ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 7, Suppl 1, 2014

ISSN - 0974-2441

Research Article

# PRO-VESICULAR (PV)-BASED GEL FOR THE TOPICAL DELIVERY OF NAPROXEN: PREPARATION, CHARACTERIZATION AND *IN VIVO* EVALUATION

**VURE PRASAD [1*], SARITHA.T[1], PRAKASH V DIWAN[1], TRIVENI CHENNA [1],**

**[1]Department of Pharmaceutics, School of Pharmacy (Formerly Lalitha College of Pharmacy), Anurag Group of Institutions, Ghatkesar, Hyderabad-501301, India. Email**: vureprasad@gmail.com

***Received: 4 September2013, Revised and Accepted: 26 September2013***

**ABSTRACT**

Objective

The objective of the present investigation was to develop and characterize a vesicular drug carrier system (Proliposomes) for topical delivery of naproxen to overcome the gastrointestinal complications occurred when taken by oral route.

Methods

Proliposomes were prepared by film deposition on carrier method and characterized for size, entrapment efficiency, surface morphology, drug content, percentage yield. Proliposomal gels were prepared by using 1% carbopol as a polymer and gels were evaluated for $P^H$, viscosity, in-vitro, ex-vivo, pharmacodynmic studies and stability studies. The size and surface morphology were studied using optical microscope and scanning electron microscope.

Results

The maximum entrapment efficiency of reconstituted liposomes was 96% whereas drug content in Proliposomes was found to be more than 90%. FTIR studies showed no possible interaction between drug and excipients. In-vitro and ex-vivo studies shows that liposomes not only enhance the penetration of drug molecules but also help to localize the drug within the skin indicating sustain release of drug. In-vivo studies concluded that proliposomal gel shows greater percentage of inhibition of paw oedema when compared to marketed gel.

Conclusion

It was found that Proliposomes exhibited more stability as compared to liposomes. Hence Proliposomes drug delivery system was better choice for sustained release of drug through topical drug delivery.

**Keywords:** Naproxen, liposomes, Proliposomes, sustained release, transdermal delivery.

## INTRODUCTION

Rheumatoid arthritis, in which the immune system attacks the body's own tissues, is a chronic, systemic inflammatory disorder that may affect many tissues and organs but mainly attacks synovial joints. The pathology of disease process leads to the destruction of articular cartilage and ankylosis (fusion) of the joints [1, 2].

Naproxen is chemically 2-(6-methoxy naphthalene-2yl) propanoic acid, is a non-steroid anti-inflammatory drug with anti-inflammatory, analgesic and antipyretic properties. It is used in the treatment of inflammations, rheumatoid arthritis, musculoskeletal disorders and gout. Most NSAIDS act as non-selective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1(COX-1) and cyclooxygenase-2(COX-2) isoenzymes. COX catalyses the formation of prostaglandins and thrombaxane from arachidonic acid. Prostaglandins are responsible in the process of inflammation [3].

The oral administration of naproxen has often side effects, including epigastric pain, nausea, vomiting, peptic ulcer and hepatic impairment[4] .These side effects can be overcome by the topical administration of drug and also offer many advantages, such as increased patient compliance and possibility for continuous and controlled absorption[5].Clinical evident suggest that topically applied non-steroidal anti-inflammatory drugs more safer and efficacious as oral NSAIDS in the treatment of rheumatoid arthritis[6].

Topical liposomal formulation has been studied for many purposes but unstable nature and poor skin permeation limit their use for topical delivery of drugs. Liposomes also pose many problems such as aggregation, sedimentation, fusion, hydrolysis and/or the oxidation of phospholipids. The concept of Proliposomes was proposed in order to overcome the stability problems associated with liposomes [7-8].

Proliposomes are defined as dry, free flowing powder formulations containing water soluble carrier particles coated with phospholipids that immediately form a liposomal dispersion on contact with water in the body [9-10]. The resulting liposomes may act as a sustained release dosage form of the loaded drugs. They could be prepared by various methods such as crystal film method, film deposition on carrier method, fluidized-bed method, powder bed grinding method, freeze drying method and spray drying method. In this film deposition on carrier method was chosen to prepare naproxen Proliposomes based on laboratory conditions [7]. The aim of the present study was to develop and characterize a vesicular drug carrier system (Proliposomes) for topical delivery of naproxen to overcome the problems associated with oral route of administration.

## MATERIALS AND METHODS

### Materials

Naproxen [API] was gift sample from Dr.Reddy's laboratories, Hyderabad. Phosphotidyl choline was gift sample from Simson Labs, Hyderabad. Mannitol, cholesterol, Propylene Glycol used was supplied by S.D fine chemicals, Mumbai. Chloroform and methanol obtained from Merck laboratories, Mumbai. Carbopol 934 was purchased from Yaro chemicals, Mumbai. Triethanolamine was obtained from Fisher scientific, Mumbai. All other reagents and chemicals used were of analytical grade.

### Methods

### Preparation of naproxen-loaded Proliposomes

The Proliposomes containing naproxen was prepared by film deposition on carrier method using vacuum rotary evaporator [11] .The optimization of naproxen Proliposomes was done by preparing the different formulations by varying the concentration of mannitol,

Phosphotidylcholine and cholesterol. Mannitol (1 g, sieved with 100 mesh) was placed in 100ml round bottom flask which was held at 60-70$^0$C temperature and the flask, rotated at 80-90 rpm for 30 min under vacuum. After complete drying the temperature of water bath was lowered to 20-30$^0$C. Naproxen (10 mg), Phosphotidylcholine and cholesterol were dissolved in mixture of organic solvents (chloroform: methanol, 6:4, v/v) and 5ml of aliquot of organic solution was slowly introduced into the flask via the solvent inlet tube. After complete drying second aliquot (5ml) was introduced. After complete dying, the vacuum was released and Proliposomes were placed in a desiccator over night and then sieved with 100 mesh.

**Preparation of carbopol gel base**

1gm of carbopol 934 was weighed and dispersed in distilled water. Then, propylene glycol was added and the mixture was neutralised by drop wise addition of 1% triethanolamine. Mixing was continued until the transparent gel was obtained and allowed to swell for 24 hours. Similarly 2% and 3% (w/w) carbopol gels were prepared.

**Preparation of proliposomal gels**

Proliposomes containing naproxen (separated from the unentrapped drug) were mixed into the 1% carbopol gel with an electric mixer (25 rpm, 2min), the concentration of Proliposomes in the gel being 1%. All optimized formulations were incorporated into different carbopol gels (1%, 2% and 3% w/w).

**Table1: Composition of optimized naproxen proliposomal formulations.**

| Formulation | Naproxen (mg) | Mannitol (g) | Phosphotidyl choline (mg) | Cholesterol (mg) | Chloroform (ml) | Methanol (ml) |
|---|---|---|---|---|---|---|
| F1 | 10 | 1 | 100 | 150 | 6 | 4 |
| F2 | 10 | 1 | 100 | 100 | 6 | 4 |
| F3 | 10 | 1 | 150 | 50 | 6 | 4 |
| F4 | 10 | 1 | 150 | 100 | 6 | 4 |
| F5 | 10 | 1 | 50 | 100 | 6 | 4 |
| F6 | 10 | 1 | 150 | 150 | 6 | 4 |
| F7 | 10 | 1 | 100 | 50 | 6 | 4 |
| F8 | 10 | 1 | 50 | 50 | 6 | 4 |
| F9 | 10 | 1 | 50 | 150 | 6 | 4 |

**Characterization of Proliposomes**

Proliposomes were characterised by following parameters.

**Vesicle size and count**

A drop of distilled water was added to Proliposomes granules on a glass slide without a cover slip, and the process of liposome formulation was observed using optical microscope (Meltzer 5000DTM) with 40X magnification. Then, vesicle size and count was recorded [12]

**Surface morphology**

The surface morphology of Proliposomes was examined by scanning electron microscopy (SEM) after coating with gold [12].

**Drug content**

Proliposomes (100mg) were dissolved in 10ml methanol by shaking the mixture for 5 mins. One ml of the resultant solution was taken and diluted to 10ml with methanol. Then, absorbance was recorded at 230nm using U-visible spectrophotometer (Lab India 3200) [12].

**Entrapment efficiency**

The entrapment efficiency of Proliposomes was determined after hydration with distilled water. 10ml of phosphate buffer ($P^H$ 7.4) was added to Proliposomes granules and then subjected to sonication for 10 mins using ultra sonicator (Citizen, India). The liposomal suspension was subjected to centrifugation on a cooling centrifuge (REMI TR-01) at 15000 rpm for 30 mins for the separation of unentrapped drug. The clear supernatant (1ml) was taken and diluted to 10ml with buffer and absorbance was recorded at 230nm using UV-visible spectrophotometer (Lab India 3200). This procedure repeated for 3 times for each formulation and then calculates the percentage drug in the each formulation [12].

Entrapment efficiency (%) = $[(C_t - C_f) / Ct] X100$

$C_t$ – concentration of total drug

$C_f$ – concentration of free drug

**Surface charge**

The optimized proliposomal formulation was dissolved in phosphate buffer (pH 7.4) a made the serial dilutions until the clear solution was obtained. Then the sample was analysed for surface charge using zeta sizer (Malvern) [12].

**Yield of Proliposomes**

After complete drying, the Proliposomes powder was collected and weighed accurately [12]. The yield of Proliposomes was calculated using the formula

Percentage yield = [total weight of Proliposomes / (total weight of drug + weight of added materials)] X100

**Drug-excipients interaction studies by FTIR**

The drug-excipients interaction studies were done by FTIR (Bruker Alpha- T). The IR spectra of Drug, Phosphotidylcholine, cholesterol, mannitol and naproxen Proliposomes were recorded using Fourier transform infrared spectrophotometer [12].

**Characterization of gels:**

**Physical appearance**

The physical appearance was virtually checked for the colour, consistency, olfactory and greasiness of formulations.

**$P^H$ of formulation**

The $P^H$ of all formulations was determined by using digital pH meter (Lab India SAB 5000). Electrodes were completely dipped into gel and the pH was noted [13].

**Rheological properties**

The rheological properties of prepared gels was estimated using a Brookfield viscometer apparatus (DV-II+ pro), equipped with standard spindle LV1 with 61 marking. Viscosity of 1, 2 and 3% carbopol gel was determined and selects the optimized formulation [14].

**Stability studies**

Stability studies were carried out by storing the prepared gels in tightly sealed amber colour glass bottles at various temperature conditions like refrigeration temperature (2-8$^0$c), room temperature (25±0.5$^0$c) and elevated temperature (45±0.5$^0$c) from a period of one month to two months. Drug content and variation in colour, morphology and consistency were periodically monitored [14].

**In vitro studies**

**Percent amount of drug release from semi permeable membrane**

Franz diffusion cell was used for the in vitro drug release studies. Semi permeable membrane was placed between donor and receptor chamber of diffusion cell. Receptor chamber was filled with freshly prepared 30ml 7.4 PH phosphate buffer. Proliposomal gel equivalent to 1gm was placed on dialysis membrane. The Franz diffusion cell was placed over magnetic stirrer with 500rpm and temperature was maintained at 37±1$^0$C. 5ml of samples were withdrawn periodically and replaced with fresh buffer. The withdrawn samples were periodically diluted and analysed for drug content using UV visible spectrophotometer (Lab India 3200) [14].

**Ex-vivo studies**

**Preparation of skin**

Drug permeation study was performed after obtaining the approval of the institutional animal's ethical committee in accordance with disciplinary principles and guidelines of the committee for the purpose of control and supervision of experiments on animals (CPCSEA-Protocol number II/ IAEC/ LCP/ 037/ WR24).

Abdominal skin of male Wister rats was used in the study. Rats (250-280 g) were anesthetised slightly by ether and hairs removed from the abdominal skin. The rats were sacrificed and the abdominal skin of the rat was separated. The skin was stored at −20°C until the permeation study, the skin was hydrated in normal saline at 4°C and the adipose tissue layer of the skin was removed by rubbing with a cotton swab.

**Percent amount of drug release from rat skin**

The amount of drug release from rat skin was determined by using Franz diffusion cell. The dorsal skin of Wister rat (4-6 weeks old) was placed between donor and receptor compartments of diffusion cell with the stratum corneum side facing upwards. The receptor chamber was filled with 30ml 7.4 pH phosphate buffer. Proliposomal gel equivalent to 1gm was applied onto the surface of skin evenly. The receptor chamber was stirred by a magnetic stirrer rotating at 500rpm and kept at 37±1$^0$C. The samples (1.5ml) were collected at suitable time interval.

Samples were analysed for naproxen content by UV visible spectrophotometer (Lab India 3200) at 230nm after making proper dilutions [15].

**Drug Retention Study**

The skin was removed from the diffusion cells after completion of experiments. The surface of skin specimens was washed 10 times with 1ml distilled water and dried on filter paper. The effective surface area of the skin was separated and minced with a surgical sterile scalpel then finally homogenized in a vial filled with methanol by using Homogenizer (REMI RQT-124A) at 16,000 rpm for 5 min. The tissue suspension was centrifuged for 15min at 9000rpm using cooling centrifuge (REMI TR-01). Then filtered supernatant tissue suspension was further extracted with methanol and filtered. The filtrate was assayed for cumulative amount of drug retained on the skin by using UV-visible spectrophotometer (Lab India 3200) at 230nm [16].

**In-vivo studies**

**Pharmacodynmic Studies**

Animals used for *in vivo* experiments were adult male Wister rats (150±170g), 3-4weeks. The animals were kept under standard laboratory conditions, at 25±10°C and 55±5% relative humidity with a 12 h light/dark cycle. All surgical and experimental procedures was reviewed and approved by the Institutional Animal and Ethics Committee [Protocol number II/ IAEC/ LCP/ 036/ WR09-CPCSEA].

Carrageenan induced paw oedema method was used to study the in vivo performance of the prepared drug delivery system. Anti-inflammatory activity was determined by measuring change in the volume of inflamed paw, produced by injection of carrageenan (0.1 ml of 1% w/v) using plethysmometer. Male Wister rats selected for the study were weighed and marks were made on the right hind paw just behind tibia-tarsal junction on each animal. To ensure constant paw volume, every time the paw was dipped in the plethysmograph (mercury displacement method) up to the fixed mark.

Rats were divided into three groups including one controlled group with each group comprising of 3 animals. The paw volume was noted at 0, 3 and 6 hr. The formulations were applied topically to Wister rats of respective groups, excluding the animals of controlled group. After 3 hr, 0.1ml of 1% carrageenan (in 0.9% normal saline) was injected in the sub planter region. Oedema volume was measured 3hr after the carrageenan injection; the extent of % swelling was calculated from difference between immediate volume and paw volume 3 hr after the carrageenan injection [16].

$$\text{Swelling}\ (\%) = \frac{V - Vi}{Vi} \times 100$$

V -volume 3 hr after the carrageenan injection

$V_i$ -volume immediately after carrageenan injection.

Percentage inhibition was calculated by

$$\text{Inhibition}\ (\%) = 1 - \frac{(\%\text{swelling of group treated})}{\%\text{swelling of control}} \times 100$$

**Vesicle size and count**

Observation under an optical microscope revealed that proliposome particles were rapidly converted to liposomes following contact with water. Average vesicular size and distribution were calculated as shown in [table 2].

**Table 2: Particle size of proliposomal formulations**

| S.No. | Formulation | Average particle size (µm) for 100 particles |
|---|---|---|
| 1 | F1 | 5.34±0.023 |
| 2 | F2 | 4.43±0.123 |
| 3 | F3 | 2.65±0.076 |
| 4 | F4 | 6.06±0.012 |
| 5 | F5 | 4.34±0.231 |
| 6 | F6 | 5.12±0.167 |
| 7 | F7 | 3.21±0.221 |
| 8 | F8 | 2.69±0.148 |
| 9 | F9 | 2.34±0.321 |

**Determination of entrapment efficiency**

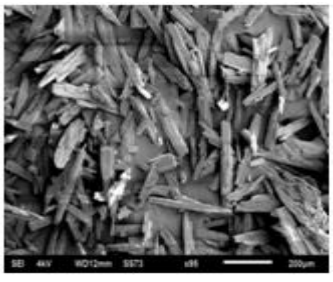
The entrapment efficiency of reconstituted liposomes from naproxen entrapped Proliposomes granules was shown in [table 3]. It is in the range of 90 to 95%. It indicates that entrapment of naproxen in reconstituted liposome was found to be dependents mainly on lipid concentration

**Table 3: Entrapment efficiency of proliposomal formulation**

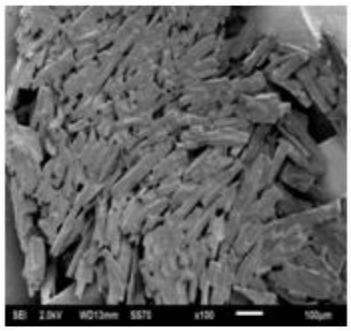
| S.No. | Formulation | Entrapment efficiency ± SD |
|---|---|---|
| 1 | F1 | 94.9±0.244 |
| 2 | F2 | 85.12±1.48 |
| 3 | F3 | 91.02±0.61 |
| 4 | F4 | 96.5±0.205 |
| 5 | F5 | 92.7±0.249 |
| 6 | F6 | 94.1±0.509 |
| 7 | F7 | 88.1±2.19 |
| 8 | F8 | 89.2±0.817 |
| 9 | F9 | 86.02±2.90 |

**Surface morphology**

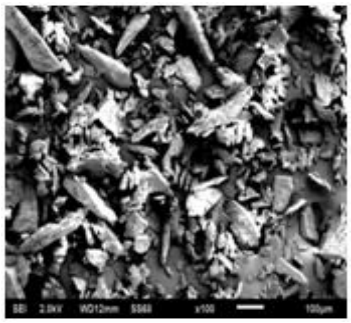
Surface morphology of Proliposomes was compared with that of mannitol of the same particle size by scanning electron microscope. From SEM photographs it is clear that, the surface of mannitol crystals becomes illegible due to deposition of phospholipids on mannitol surface.



**Mannitol at 95X**



**b. Naproxen at 100X**



**c. Naproxen Proliposomes at 100X**

**Determination of drug content**

Drug content in the Proliposomes was determined using UV visible spectrophotometer. The naproxen content in Proliposomes was in range of 89 to 99% which were shown in [table 4].

**Table 4: Drug content of proliposomal formulations**

| S.No. | Formulation | %drug content ± SD |
|---|---|---|
| 1 | F1 | 97.03±0.543 |
| 2 | F2 | 90.4±0.734 |
| 3 | F3 | 93.7±0.664 |
| 4 | F4 | 98.8±0.249 |
| 5 | F5 | 94.7±0.984 |
| 6 | F6 | 96.8±0.860 |
| 7 | F7 | 92.4±1.70 |
| 8 | F8 | 90.6±0.748 |
| 9 | F9 | 89.5±0.953 |

**Yield of Proliposomes**

The % yield of formulations was found to be increase with increase in phospholipids concentration. The results of % yield of various formulations were found to be in range of 86 to 96% (table 5).

**Table 5: Percentage yield of proliposomal formulations**

| S.No. | Formulation | Percentage yield ± SD |
|---|---|---|
| 1 | F1 | 93.4±0.324 |
| 2 | F2 | 90.7±0.534 |
| 3 | F3 | 89.5±0.654 |
| 4 | F4 | 95.4±0.123 |
| 5 | F5 | 94.3±0.221 |
| 6 | F6 | 94.8±0.212 |
| 7 | F7 | 88.7±0.321 |
| 8 | F8 | 89.3±0.187 |
| 9 | F9 | 86.5±0.265 |

**Determination of Zeta potential**

The zeta potential of optimized proliposomal formulation [F4] was determined and it was ranging from -5 to -15 which was sufficient to prevent aggregation [Fig 2].

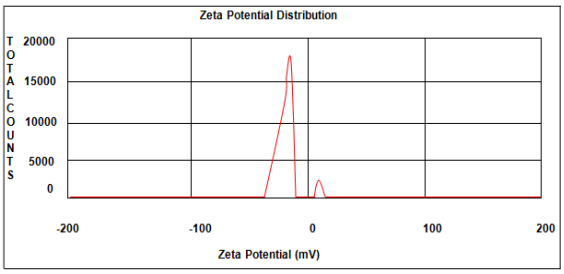



**Fig. 2: Zeta potential of optimized formulation**

**Drug-excipients interaction studies by FTIR**

On comparison of IR spectra of Proliposomes, Plain drug, Phosphotidylcholine and mannitol it was clear that, there was no significant interaction of the encapsulated drug with the lipid component and mannitol in Proliposomes [Fig 3].

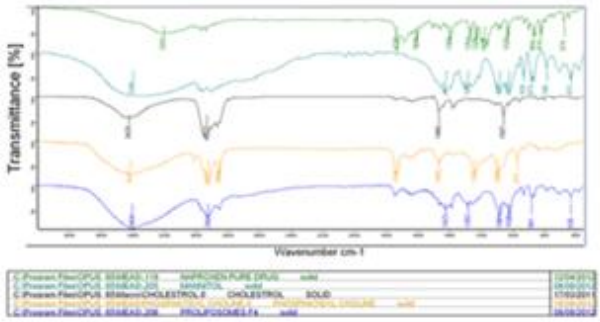



**Fig. 3: FTIR spectra of drug, excipients and optimized formulation**

**Characterization of gel**

**Measurement of viscosity**

The viscosity of proliposomal gel was found to be 1156cps at 100rpm.

**Measurement of pH**

The $P^H$ of the developed formulation was in accordance with human skin $p^H$ rendering them more acceptable. Therefore formulated proliposomal gel was suitable for topical application. The $P^H$ values of prepared proliposomal gels were within the limits of 5.5 to 5.8.

**In-vitro studies**

The cumulative percentage of naproxen release from naproxen loaded Proliposomes of various formulations in phosphate buffer (pH 7.4) were given in fig.no.5. It was seen that increase in the phospholipids concentration further retarded the release of drug from Proliposomes, indicating sustained release of drug for a longer period of time.

**Table 6: Cumulative percentage drug release of proliposomal formulations for 14hrs**

| S.No | Formulation | Cumulative percentage drug release |
|---|---|---|
| 1 | F1 | 76.01 |
| 2 | F2 | 55.4 |
| 3 | F3 | 55.5 |
| 4 | F4 | 80.5 |
| 5 | F5 | 69.8 |
| 6 | F6 | 74.1 |
| 7 | F7 | 60.5 |
| 8 | F8 | 58.9 |
| 9 | F9 | 64.4 |
| 10 | Marketed gel | 95.1 |

**Drug permeation study and retention study**

The objective of this study was to examine the feasibility of Proliposomes as a transdermal dosage form. The cumulative amounts of drug permeated naproxen Proliposomes of various formulations in phosphate buffer (pH 7.4) to the receptor compartment through rat skin were conducted. Results clearly indicate that the amount of drug retained in the skin was considerably higher in case of proliposomal gels when compared to marketed formulation). This shows that liposomes not only enhance the penetration of drug molecules but also helps to localize the drug within the skin [Fig 4]

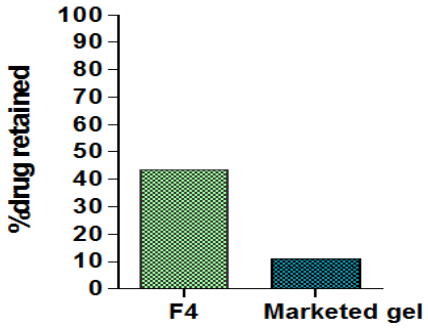



**Fig 4: Percentage drug retention of proliposomal `gel and marketed gels**

**In-vivo studies**

*In-vivo* performance of selected Naproxen proliposomal gel was carried out using carrageenan induced paw oedema model. Results of percentage swelling and percentage inhibition was calculated and given in [Table 7]. The optimized Naproxen proliposomal gel showed a greater percentage of inhibition at 6 hr of 67.4% when compared to standard marketed naproxen gel that showed 59% of inhibition. The possible reason could be the drug localization at applied site for longer duration there by showing a sustain release at site when compared to standard naproxen gel.

**Table 7: Anti inflammatory activity results of optimised proliposomal gel**

| Groups | Treatment | Paw volume | | %Swelling | %Inhibition |
|---|---|---|---|---|---|
| | | 0hr | 3hr | | |
| 1 | Control | 1.11 | 2.13 | 91.8 | - |
| 2 | Standard naproxen gel | 1.51 | 2.09 | 38.4 | 59 |
| 3 | Naproxen proliposomal gel | 1.40 | 1.82 | 30 | 67.4 |

**Stability studies**

Stability studies of optimized Proliposomes was performed at 8$^0$C, RT, and at 40$^0$C for three months and analysed for visual appearance, drug content and entrapment efficiency (table 6). After 3 months of storage period the naproxen Proliposomes still appeared free flow and immediately form a liposomal dispersion on contact with water. The results indicated that at elevated temperature and freezing temperature there was slightly but insignificantly decreases in drug content and entrapment efficiency for Proliposomes. So the proliposomal products should be stored in refrigeration conditions, to minimize the drug leakage from the proliposomal systems compared to marketed gel formulation

**Table 6: Stability study of the F4 proliposomal formulation**

| Time (days) | Temperature($^0$C) | Drug content | Entrapment efficiency |
|---|---|---|---|
| 15 | RT | 95.4 | 94 |
| 15 | 8 | 95.2 | 93.5 |
| 15 | 40 | 94.5 | 92.6 |
| 30 | RT | 94.1 | 93.2 |
| 30 | 8 | 93.7 | 92.1 |
| 30 | 40 | 93.6 | 91.4 |
| 60 | RT | 93.5 | 92.5 |
| 60 | 8 | 92.3 | 91.5 |
| 60 | 40 | 91.2 | 90.7 |

**DISCUSSION**

In this study, it was found that as the increased phospholipids concentration resulted in corresponding increase in the entrapment efficiency of reconstituted liposomes. The phospholipids-rich domains of vesicle might have helped to enhance the percent entrapment of lipophilic drug molecule like naproxen in lipid bilayer, which indicate that entrapment of naproxen in reconstituted liposome was found to be dependent mainly on the lipid concentration. Increase in lipid concentration in Proliposomes was also able to control the release of the active for longer period of time, which shows the sustained release behaviour of formulations.

A sustained delivery of naproxen can be achieved by proliposomal drug delivery system. Phospholipids, being the major component of liposomal system, can easily get integrated with the skin lipids and maintain the desired hydration conditions to improve drug permeation. Fusion of lipid vesicles with skin contributed to the permeation enhancement effect. The phospholipids was found to have a significant influence on the lipid matrix of the stratum corneum, suggesting a disruption of the intercellular lipid lamellar structure and act as penetration enhancer. Hence as the phospholipids concentration was increased, it would increase the permeation of drug following application on the skin. The free flowing properties of the Proliposomes granules will be beneficial in formulating the Proliposomes as a solid dosage form.

In-vitro studies concluded that enhance skin permeation and retention of naproxen was observed and was due to lipo-solubilized state of drugs within Proliposomes which helped to produce the depot effect.

Ex-vivo studies concluded that the proliposomal formulation showed higher permeation and residence within skin than the marketed gel indicating sustained release of drug at site which prevents further inflammation.

In-vivo studies concluded that proliposomal gel showed greater anti-inflammatory activity than marketed gel using rat paw oedema model.

**CONCLUSION**

It was found that Proliposomes exhibited more stability as compared to liposomes. Hence Proliposomes drug delivery system was better choice for sustained release of drug through topical drug delivery.

**REFERENCES**

1. Grahame R. The NSAID patch. Eur J Rheumatol Inflamm 1994; 14 (4):1-2.
2. Grahame R. Transdermal non steroidal anti-inflammatory agents. J. Clinical Practice 1995; 49 (1): 33-35.
3. Pakhuri Mehta, Chandra Shekhar Sharma, Deepak Nikam and M. S. Ranawat. "Development & Validation of Stability-Indicating UV Spectrophotometric Method for Estimation of Naproxen in Pharmaceutical Dosage Form". *Asian Journal of Biochemical and Pharmaceutical Research.* 2012; 2 (1): 2231-2560.

4. Dalia A. Attia. "In Vitro and in Vivo Evaluation of Transdermal Absorption of Naproxen Sodium". *Australian Journal of Basic and Applied Sciences.* 2009; 3(3):2154-2165.
5. Lee J, Lee Y, Kim J, Yoon M, Choi WY. Formulation of microemulsion systems for transdermal delivery of aceclofenac. *Arch Pharm Res.* 2005; 28:1097–1102.
6. Heyneman CA, Lawless-Liday C, Wall GC. Oral versus topical NSAIDS in rheumatic disease: A comparison. *Drugs.* 2000;60:555–74
7. Xiao Yan-Yu, Song Yun-mei, Chen Zhi-peng and Ping Qi-neng. "Preparation Of Silymarin Proliposome: A New Way to Increase Oral Bioavailability of Silymarin in Beagle Dogs". *International Journal of Pharmaceutics.* 2006; 319(1-2): 162-168.
8. Keon- Hyoung Song, Suk-jae Chung and Chang- Koo Shim. "Preparation and Evaluation of Proliposomes Containing Salmon Calcitonin". *Journal of Controlled Release* 2002; 84: 27-37.
9. Vandana Gupta, Ashok K. Barupal, and Suman Ramteke. "Formulation Development and In Vitro Characterization of Proliposomes for Topical Delivery 0f Aceclofenac". *Indian Journal of Pharmaceutical Sciences*. 2008; 70(6): 775.
10. Hongtao Xu, Ling He, Shufang Nie, Jin Guan, Xiaoning Zhang, Xinggang Yang and Weisan Pan. "Optimized preparation of vinpocetine proliposomes by a novel method and in vivo evaluation of its pharmacokinetics in New Zealand rabbits". *J. Control. Release.* 2009; 140:61-68.
11. Ahniah BK, Kim SK, Shim CK, Arien A, Dupuy B. Preparation and evaluation of encapsulation of calcitonin in lipoproteins. Journal of microencapsulation 1995; 12 (4):363–375.
12. Noh YC. Proliposome as a delivery system for poorly water soluble drugs. J. microencapsulation 1984; 1(2):105-112.
13. Vinod L. Gaikwad, Vishal D.Yadav, Rakesh P. Dhavale, Prafulla B. Choudhari and Swapnil D Jadhav. "Effect of Carbopol 934 and 940 on Fluconazole Release from Topical Gel". *Current Pharma Research.* 2012;2(2):487-493.
14. Chen QI, Huang YU, Gu XQ Qi-neng. A study on preparation of proliposomes by spray drying method. J. Shenyang pharm univ. 1997; 1(4):166-169.
15. D. R. Rathod, M. N. Dole, and S. D. Sawant, "Spectrophotometric determination of glipizide in bulk and tablet dosage form by absorption maxima, first order derivative spectroscopy and area under the curve," Asian Journal of Pharmaceutical and Clinical Research 2012; 5(3):102–104.
16. Mallesh Kurakula, C. Srinivas, Nagasree Kasturi and Prakash V Diwan. "Formulation and Evaluation of Prednisolone Proliposomal Gel for Effective Topical Pharmacotherapy". *International Journal of Pharmaceutical Sciences and Drug Research.* 2012. 4(1). 35-43.