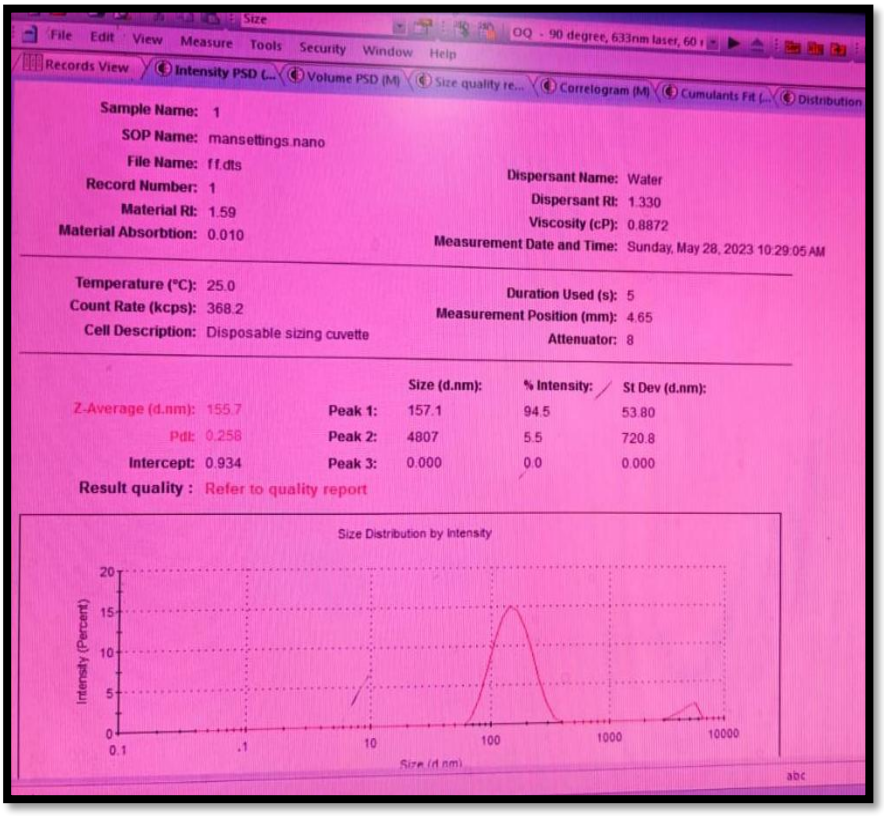
Independent Variables	**Optimum value (%)**	
Brij O20	0.050	
Glycerol monostearate	0.6059	
Polysorbate 80	0.0701	
Dependent Variables	**Predicted Response**	**Observed Response**
Particle size	158.8	155.7
Zeta potential	0.281	0.258

Particle size and PDI of final predicted formulation were observed within the range of predicted responses. Combination of brij O20 0.050%, glycerol monostearate 0.6059% and polysorbate 80 0.0701% were used in formulation development.

Characterization of nanostructured lipid carriers

Particle size and zeta potential

Piroctone olamine loaded nanostructured lipid carriers were analyzed using malvern zetasizer. Average sum of three measurement was calculated. Particle size of piroctone olamine loaded nanostructured lipid carriers was 155.7 nm. Polydispersity index was observed 0.258.



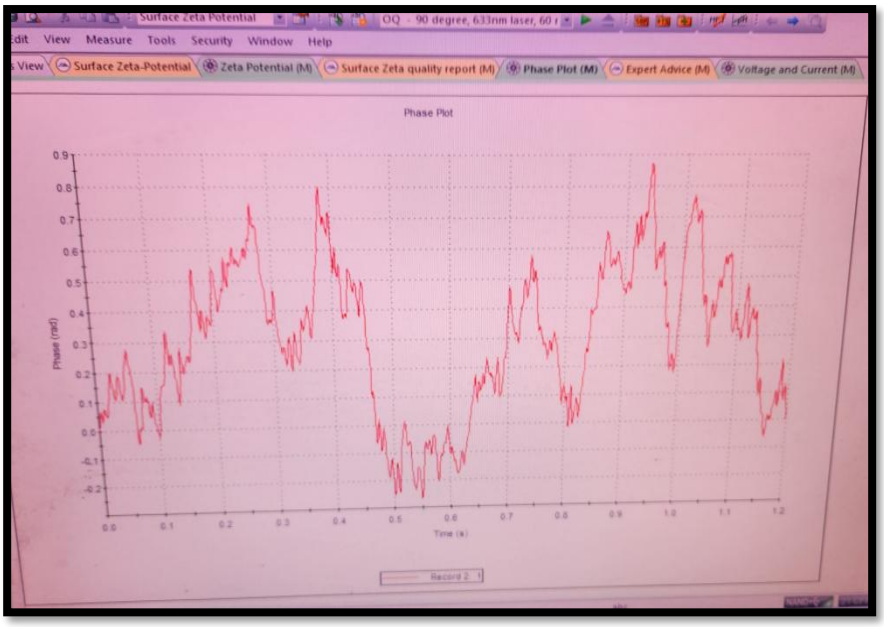


Figure 12: Particle size, PDI and zeta potential results of optimized formulation

Entrapment efficiency

The entrapment efficiency of nanostructured lipid carriers was determined by using centrifugation method. 98.93% entrapment of piroctone olamine was observed in nanostructured lipid carriers.

Entrapment efficiency= Weight of the drug incorporated/Weight of the drug initially taken*100

Morphology of nanostructured lipid carriers

The morphology and particle size of nanostructured lipid carriers were observed by using transmission electron microscopy (TEM). A good correlation was observed particle size observed in TEM and zetasizer. Results shows nearly spherical shape particles. Aggregation did not observe in the TEM analysis.

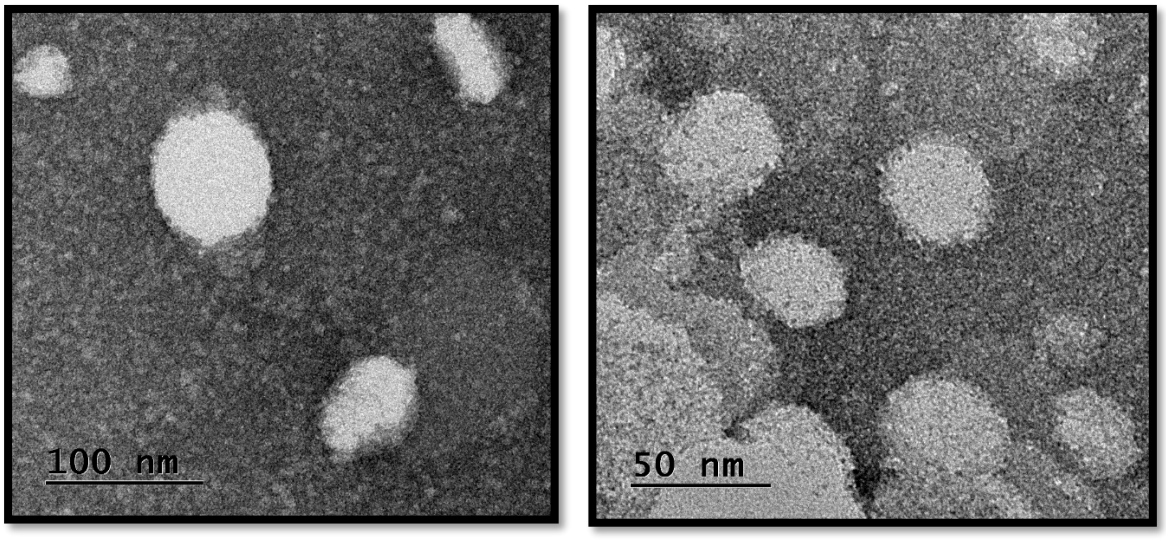


Figure 13: Transmission electron microscopy images of nanostructured lipid carriers

Stability of nanostructured lipid carriers

Stability of nanostructured lipid carriers was carried out at room temperature condition. Suspension of nanostructured lipid carriers was observed stable till 12 months time point. Suspension was analysed at 15 days, 1M, 2M, 3M, 6M, 9M, 12M and 15M time points. Results were summarized in the table below.

Table 5: Stability results of nanostructured lipid carriers

Observations at room temperature		
Stability time points	**Particle size (nm)**	**PDI**
Initial	231	0.208
15 days	230.7	0.181
1M	215.6	0.279
2M	212.1	0.249
3M	219	0.233
6M	230	0.325
9M	218.3	0.306
12M	218	0.263
15M	545.6	0.824

4. SUMMARY AND CONCLUSION

Skin is the largest organ of the body. Epidermis plays an important role in the drug delivery of skin. Stratum corneum is the outermost layer works as barrier for the drug delivery. A part from the conventional delivery systems nanocarrier based drug delivery systems are used in the topical delivery. An API carrier which is known for the antifungal activity was selected. Development of a nanocarrier system by using solid and liquid lipids was carried out by using homogenization technique. Nanostructured lipid carriers of piroctone olamine was prepared by using glycerol monostearate as a solid lipid and sesame oil is a liquid lipid. Seasame oil also has an antifungal property. A chemical antifungal moiety piroctone olamine and a natural antifungal moiety seasame oil were used in development of nanostructured lipid carriers. Capryol 90, Brij O20 and emuledge surfactant were selected for formulation development. Optimum particle size and PDI was observed when formulation was prepared by using brij O20 as a surfactant. Further optimization of formulation was carried out by using Design of Experiment. Formulation was optimized on the basis of three factors by using Box-Behnken design. Concentration of brij O20 (Polyoxyethylene (20) oleyl ether), glycerol monostearate and polysorbate 80 was considered as independent variables. Whereas, vesicle size and PDI was selected as dependent variables. Formulation for all 17 runs were prepared. Analysis of particle size and PDI by ANNOVA was performed F and P values indicates that model terms are significant. Predicted R^2 value is in reasonable agreement with adjusted R^2. All the results were analyzed by using design expert software. Particle size (155.7 nm) and PDI (0.258) of final predicted formulation were observed within the range of predicted responses. Combination of brij O20 0.050%, glycerol monostearate 0.6059% and polysorbate 80 0.0701% were used in formulation development. 98.93% of piroctone olamine was successfully entrapped in the core of solid lipid nanopartciles. Prepared nanoparticle based topical formulation was developed and found stable for a year at room temperature

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