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Nano-Transfersomes of Vitamin-E and Aloe-Vera for The Management of Psoriasis

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Abstract: Psoriasis is a topical disease that leads to red and scratchy skin, most commonly on the knees, elbows, trunk and scalp. Psoriasis is an inflammatory constrains, and *aloe-vera*, a natural product, reported to have anti-inflammatory properties. Further, Vitamin-E has antioxidant properties and it can aid to protect against some of the oxidative burden that occurs with psoriasis. Naturally, vitamin E has broad spectrum benefits for health, skin, and hair. The aim of present research was to prepare and characterized Nano-Transfersomes of Vitamin-E and *aloe-vera* for the management of psoriasis. Nano-Transfersomes pharmaceutical formulation was prepared and evaluated for particle size, Zeta potential, drug entrapment, shape and surface morphology, pH, viscosity, *in vitro* drug release, skin irritation and *in vitro* stability. The mean size, poly disparity index (PDI), Zeta potential and entrapment efficiency of optimized Nano-transfersomal vesicles prepared were 146.8±0.98 nm, 0.593, -38.5 Mv and 92.29±4.51% respectively. The prepared formulation revealed prolonged drug release during the study of 24h and results revealed that the drug is more permeable through the egg membrane from Nano-Transfersomes gel formulation in comparison to marketed formulation (Vitamin E Gel Moisture Cream). Vitamin-E and *aloe-vera* containing Nano-Transfersomes was found to be highly efficacious as topical formulation, as optimized preparation indicated no any evidence of skin irritancy in mice. The present formulation indicated the compatibility of formulations with skin which divulged the therapeutic efficacy of natural formulation in sustainable, biodegradable and biocompatible manner in the management of psoriasis.

Keywords: Nano-Transfersomes, Vitamin-E, aloe-vera, psoriasis, dermal disease, Nano-formulation

1. Introduction

Psoriasis is an enduring inflammatory derma disease with a strong genetic predisposition and autoimmune pathogenic property. Psoriasis is observed as a very annoying, long-lasting and arbitrary topical disorder, related with immunological impairment of T-cells. It is an immunological disorder produced by redness of dermal cells which can multiply up to tenfold faster than the normal cells. Although the foremost reasons for disease are not apparently known, it is assumed as an impairment of keratinocytes [1].

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Vitamin-E has antioxidant property, which can help to protect against some of the oxidative distress that occurs with psoriasis. Naturally, vitamin E has a wide range of advantages for health, skin, and hair. Scientific reports state that consistent consumption of vitamin E-rich diet and topical application of the oil can reduce psoriasis [2].

Natural components acquire the advantages of high competence and low toxicity and thus are immensely encouraging therapeutic options for psoriasis [3,4]. Flavonoids have been shown to possess medicinal properties, and their exceptional anti-inflammatory consequence plays a vital role in the management of psoriasis. [5,6]. Additionally, luteolin was found to protect the psoriatic skin by the inhibiting the tyrosine. Coumarins, an important class of natural contents, have been reported to minimize the utterance of inflammatory chemokines, thereby indicating anti-psoriatic action [7,8]. Phenyl propionic acids, like ferulic acid and danshensu, have exhibited favorable outcome in psoriasis [8]. Curcumin, a polyphenolic element extracted from the roots of curcuma longa, has unique benefits for the management of psoriasis [9,10]. Kang *et al*. observed the anti-psoriasis consequences of curcumin by means of keratin 14-VEGF transgenic mice orally (40 mg/kg) [11]. Gallic acid is a natural, small moiety, which shows a wide spectrum of important pharmacological effects, among which an anti-psoriasis response has been the focus of research consideration in recent years [12]. Moreover, terpenoids, a type of natural component with anti-inflammatory multi-target activity, have the therapeutic property to treat the psoriasis [13]. Liu *et al.* studied about the anti-psoriasis effects of betulinic acid on psoriasis mice [14]. Alkaloids, a category of basic components containing nitrogen, are broadly distributed in plants, bacteria, and fungi. Alkaloids, such as indirubin, oxymatrine, and capsaicin, are considered to have the property of treating the psoriasis because of their strong anti-inflammatory impact [15-17]. Steroids exert a broad spectrum of pharmacological properties, especially in the treatment of psoriasis. Wu *et al.* observed the efficacy of diosgenin in the management of psoriasis [18].

Aloe vera gel is procured from inside the leaves of the aloe vera plant. It's believed to have soothing properties when applied to irritated, sunburned, or environmentally damaged skin. The gel may also have antibacterial and anti-inflammatory characteristics. Because of its soothing abilities, *aloe-vera* may be helpful as a supplemental cure for psoriasis. *Aloe vera* has also proven productive on the cutaneous burn and wound healing [19].

Transdermal drug delivery system has been an increased attentiveness in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery of drugs [20]. The term "Nano-Transferosomes" was preferred by Cevc *et al*., which are also called deformable liposomes or elastic or ultra-flexible liposomes. Nano-Transferosomes have been defined as specially originate vesicular particles consisting of at least one inner aqueous compartment enclosed by lipid vesicles; liposomes in morphology, but, functionally, nano-transferosomes are suitably deformable to go through pores of skin much lesser than their own size. Because of their self-optimized and ultra-flexible membrane properties, they are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency [21].

2. Materials and Method

Vitamin E was received as a gift sample from Lupin Pharmaceuticals Pvt Ltd, India. *Aloe-vera* was procured from the herbal garden of the Mittal Institute of Pharmacy, Bhopal, M.P., India. All other chemicals (Soya lecithin, sodium cholate, sodium deoxy cholate, span 80 and tween 80) used in this study were of analytical grade.

2.1 Preparation of Vitamin-E Loaded Nano-Transfersomes by Hand-Shaking Method

The modified hand-shaking method was applied to develop Vitamin-E loaded Nano-Transfersomes. The method has the same basic principle as the rotary evaporation-sonication method. In the modified hand-shaking process, an appropriate amount of soya lecithin, edge activator (sodium deoxycholate) and Vitamin-E were dissolved in organic solvent (isopropyl alcohol) in a round-bottom flask. All the excipients were completely dissolved in the solvent and a clear solution was obtained. Then, the organic solvent was removed by evaporation while hand-shaking. Meanwhile, the flask was slightly submerged in the water bath at a temperature of 60°C ± 2°C. A uniform thin lipid film was formed inner wall of the flask. The flask was retained overnight to achieve complete evaporation of the residual solvent. In addition, the formed film was hydrated with the aqueous phase i.e. phosphate buffer saline solution (pH 7.4) with manual shaking at a temperature above its phase transition temperature for 15 minutes [22].

2.2 Incorporation of Vitamin-E Loaded Nano-Transferosomes in *Aloe-Vera* Gel

(a) Preparation of Aloe-Vera Gel Base

0.5 g *aloe-vera* gel was weighed and dispersed in aqueous phase with gentle stirring and allowed to bloat for 24 hours to obtain 0.5% gel. Further, 2 ml of glycerin was introduced to the gel to maintain the consistency.

(b) Preparation of Aloe-Vera Gel Base

One gram of nano-transferosomes formulation was dispersed in 10 ml of isopropyl alcohol and centrifuged at 6000 rpm for 20 minutes to eliminate the unentrapped medicament. The supernatant was decanted and sediment was

assimilating into the *aloe-vera* gel base. The integration of the nano-transferosomes into gels was achieved by slow mixing at 25 rpm for 10 minutes.

2.3 *In Vitro* Characterization and Evaluation of Prepared Nano-Transferosome Gel

(a) Vesicle Size Determination

The vesicle size of nano-transferosome was determined by appropriate hydration of preparation (100 mg) using aqueous phase (10 mL) with hand shaking for 5 minutes. The vesicle size distribution study of nano-transferosomes was carried out by Zetasizer (Horiba Instruments Ltd., United Kingdom).

(b) Zeta Potential Measurements

Zeta potential measurement of nano-transferosome formulations were done by appropriate hydration of preparation (100mg) using aqueous phase (10mL) with hand shaking for 5min. The Zeta potential result of nano-transferosomes formulations were determined by Zetasizer. For Zeta potential estimation, diluted preparation was placed into the cataphoretic cell (cuvette) followed by measurement of Zeta potential.

(c) Surface Morphology

Light microscopy was applied for the structural evaluation of the vesicles, according to the reported method. Light microscopy was carried out by proper dilution of the nano-transferosomes formulation (100 mg) with 10 mL phosphate buffer saline (pH 7.4) and shaking the mixture gently for 5 minutes. A drop of diluted formulation was placed on a microscopic slide without a cover slip, and the process of vesicles formation was monitored optically through light microscope (Leica DM11) at 1000x and a microphotograph was taken.

(d) Determination of Entrapment Efficiency

The percentage entrapment efficiency was calculated after separating the unentrapped drug. Nano-transferosomes gel formulation (100mg) was diluted with 10mL of aqueous phase i.e. phosphate buffer saline (pH 7.4) and hand shaken for 5 minutes. Further, separation of the unentrapped drug was accomplished by centrifugation of formulation at 5000 rpm for 30min followed by removal of supernatant. One mL of this supernatant was taken and after appropriate dilution, absorbance was observed using UV/Visible spectrophotometer (Shimadzu 1900, Japan). The sediment (1 mL) was resuspended in 1mL of aqueous phase i.e. phosphate buffer saline (pH 7.4). After proper dilution, the absorbance was recorded. The entrapment efficiency was then calculating using following equation:

$$\%\ Entrapment\ efficiency = \frac{Amount\ of\ drug\ in\ sediment}{Total\ amount\ of\ drug\ added}\ x\ 100 \qquad (1)$$

Amount of drug in supernatant and sediment gave total amount of drug. Estimation of Vitamin-E was done by UV/Visible spectrophotometer (Shimadzu 1900, Japan) at its absorbance maxima (λ_{max}) 274 nm.

(e) pH Measurement

pH was determined by digital pH meter. The pH of the various nano-transferosomes gel formulations was determined directly in samples at room temperature by using digital pH meter (Systronic µ pH system 361).

(f) Viscosity Measurement and Rheological Behavior of Nano-Transferosome Gel Formulation

The rheological properties of the prepared nano-transferosomes gel formulations were determined by DVII+ Pro Brookfield Viscometer (Brookfield Engineering Laboratories, Stoughton, MA, United States, with software). Brookfield viscometer was employed to determine the flow properties and physical stability of the formulation by visual inspection of formulations and by performing the rheological measurements. The DVII+ Pro Brookfield Viscometer (Brookfield Engineering Laboratories, Stoughton, MA, United States, with software) with small sample adaptor (spindle and chamber SC4-18/13R) was used to determine flow properties of the various Vitamin-E loaded nano-transferosomes gel formulations between the percentage torque values of 10-100 using following equations (Equations 2 and 3).

$$\tau = K\ r\ n \qquad (2)$$

Where, τ = shear stress, r = shear rate, K = consistency index, n = flow index. By taking log on both sides;

$$Log\,\tau = Log\,K + n\,Log\,r \quad (3)$$

(g) Drug Permeation Study (Using Egg Membrane)

The drug permeation experiments were carried out by diffusion cell (Franz diffusion cell) using biological membrane (egg membrane). The shell membrane of the egg (Gallus domesticus) that located inside the shell just under the firm calcified covering, was separated by immersing the egg in HCL 0.01N solution for 6 hours to dissipate the calcified layer and the membrane was cut deliberately to remove the content of egg and washed it with normal saline solution (0.9% NaCl).

Franz diffusion cell was used for the drug permeation studies. Nano-transferosomes gel (100 mg) was applied topically on surface of egg membrane evenly. The egg membrane was clamped between the donor and receptor compartments of diffusion cell (Fig. 1). The receptor compartment was filled with 10mL phosphate buffer saline (PB pH 7.4) and agitated over a magnetic stirrer. The temperature of the receptor compartment was maintained at 37±1°C with an external, constant temperature circulating water bath. At predetermined intervening time, aliquots (1.0 mL) were withdrawn from the receptor compartment and replaced with an equivalent volume of fresh phosphate buffer saline solution (pH 7.4) to maintain sink condition. Sample was analyzed for drug content (Vitamin-E) by UV visible spectrophotometer at its absorbance maxima (λ_{max}) 274 nm after appropriate dilution.

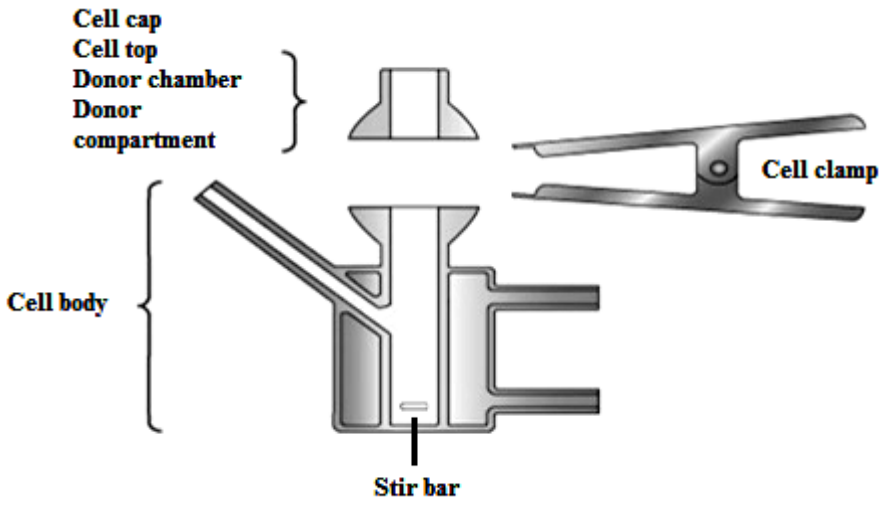

Fig. 1 - Various segments of Franz diffusion cell for drug permeation studies. Schematic diagram of different section of diffusion cell

(h) Skin Sensitization Studies

Skin sensitization studies were carried out as per the method reported by Kulkarni and Jain [23]. The hairs were removed from the dorsal surface of the mice by using hair removing cream; an area of 4 cm^2 was marked. One group dealt as control while the other as test group. Animals were used for the study post 24 h of depilation. The preparation was employed (100 mg/mice) once a day for 7 days. The mice were observed for response and the reaction if any recorded during the studies and was coded as:

0 : No erythema
0.5 : Slight erythema
1.0 : Slight but concurrent or moderate patchy erythema
1.5 : Moderate erythema
2.0 : Severe erythema with or without edema

(i) Stability Studies

The prepared developed formulation was subjected to stability studies in amber colored glass containers at three different temperatures (4°C, RT, and 40°C) and evaluated periodically (every 15th day) for percent drug content, pH, color change, phase separation, and rheological property for a period of 60 days.

3. Results and Discussion

In the present work, Nano-Transfersomes of Vitamin-E was incorporated in *aloe-vera* natural gel in order to manage the dermal disease psoriasis. For this purpose, the formulations were prepared and evaluated.

3.1 Vesicle Size

The vesicles size and size distribution were estimated by dynamic light scattering method (DLS), using a computerized inspection system (Horiba Instruments). Nano-transferosome vesicles formed upon hydration of drug-loaded optimized nano-transferosome gel formulation possessed an average particle size of 146.8 ± 0.98 nm. For vesicles size determination, vesicular suspension was diluted with aqueous phase i.e. phosphate buffer saline (pH 7.4) and the measurements were performed in triplicate (n=3).

All formulations were found to be in the nano size range with the moderate values of polydispersity index (PDI). PDI is the ratio of the standard deviation to the mean vesicle size and signifies the uniformity of the vesicle size within the formulation [24]. The value of PDI within 0.5 indicates a moderate distribution and uniformity of the vesicle size within the formulation (Fig. 2).

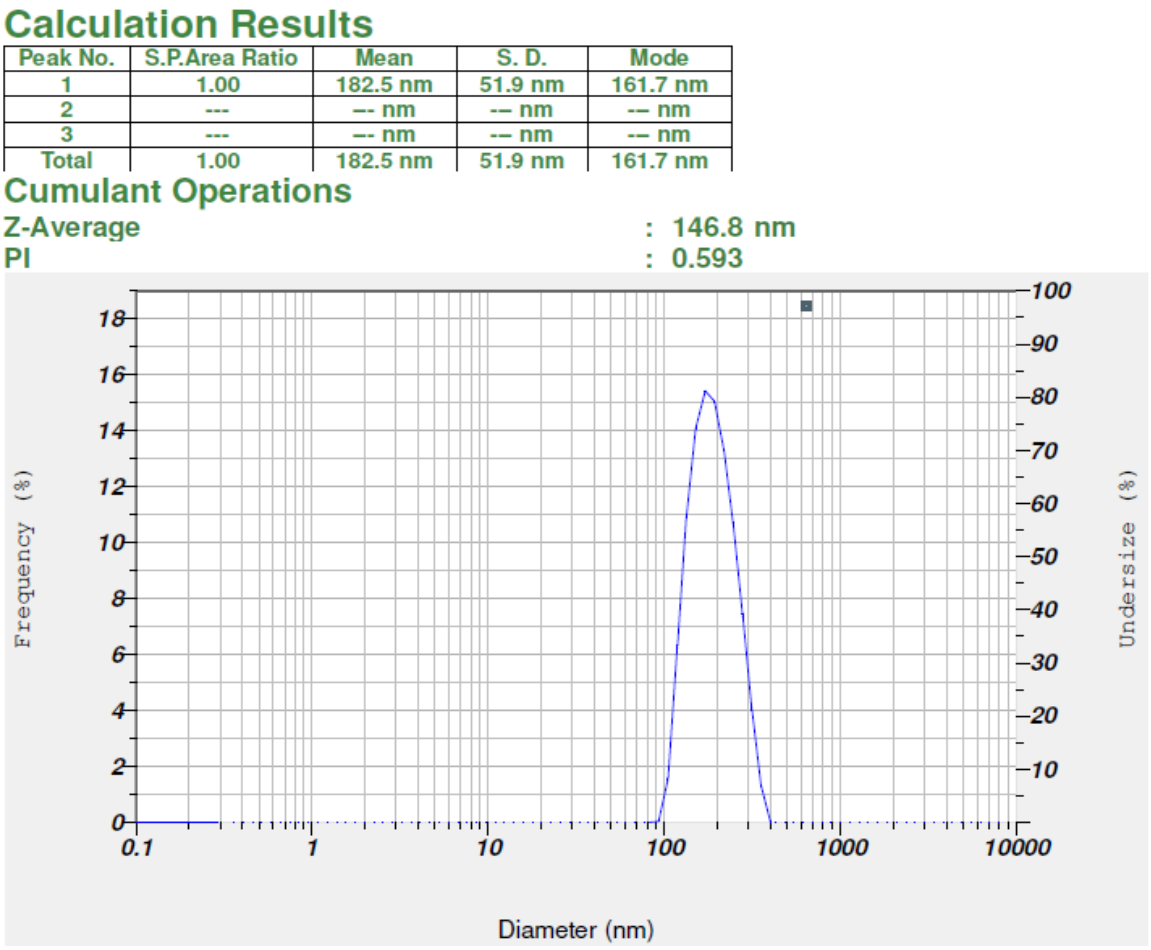

Fig. 2 - Vesicles size of optimized Vitamin-E loaded Nano-Transfersomes *aloe-vera* gel formulation

3.2 Measurement of Zeta Potential

The Zeta potential value showed a high negative surface charge for prepared formulation, suggesting a stable nano-transferosome vesicular formulation. The surface charge distribution in colloidal vesicles generally depends on the chemical structure of phospholipids and their arrangements in the vesicular bilayer. The data revealed that these vesicles were not aggregated and stable in the gel after the preparation of the nano-transferosomes gel formulations [25]. Zeta potential of nano-transferosome vesicles was found to be -38.5mV (Fig. 3).

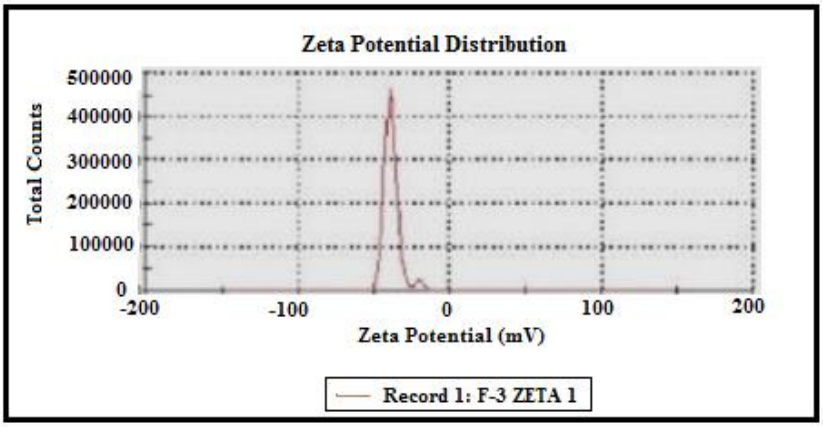

Fig. 3 - Zeta potential curve of optimized nano-transferosomes gel formulation after hydration

3.3 Surface Morphology

Optical microscopy was used to visualize the vesicles of various Nano-Transfersomes gel formulations, and to study their shape and lamellarity. Optical inspection revealed that Nano-Transfersomes appeared as bilayered vesicles, with the lamellae of vesicles uniformly spaced to the core and no aggregation irregularities were observed in the prepared formulation. Results of an optical microscopic image in which nano-transferosomes emerged as vesicular structures are confirming the spherical shape (Fig. 4).

The optical microscopy image clearly indicates that nano-transferosomes gel vesicles post hydration with phosphate buffer saline (pH 7.4) which showed even surface, spherical shapes and bilayer in the vesicular structure.

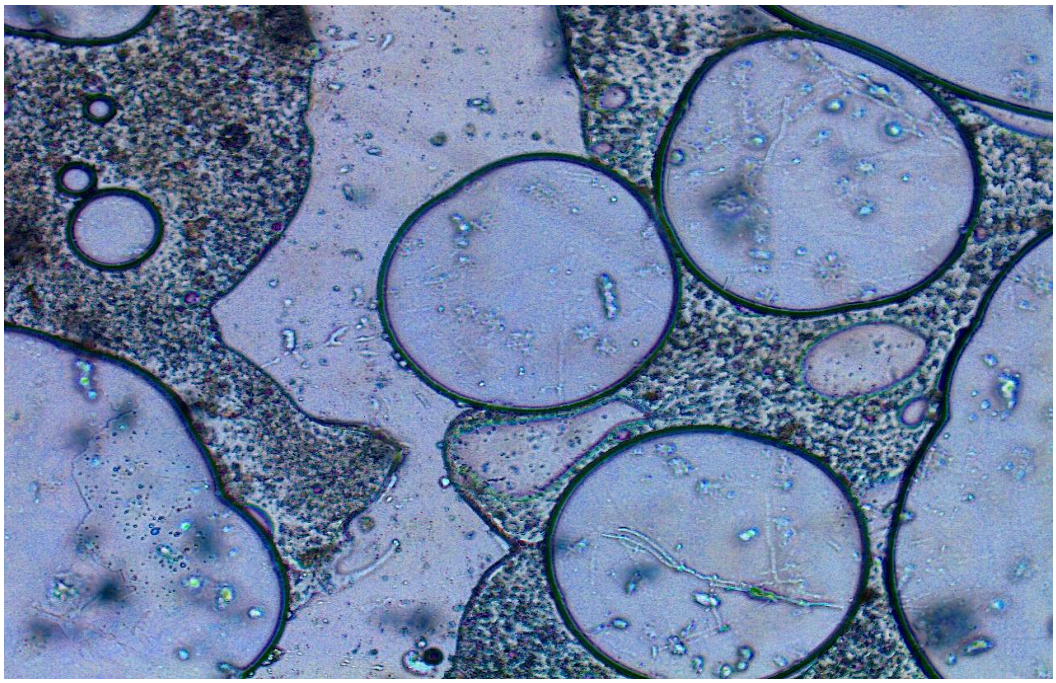

Fig. 4 - Optical microscopic images showing vesicular structure of Vitamin-E loaded optimized *aloe-vera* gel formulation. Microphotograph image of the formulation shows the smooth surface, spherical shapes and bilayer vesicular structure at 10000x magnification

3.4 Percentage Entrapment Efficiency

The entrapment efficiency was measured as the difference between two, i.e. initial drug quantity and free unentrapped quantity of drug in the supernatant with respect to the total quantity incorporated in the Nano-Transfersomes preparation. Percent entrapment efficiency of prepared optimized Nano-Transfersomes formulation was found to be 92.29±4.51. As anticipated, the percentage entrapment efficiency (EE) of the Vitamin-E was found to be inflated, which may be due to a greater availability of lipid to accommodate the lipid soluble Vitamin-E.

3.5 pH Measurement

The pH data of the formulated nano-transferosomes gels was found to be in the range of 6.87-6.99. The pH of developed preparation was found to be 6.3± 0.21. The pH of the Nano-Transfersomes gel formulation was compatible with the dermal pH (slightly acidic) indicating no risk of dermal hypersensitivity reaction [26].

3.6 Viscosity Measurement

The viscosity of gels was determined by using a Brookfield viscometer DV-II model. T-Bar spindle along with a helipath stand was employed to calculate the viscosity and to avail appropriate readings.

Five readings (n=5) were taken over a duration of 60 seconds and were averaged to obtain mean viscosity value. The viscosity of optimized preparation was found to be 63.8± 4.9 cps. Rheological behaviour of Vitamin-E loaded Nano-Transfersomes *aloe-vera* gel formulation was found to be appropriate which could make them acceptable for topical use.

3.7 Drug permeation Studies (Using Egg Membrane)

The results of permeation studies (Fig. 5) have shown the permeation and partitioning of the nano-transferosomes through the egg membrane. Results reveal that the drug is more permeable in the egg membrane through Nano-Transfersomes gel formulation in comparison to marketed formulation (vitamin E gel moisture cream).

The Vitamin-E loaded Nano-Transfersomes gel formulation, where *aloe-vera* was incorporated, showed higher spread ability and high release as compared to marketed preparation where *aloe-vera* was not added. *Aloe-vera* would expedite the permeation of relatively large moieties across lipid bilayer whereas permeation of small molecules remains unaffected.

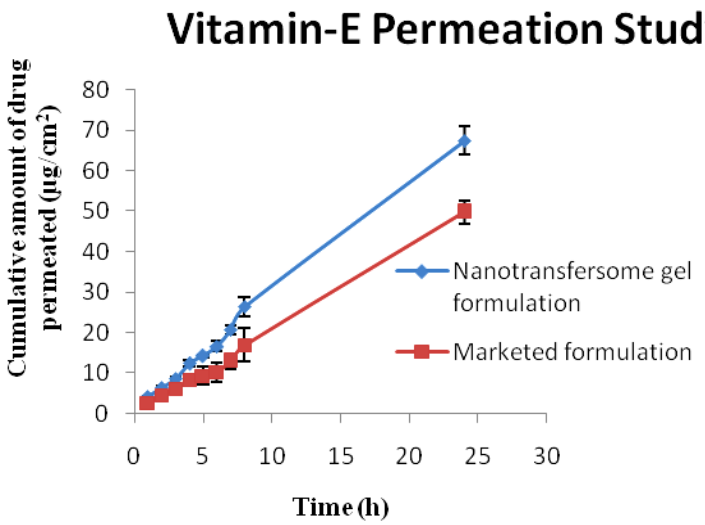

Fig. 5 - Comparative study of Vitamin-E permeation across egg membrane between the Vitamin-E Loaded Nano-Transfersomes *aloe-vera* gel formulation and Vitamin-E marketed formulation

3.8 Skin Sensitization Studies

The skin sensitization studies were carried out by applying the Vitamin-E loaded Nano-Transfersomes gel on mice dorsal surface for 7 days. During the study the mice were observed for its responsiveness and reaction against the applied preparation. The developed Nano-Transfersomes gel preparation showed no remarkable level of skin sensitization in mice indicating the compatibility of formulations with dermal tissues.

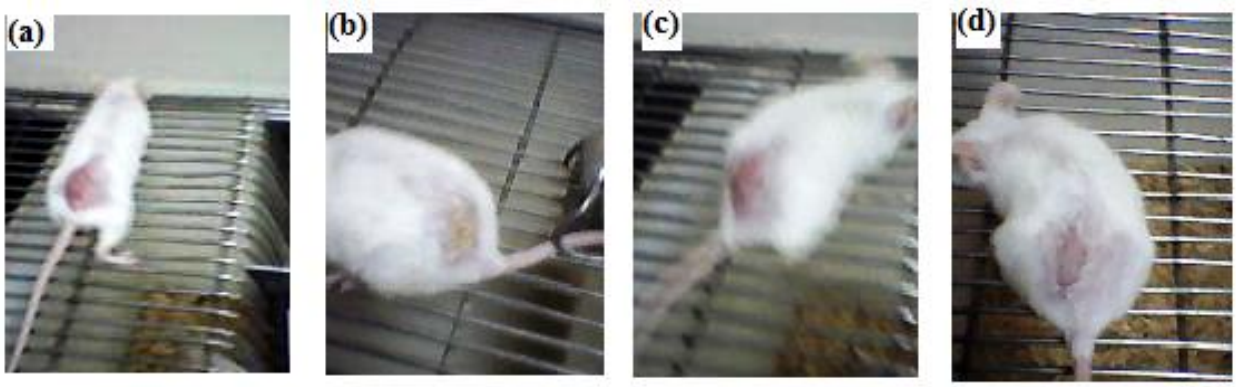

Fig. 6 - The skin irritation results of treated group; (a) before; (b) after and control group; (c) before; (d) after

3.9 Stability Studies

Sixty days' stability study at (4°C, RT, and 40°C) and 75±5% was carried out for optimized nano-transferosome gel formulation [27]. It showed negligible change over the time for parameters like percent drug content, pH, appearance, phase separation, and viscosity. Stability studies (Table 1) of Nano-Transfersomes gel formulation was revealed that the best temperature for storage of formulation is 4°C.

Table 1 - Stability studies of optimized Nano-Transfersomes gel formulation

Time (days)	Temperature	Appearance	% Drug content (mean±SD)	Viscosity (mean±SD)	pH (mean±SD)	Phase separation
0	RT	-	92.82±1.23	63.8±4.9	6.3±0.21	Not detected
15	4°C	-	92.66±1.11	64.4±3.8	6.2±0.12	Not detected
30	4°C	-	92.55±1.13	63.5±3.5	6.0±0.31	Not detected
45	4°C	-	92.52±1.10	63.2±2.6	6.1±0.11	Not detected
60	4°C	-	92.12±1.15	63.4±3.3	6.0±0.10	Not detected
15	RT	-	92.49±1.25	63.2±2.8	6.3±0.42	Not detected
30	RT	-	92.23±1.10	62.7±4.1	6.2±0.67	Not detected
45	RT	-	92.21±1.08	63.8±3.2	6.4±0.23	Not detected
60	RT	-	91.96±1.05	61.8±3.6	6.9±0.22	Slight
15	40°C	-	92.26±1.07	63.2±3.6	6.3±0.41	Not detected
30	40°C	-	91.51±1.05	62.6±2.9	6.7±0.61	Not detected
45	40°C	-	90.49±1.20	62.9±3.6	6.6±0.92	Slight
60	40°C	+	88.84±2.12	60.7±2.4	6.8±0.82	Slight

– no change, + slight change
- SD standard deviation
- n = 3 (number of experiments in triplicate)

4. Conclusion

Number of substantial groups of conventional dermal formulation has been applied for psoriasis, but they provide a relatively low rate of absorption as the psoriasis is a chronic, systemic immune-mediated disease. In eminently advanced stages of psoriasis, systemic routes of drug administration including oral and parenteral are considered. Nonetheless, in systemic treatment, drug molecules are required at high doses which correspondingly invite many side effects. There are number of options available for anti-psoriatic therapy. Nevertheless, none of them are completely safe and efficient to treat the disease without negotiating patient compliance. The available treatment options based on conventional formulations are non-specific and associated with considerable systemic toxicity side effects. From the present investigation, it was concluded that Vitamin-E loaded Nano-Transfersomes *aloe-vera gel* formulation is effective and promising for carrying the drug into deeper layers of the skin. The Nano-Transfersomes formulation is an effective carrier for applying Vitamin-E topically in psoriatic lesions. Furthermore, Nano-Transfersomes holds smooth entry into the skin and offer deeper penetration to the lesion because of its nano size and deformability properties.

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