



## FORMULATION AND EVALUATION OF PRNIOsome BASED TRANSDERMAL GEL OF SUMATRIPTAN SUCCINATE

Ashok Mateti<sup>1</sup>, Mohammed Habibuddin<sup>2</sup>, Raju Jukanti<sup>3\*</sup>

<sup>1</sup>*Department of Pharmaceutics, Trinity College of Pharmaceutical Sciences,  
Peddapalli, Karimnagar, Telangana, India*

<sup>2</sup>*Department of Pharmaceutics, Alliance Institute of Advanced Pharmaceutical & Health Sciences,  
Hyderabad, Telangana, India*

<sup>3\*</sup>*Department of Pharmaceutics, St. Peter's Institute of Pharmaceutical Sciences, Warangal, Telangana, India*

\*Corresponding Author Email: [drjukanti@gmail.com](mailto:drjukanti@gmail.com)

### ABSTRACT

The objective of the present work was to develop transdermal proniosomes of Sumatriptan succinate to improve the bioavailability and to study the effect of different surfactants on drug release. Proniosomes were prepared using spans as surfactants, cholesterol as stabilizer and lecithin as permeation enhancer and ethanol as solvent. Different formulations were prepared with and without lecithin varying the type of spans. Effect of different spans i.e., span 20, span 40, span 60, span 80 on drug release through dialysis membrane was studied. Ex vivo study of all prepared formulations was performed using rat abdominal skin. Ex vivo drug permeation and entrapment efficiency were found higher in formulations containing lecithin. Among all these, formulation containing span 60 was optimized as it showed better permeation profile along with good entrapment efficiency. The optimized formulation was visualized under scanning electron microscopy. Proniosomal transdermal gel of Sumatriptan succinate was formulated and was found promising dosage form to improve the bioavailability.

### KEY WORDS

Transdermal, Sumatriptan succinate, proniosomes, permeation, Span 60, lecithin.

### INTRODUCTION

Now a days transdermal route is widely used as it is convenient, safe and offers several advantages over conventional dosage forms that includes: avoidance of first pass metabolism, huge surface area of the skin, enhanced bioavailability, can maintain a suitable plasma concentration, provides utilization of drugs which having short biological half life, narrow therapeutic window, ease of administration and termination of action, reduces number of doses, improved patient compliance, and also able to deliver the drug in a controlled manner makes the route more attractive for drug delivery<sup>1</sup>. However the major problem in transdermal delivery is limited facilitation of the drug to permeate across the skin because of the presence of stratum corneum (SC) which acts as a barrier and hinders the drug absorption. Vesicular drug delivery is one of the

approaches which encapsulate the drug to overcome the barrier function of stratum corneum. Eg: liposomes, niosomes, ethosomes, pharmacosomes, transferosomes which showed a significant improvement in the transdermal permeation of drugs<sup>2</sup>. The basic mechanisms for improvement in permeation from vesicular systems include a) fusion of vesicles with the provide a better contact with skin surface leading to higher vesicle-skin interactions b) the intercalation of vesicles into the intercellular lipid layers of the skin may also lead to disorganization of structure stratum corneum with altered permeability characteristics thus inhibit the barrier function stratum corneum. But, the problem with these liposomes and niosomes is their instability due to aggregation, fusion, hydrolysis, sedimentation during storage. To minimize physical instability of vesicular system provesicular systems was discovered such, as

proniosomes and proliposomes. Proniosomes are semisolid liquid crystal (gel) product of nonionic surfactant which upon hydration converts into niosomes<sup>3,4</sup>. Proniosomes when applied onto the skin surface transform into niosomes due to the hydration by water from the skin which would provide an occlusive condition and offer potential for drug delivery via the transdermal route<sup>5</sup>. The aim of the present study is to examine the feasibility of proniosomes as a transdermal drug delivery system of Sumatriptan succinate.

Sumatriptan is a 5-hydroxy tryptamine 1D (5-HT1D)-receptor agonist, it was the first triptan available to use in the treatment of migraine. Sumatriptan is metabolized primarily by monoamine oxidase A and excreted in the urine and bile<sup>6</sup>. Sumatriptan seems to act selectively on blood vessels located within the carotid circulation. Sumatriptan is generally given by oral or parental routes. Oral administration (as succinate) suffers from poor bioavailability problem due to pre-systemic metabolism and a substantial proportion of patients suffer from severe nausea or vomiting during their migraine attack, which may make oral treatment unsatisfactory<sup>7</sup>. Transdermal delivery of sumatriptan may prove particularly helpful for migraineurs with gastric stasis. Whereas transdermal patches may have several limitations such as fluid leakage and increased skin irritation, likely from uneven contact to increased current density<sup>8</sup>. The present research involves the formulation and evaluation of Sumatriptan succinate proniosomal gels. Further *ex-vivo* permeation study was carried out to evaluate the feasibility of

proniosomal gels for efficient delivery of Sumatriptan succinate.

## MATERIALS AND METHODS

Sumatriptan succinate was a kind gift sample from Dr. Reddy's laboratories, Hyderabad. Sorbitan monopalmitate was purchased from Sigma chemical co., St. Louis, MO, USA. Cholesterol was obtained from E. Merck, Mumbai, India. Sodium azide and dialysis tube (DM-70; MW cut off 12,000 to 14,000) were purchased from Himedia, Mumbai, India. All other chemicals and solvents used were of analytical grade. Freshly collected double distilled water was used all throughout the study.

### Preparation of proniosome gel

Proniosomes were prepared using Co-acervation phase separation method<sup>9</sup>. The compositions of different proniosomal formulations are listed in Table 1. Required quantities of Sumatriptan succinate, surfactant, lecithin, and cholesterol were mixed with 0.5 ml of ethanol in a 5ml wide mouth glass tube. Then the open end of the glass tube was covered with a lid and the tube was warmed in a water bath at  $65 \pm 3^\circ\text{C}$  for 5 min. Then 0.4 ml of pH 7.4 phosphate buffer was added and the mixture was further warmed in the water bath for about 2 min so that a clear solution was obtained. The mixture was allowed to cool to room temperature until the dispersion was converted to proniosomal gel.

**Table 1 Composition of sumatriptan succinate loaded proniosomal gels**

| Ingredients (mg)      | F1  | F2  | F3  | F4  | F5  | F6  | F7  | F8  |
|-----------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Sumatriptan succinate | 25  | 25  | 25  | 25  | 25  | 25  | 25  | 25  |
| Span 20               | 160 | -   | -   | -   | 360 | -   | -   | -   |
| Span 40               | -   | 160 | -   | -   | -   | 360 | -   | -   |
| Span 60               | -   | -   | 160 | -   | -   | -   | 360 | -   |
| Span 80               | -   | -   | -   | 160 | -   | -   | -   | 360 |
| Cholesterol           | 40  | 40  | 40  | 40  | 40  | 40  | 40  | 40  |
| Lecithin              | 200 | 200 | 200 | 200 | -   | -   | -   | -   |

### **Microscopic evaluation**

The morphology of the niosomes was examined by optical microscopy. The proniosomal gel was hydrated in a small test tube using 10 ml of pH 7.4 phosphate buffer solution. The dispersion was observed under optical microscope at 40X magnification. Photomicrographs were taken for niosomes<sup>1</sup>.

### **Entrapment efficiency**

40mg of proniosomal gel was reconstituted with 2 ml pH of 7.4 phosphate buffer in a glass tube. The aqueous suspension was sonicated in a sonicator bath (MU-8 Clifton, NJ, USA) for 30 min. Sumatriptan succinate containing niosomes were separated from untrapped drug by centrifugation at 9000 rpm for 45 min at 4°C (Remi Industries limited, Vasai, India). The supernatant was recovered and assayed spectrophotometrically using UV-Visible spectrophotometer (UV-1800 Shimadzu, Japan) at 225nm. The encapsulation percentage of drug (EP) was calculated by the following equation<sup>10</sup>.

$$EP = [(C_t - C_r) / C_t] * 100$$

Where,  $C_t$ , concentration of total Sumatriptan succinate,  $C_r$ , concentration of free Sumatriptan succinate.

### **Vesicle physical analysis**

The shape, surface characteristics, and size of the niosomes were observed by scanning electron microscopy. 200 mg of the proniosome gel in a glass tube was diluted with 10 ml of pH 7.4 phosphate buffer. The niosomes were mounted on an aluminium stub using double-sided adhesive carbon tape. Then the vesicles were sputter-coated with gold palladium (Au/Pd) using a vacuum evaporator (Edwards) and examined using a scanning electron microscope (Hitachi 3700N, Germany) equipped with a digital camera, at 10 kV accelerating voltage<sup>10</sup>.

### **Rheological studies**

The spreadability of the topical formulations meant to be applied onto the skin depends on the degree of consistency and resistance offered by the preparation which can be measured in terms of viscosity. The rheological behavior of proniosomal formulations was studied by using a controlled stress rheometer with the cone (24 mm) and plate geometry (Brookfield Rheometer, DV-II, USA). Before carrying out the

measurement the sample was allowed to equilibrate for 5 min and the torque sweep was in the range of 10 to 110%. The measurements were performed in triplicate at ambient temperature. The rheological properties were calculated using Rheocalc 32 software.

### **In- vitro release study**

*In- vitro* release studies were carried out using unjacketed vertical franz diffusion cells. (surface area of 5.722 cm<sup>2</sup> and 20 ml of receptor cell volume). Prior to the study, the cellophane membrane (Himedia laboratories Pvt Ltd., Mumbai) was soaked in pH 7.4 phosphate buffer for overnight. After that membrane was fixed between two compartments. The donor chamber and the sampling port were covered with lid to prevent evaporation during the study. 200 mg of proniosomal gel equivalent to 12 mg of Sumatriptan succinate was placed on the upper side of the membrane (donor compartment). Then the diffusion was carried out using 20 ml pH 7.4 phosphate buffer in the receptor compartment (containing 0.02% w/v of ethanol to retard microbial growth) was maintained at 37±2°C under constant stirring up to 24 hrs<sup>11</sup>. Aliquots of 5 ml were withdrawn periodically at different time intervals (0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hrs) and replaced with equal volume to maintain constant receptor phase volume. Same procedure was performed with pure drug. The samples were suitably diluted and the amount of drug was determined spectrophotometrically using UV-Visible spectrophotometer at 225 nm. (n=3).

### **Ex- Vivo Permeation Study Using Excised Rat Abdominal Skin**

Male albino rats (150-200 g) were used in the study was obtained from Mahaveer Enterprises (146-CPCSEA no: 199; Hyderabad, India). The animals were housed in separate cages and maintained under controlled condition of temperature and the rats had free access to water and food until they were sacrificed for skin harvesting Euthanasia and of carcass was in accordance of the guidelines. The rats were sacrificed by using excess amount of anaesthetic ether. Before surgical removal of the skin, hair on dorsal side was removed with hair clipper taking extreme precautions not to damage the skin. The epidermis was prepared by a heat separation

technique<sup>12</sup>, which involved soaking of the entire abdominal skin in water at 60°C for 45 seconds, followed by careful removal of the epidermis. The epidermis was washed with water, wrapped in aluminium foil and stored at -20°C till further use<sup>13</sup> (used within 2 weeks of preparation).

*Ex- Vivo* permeation studies were carried out using unjacketed vertical franz diffusion cells with a diffusional surface area of 5.722 cm<sup>2</sup> and 20 ml of receptor cell volume. The skin was brought to the room temperature and mounted between the donor and receiver compartment of the franz diffusion cell, where the stratum corneum side faced the donor compartment. Before being dosed the skin was allowed to equilibrate for 1 h and formulation equivalent to 12 mg of Sumatriptan succinate was placed on the dorsal side of the skin. The receptor compartment consisting of PB pH 7.4 (containing 0.02% w/v of ethanol to retard microbial growth) was maintained at 37±2°C under constant stirring up to 24 hrs. The receptor compartment was constantly stirred at 300 rpm<sup>14</sup>. The donor chamber and the sampling port were covered with lid to prevent evaporation during the study. Aliquots of 5 ml were withdrawn periodically at different time intervals (0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hrs) and replaced with equal volume to maintain constant receptor phase volume. Same procedure was performed with pure drug. The samples were suitably diluted and the amount of drug was determined spectrophotometrically using UV-Visible spectrophotometer at 225 nm (n=3).

#### Permeation Data Analysis

The cumulative amount of drug permeated through a unit area of skin was plotted as a function of time.

#### Flux

The Steady state Flux was calculated by using the slope of the graph where  $J = \text{Flux } (\mu\text{g}/\text{cm}^2/\text{hr})$ ,  $A = \text{Surface area}$ ,  $dQ/dt = \text{Cumulative amount permeated per unit area per unit time}$ . Containing cumulative amount permeated through unit area (CAP) Vs Time.

$$J_{ss} = (dQ/dt) * (1/A)$$

#### Permeability co efficient (Kp)

Permeability co efficient which represents the correlation between the flux and initial drug load was calculated using the following equation<sup>15</sup>.

$$Kp = J_{ss}/C$$

Where, Kp=Permeability co efficient (cm/hr)

J= transdermal flux

C= Initial concentration of drug in the donor compartment.

#### Enhancement Ratio

The penetration enhancing effect of various formulations containing proniosomal gels were calculated in terms of Enhancement Ratio (ER) by using the following equation<sup>15</sup>.

$$ER = J_{ss} \text{ of formulation} / J_{ss} \text{ of reference}$$

#### Drug content deposited in skin layers

The extent of drug deposited in the epidermal layers was determined as described earlier in reports<sup>16</sup>. After completion of *ex-vivo* diffusion study (24hrs), the skin was separated from the Franz-diffusion cell, washed briefly in methanol (25 ml) for 15 sec to remove the adhering formulation. The skin was allowed to dry at room temperature for 10 min, chopped into pieces, homogenized in 10 ml of 40% (v/v) ethanolic phosphate buffered saline (pH 7.4) and sonicated for 30 min using bath sonicator (Sonica, Italy) to leach out the drug. The samples were centrifuged and the supernatant layer was recovered and assayed for Sumatriptan succinate using UV-Visible spectrophotometer wavelength at 225 nm.

#### Skin irritancy test

The skin irritancy potential of the proniosome formulations was evaluated using albino rats. The hair was removed on the back of the animal and the formulations were applied, and the animals were examined for any signs of skin irritation and erythema for a period of week.

#### Stability Studies

The formulations were stored in glass vials covered with aluminium foil were kept at room temperature and in refrigerator (4-8°C) for a period of 3 months. Measure the amount of entrapped drug content of preparation after 72hrs and at definite time intervals (1, 2, and 3 months)<sup>17</sup>. Formulations which retains its entrapment efficiency for 3 months duration

considered as stable formulation (generally formulation those have >60% entrapment efficiency) by using the formula given below <sup>18</sup>. samples were withdrawn and hydrated with phosphate-buffered saline (pH 7.4) and observed for any sign of drug crystallization under optical microscope. Furthermore, the samples were also evaluated for particle size and percent retention of Sumatriptan succinate <sup>19</sup>.

#### Sumatriptan succinate in proniosomes

= **Entrapped STS after storing**

**Entrapped STS before storing**

#### Statistical Analysis

Statistical analysis of the data obtained was performed using one-way ANOVA followed by Neuman keuls post test with Graph Pad Prism software (version 4.00; Graph Pad Software, San Diego California). The level of statistical significance was chosen as less than  $P < 0.05$ .

### RESULTS AND DISCUSSION

#### Percent drug content, entrapment efficiency, particle size and viscosity

The percentage drug content, particle size and Entrapment efficiency of all the formulations were found to be 96-99%, 10-13 $\mu$ m and 91-93% respectively (Table 2), resembles and showing that uniform particle distribution, uniform Entrapment efficiency and drug content.

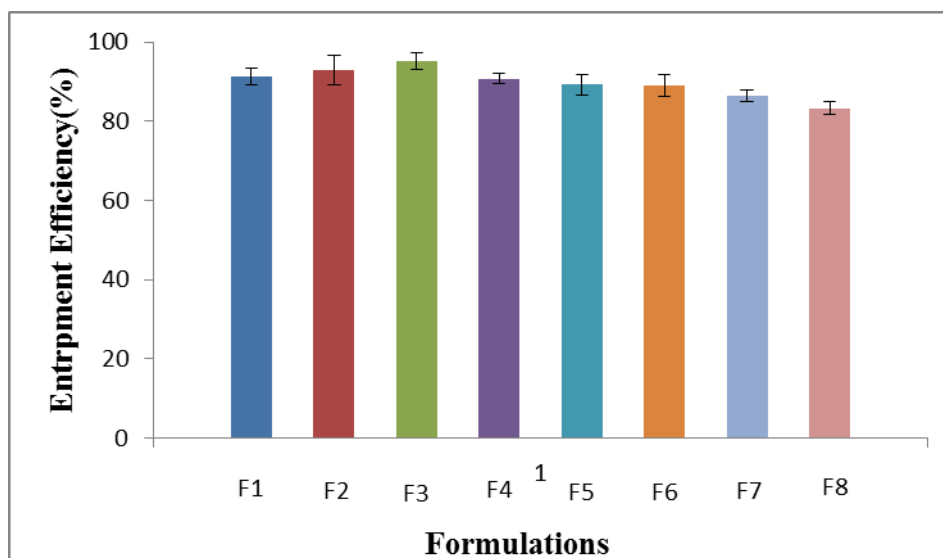
**Table 2 Percentage of drug content, entrapment efficiency, particle size and viscosity of sumatriptan succinate proniosomal gel (Mean  $\pm$  SD; n=3)**

| Formulation Code | Percent drug content | Percent Entrapment efficiency | Particle size ( $\mu$ m) |
|------------------|----------------------|-------------------------------|--------------------------|
| F1               | 92.97 $\pm$ 2.34     | 92.36 $\pm$ 2.15              | 15.73 $\pm$ 0.37         |
| F2               | 90.64 $\pm$ 1.51     | 93.20 $\pm$ 3.69              | 14.86 $\pm$ 0.54         |
| F3               | 94.57 $\pm$ 1.02     | 94.13 $\pm$ 2.14              | 11.26 $\pm$ 0.43         |
| F4               | 92.08 $\pm$ 1.48     | 91.82 $\pm$ 1.43              | 10.33 $\pm$ 0.67         |
| F5               | 91.20 $\pm$ 2.11     | 85.40 $\pm$ 2.54              | 13.31 $\pm$ 0.47         |
| F6               | 90.13 $\pm$ 2.15     | 88.92 $\pm$ 2.79              | 12.26 $\pm$ 0.57         |
| F7               | 91.55 $\pm$ 2.27     | 90.22 $\pm$ 1.53              | 11.23 $\pm$ 0.74         |
| F8               | 90.48 $\pm$ 3.14     | 81.26 $\pm$ 1.63              | 10.34 $\pm$ 0.24         |

Among the all formulations, formulations prepared with span 60 and span 40 (F3 and F2) showed maximum entrapment efficiency that 95.80 and 94.13 respectively. This maximum entrapment efficiency may be due to the highest phase transition temperature (TC) of span 60 and span 40 and these are solids at room temperature. The surfactants having highest phase transition temperature were investigated to have the highest entrapment efficiency <sup>20,21</sup> and all spans are having similar head groups and even through changing the length of alkyl chain no significant change ( $p < 0.05$ ) in entrapment efficiency <sup>22</sup>. Incorporation of lecithin leads to more compact and well organized bilayers which prevent

the leakage of drug <sup>3</sup>. Entrapment efficiency of various sumatriptan succinate proniosomal formulations are represented in Figure 1. proniosomes of span 20 produced niosomes of larger size and proniosomes of span 60 produced niosomes of smaller size. This effect is related to the inverse relationship between hydrophobicity of the non-ionic surfactant and vesicle diameter of niosomes, decreasing the hydrophobicity of the surfactant resulted in an increase of vesicle size. The observed relationship between the vesicular diameter and hydrophobicity of surfactants has been attributed to the decrease in surface free energy with increasing hydrophobicity, resulting in smaller vesicles <sup>20</sup>. Vesicle

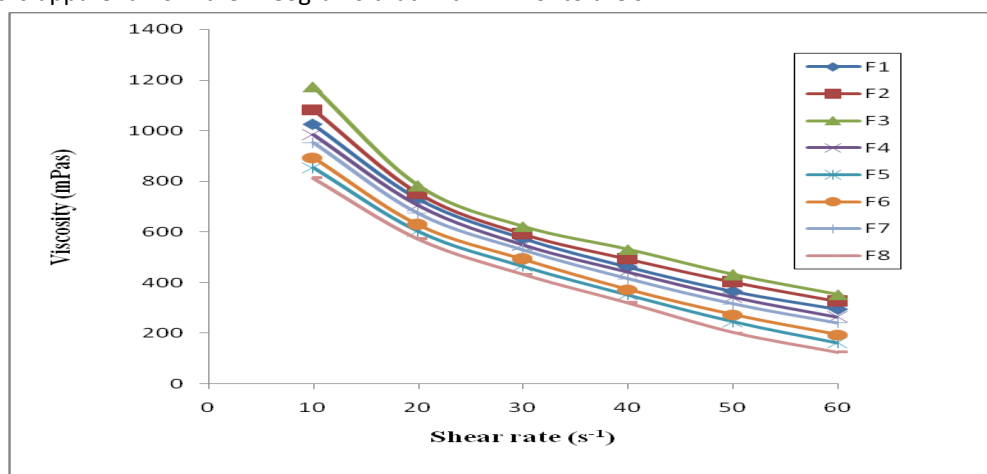
size followed the trend Span 20 (HLB=8.6)>Span 40 (HLB=6.7)>Span 60 (HLB=4.7)>Span 80 (HLB=4.3).



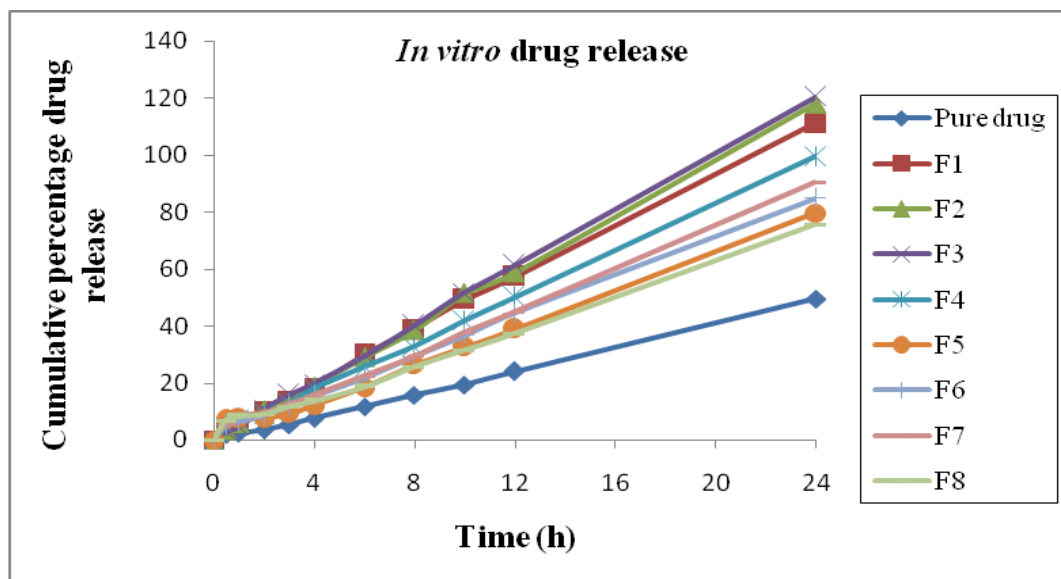
**Figure 1 Entrapment efficiency of various sumatriptan succinate niosomes (%EE±S.D)**

The rheological behaviour (consistency) is an important parameter to be evaluated for transdermal application because it influences the uniform and easy application of the formulation. The rheograms of different proniosomal formulations are depicted in Figure 2. It is apparent from the rheograms that with

increase in shear rate the viscosity was decreased and the formulations exhibit good flow behaviour. The viscosity of the optimized formulation was 1200mPas. The rheological behaviour of the formulations clearly indicates their ease of application onto the skin.



**Figure 2 Rheograms of various sumatriptan succinate proniosomal gel formulations**



**Figure 3** Graph representing *in vitro* percentage drug release profiles of sumatriptan succinate from different proniosomal gel formulations through cellophane membrane (Mean  $\pm$  SD; n=3)

#### ***In vitro* release study**

The *in vitro* release behaviour of Sumatriptan succinate from proniosomes was studied. The percentage drug release from different formulations was represented in Fig 3. A typical biphasic release pattern was observed with proniosomal formulations. Initially a rapid burst release followed by sustained release for a period of 24 h was observed. The high concentration gradient prevailing at the initial time points might have contributed for the rapid drug release and also may be due to the faster release of untrapped drug from the proniosome formulations.

#### ***Ex vivo* permeation study**

Proniosomes should be hydrated to form niosomal vesicles before the drug is released and permeates across the skin. Several mechanisms could explain the ability of niosomes to improve drug permeation across skin. Including (i) adsorption and fusion of niosomes onto the surface of skin would facilitate drug permeation, (ii) the vesicles act as penetration enhancers to reduce the barrier properties of the stratum corneum, and (iii) the lipid bilayers of niosomes act as a rate-limiting membrane barrier for drugs.

One of the possible mechanisms for niosomal enhancement of the permeability of drugs is structure

modification of the stratum corneum. It has been reported that the intercellular lipid barrier in the stratum corneum would be dramatically looser and more permeable following treatment with liposomes and niosomes. Both phospholipids and nonionic surfactants in the proniosomes can act as penetration enhancers, which are useful for increasing the permeation of many drugs<sup>3</sup>.

The *ex-vivo* permeation study was conducted across the rat abdominal skin to check the permeability of Sumatriptan succinate proniosomes through skin and to determine the effect of lecithin and different non-ionic surfactants in drug permeation. Significant permeation of Sumatriptan succinate achieves only after hydration of proniosomal formulation with skin fluids<sup>23</sup>. Interestingly, the amount of drug released across the cellophane membrane was significantly higher than the permeation across skin, indicates the barrier properties of the skin. The results are in consistent with the reports<sup>3</sup>. The percentage drug release from different formulations was represented in Fig 4. All the formulations (with lecithin and without lecithin) showed significant improved flux ( $p < 0.05$ ) compared to pure drug permeation across rat skin. The non-ionic surfactants in proniosomes generally act as permeation enhancers. The

permeation enhancement assessed in terms of permeation parameters (flux, permeability coefficient and enhancement ratio) were calculated and showed in Table 3. The maximum flux obtained was 77.52 and 70.54  $\mu\text{g.h.cm}^{-2}$  from proniosomal formulations with

span 60 and span 40 (F3&F2) respectively. This improved flux was attributed to the lipophilicity of surfactant. By increasing the lipophilicity, amount of drug permeation also increases.

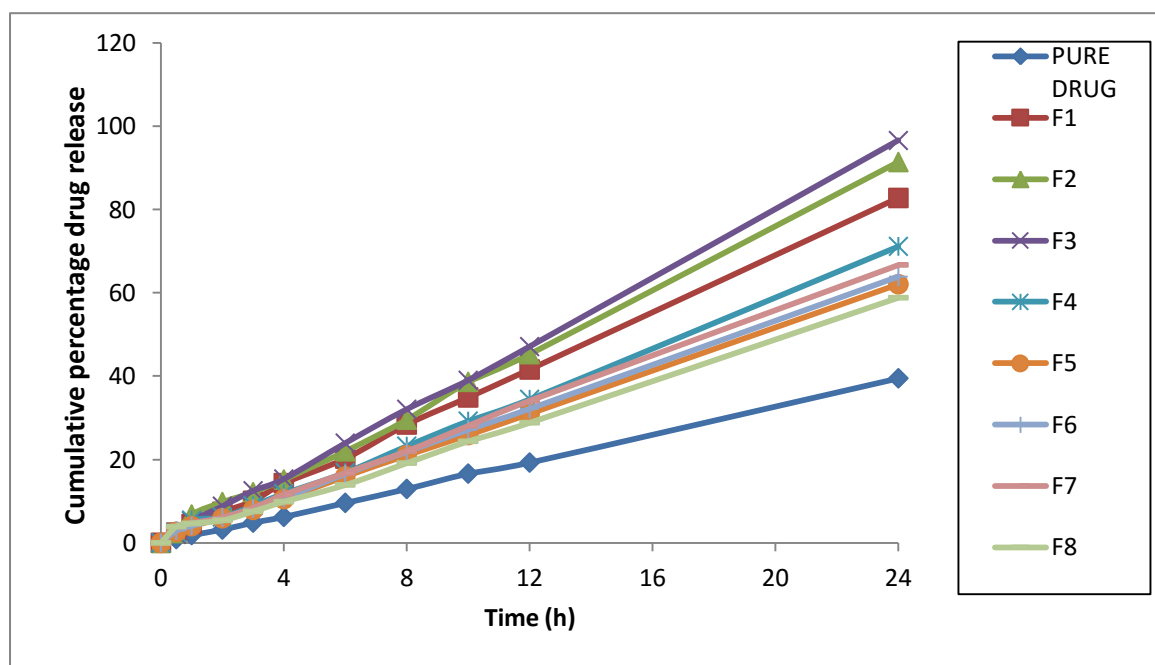


Figure 4 Graph representing the *ex vivo* percentage drug permeation profiles of sumatriptan succinate from different proniosomal gel formulations across rat skin (Mean $\pm$ SD; n=3).

Table 3 Release parameters of sumatriptan succinate from different proniosomal formulations through cellophane membrane (Mean $\pm$ SD; n=3)

| Formulation Code | Permeation parameters                   |                         |                 |
|------------------|-----------------------------------------|-------------------------|-----------------|
|                  | Jss<br>( $\mu\text{g/cm}^2/\text{hr}$ ) | Kp<br>( $\text{Cm/h}$ ) | ER              |
| Pure drug        | 43.34 $\pm$ 1.49                        | 1.73 $\pm$ 0.50         | 1               |
| F1               | 83.49 $\pm$ 1.28                        | 3.33 $\pm$ 0.06         | 1.92 $\pm$ 0.32 |
| F2               | 94.91 $\pm$ 1.37                        | 3.79 $\pm$ 0.43         | 2.18 $\pm$ 0.50 |
| F3               | 98.10 $\pm$ 1.35                        | 3.92 $\pm$ 0.42         | 2.26 $\pm$ 0.49 |
| F4               | 82.42 $\pm$ 1.38                        | 3.29 $\pm$ 1.24         | 1.90 $\pm$ 1.40 |
| F5               | 64.79 $\pm$ 1.55                        | 2.59 $\pm$ 0.60         | 1.49 $\pm$ 0.71 |
| F6               | 71.18 $\pm$ 1.61                        | 2.87 $\pm$ 1.65         | 1.65 $\pm$ 1.73 |
| F7               | 74.18 $\pm$ 4.80                        | 2.96 $\pm$ 0.92         | 1.71 $\pm$ 0.94 |
| F8               | 62.32 $\pm$ 3.58                        | 2.49 $\pm$ 0.68         | 1.43 $\pm$ 0.72 |

Jss, Kp, ER represents steady state Flux, Permeability coefficient, Enhancement ratio respectively

**Table 4 Permeation parameters of sumatriptan succinate from different proniosomal formulations across rat skin (Mean± SD; n=3)**

| Formulation code | Q24   | Permeation parameters                                                     |              |           |
|------------------|-------|---------------------------------------------------------------------------|--------------|-----------|
|                  |       | Jss<br>(µg/cm <sup>2</sup> /hr)                                           | Kp<br>(Cm/h) | ER        |
| Pure drug        | 39.49 | 35.18±1.12                                                                | 1.40±0.52    | 1         |
| F1               | 82.76 | 64.52±1.43 <sup>a 1,5,6,7,8,9 b 1,5,6,7,8,9 c 1,6,7,9</sup>               | 2.58±0.10    | 1.84±0.13 |
| F2               | 91.38 | 70.54±2.40 <sup>a 1,2,5,6,7,8,9 b 1,2,5,6,7,8,9 c 1,5,6,7,8,9</sup>       | 2.78±0.13    | 1.98±0.16 |
| F3               | 96.55 | 77.52±1.53 <sup>a 1,2,3,5,6,7,8,9 b 1,2,3,5,6,7,8,9 c 1,2,5,6,7,8,9</sup> | 3.10±0.07    | 2.21±0.09 |
| F4               | 71.14 | 58.14±1.17 <sup>a 1,6,9 b 1,9 c 1,9</sup>                                 | 2.32±1.37    | 1.65±1.02 |
| F5               | 62.05 | 51.12±2.47 <sup>a 1 b 1 c 1</sup>                                         | 2.04±0.49    | 1.45±0.50 |
| F6               | 63.87 | 53.41±1.94 <sup>a 1,9 b 1 c 1</sup>                                       | 2.13±0.91    | 1.52±0.90 |
| F7               | 66.70 | 55.87±4.28 <sup>a 1,9 b 1,9 c 1</sup>                                     | 2.23±0.26    | 1.59±0.33 |
| F8               | 58.82 | 47.92±3.63 <sup>a 1 b 1 c 1</sup>                                         | 1.91±0.57    | 1.36±0.61 |

Jss, Kp, ER represents steady state Flux, Permeability coefficient, Enhancement ratio respectively. a,b,c represents p<0.05, p<0.01, p<0.001 respectively. 1,2,3,4,5,6,7,8,9 represent pure drug, F1, F2, F3,F4,F5,F6,F7,F8 respectively.

Due to high lipophilic nature of span 60, the formed vesicles can easily fuse and penetrate through the skin. This improved flux is also due to the small vesicle size. Lower flux was observed with span 20 formulation compared with other span formulations is due to larger vesicle size that acts as barrier in the permeation of drug. The reason for less permeation of drug from formulation containing span 80 is less entrapment of drug due to smaller size of vesicles. Formulation with span 60 and span 40 showed better entrapment efficiency with optimum vesicle size leading to better permeation. Proniosome gel containing lecithin formulations (F1, F2, F3 & F4) showed greater permeability compared to the non-lecithin formulations which may be due to the presence of fatty acids in molecular structure of lecithin which are responsible for reduction of skin resistance to drug permeation but not to the drug solubility<sup>24</sup>. The maximum flux was significantly higher (p<0.05) for the formulation which contains span 60 with lecithin (F3). The enhancement ratio well above 1 indicates improved permeation and in our findings we could notice an ER greater than 1 for all proniosomal gel formulations compared to pure drug (control). Such an improvement is statistically

significant Table 4. Based on the permeation parameters, the proniosomal formulations can be ranked in the following decreasing order F3 > F2 > F1 > F4 > F7 > F6 > F5 > F8>pure drug. Overall it is evident from the results that the permeation of Sumatriptan succinate has been greatly improved from proniosome formulations.

From the above order formulation of span 60 with lecithin shows greater flux and from the stability studies it is having 81% entrapment efficiency resembles that its high stability.

#### Estimation of drug deposited in rat skin

The extent of drug deposited in the skin (DCS) layers upon treatment of rat skin with all the formulations and drug solution was shown in Fig. 5. Since the permeation was increased with all the gel formulations, obviously the drug in the skin layers was also increased. This can be well explained based on the fact that the saturation of skin layers at the termination point of the experiment i.e. 24 h could have led to the higher DCS values. The higher deposition of Sumatriptan succinate in skin layers with proniosomal gels compared to control reveals the potential of these formulations in avoiding the barrier function of the stratum corneum and

delivering the drug efficiently into the viable regions of the skin for improved bioavailability.

#### Scanning Electron Microscopy studies

The shape, surface characteristics, and size of the niosomes were observed by scanning electron microscopy. Results were shown in Figure 6.

#### Skin irritation studies

After application of proniosomal gel formulations we could not notice any marked erythema, oedema or erosion during seven days. However, a slight reddening of the skin was observed but it was subsided and normalized after 24 h of the study.

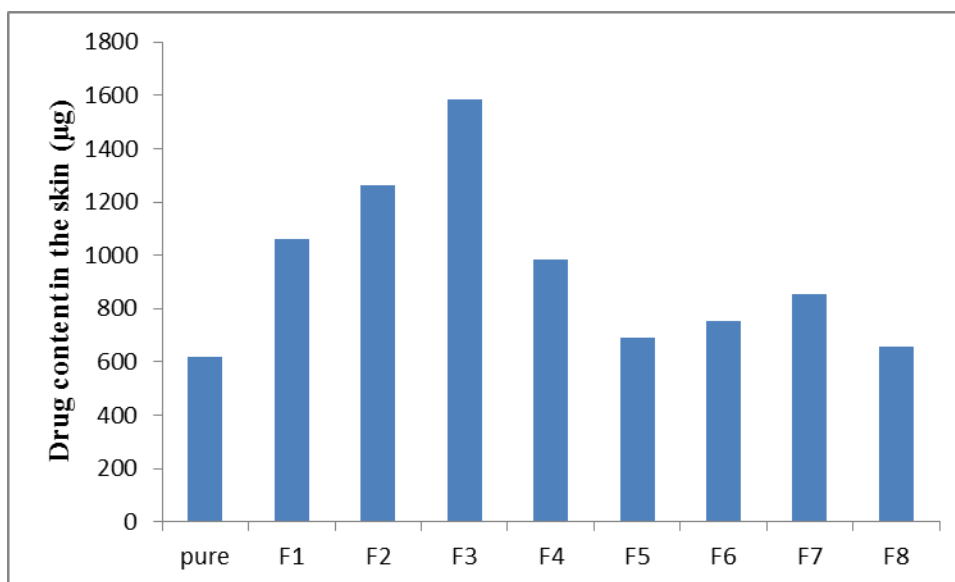


Figure 5 Drug content deposited in skin layers

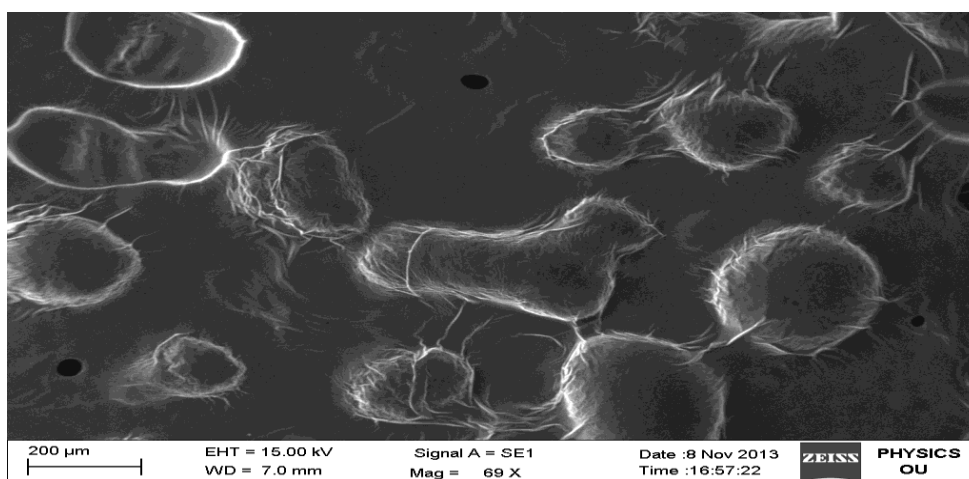


Figure 6 SEM of optimized formulation F3

## CONCLUSION

Proniosomes of Sumatriptan succinate was formulated and evaluated with the objective to improve its bioavailability through transdermal delivery. The formulations containing lecithin showed improved *ex-vivo* permeability compared to the formulations that do not contain lecithin. Among the formulations containing lecithin, formulation prepared with span 60 showed better results and was optimized. The composition of optimized formulation was Sumatriptan succinate (25 mg), span 60 (160 mg), lecithin (200 mg), cholesterol (40 mg). The present study proves that drugs like Sumatriptan succinate can be formulated as proniosomes for transdermal delivery to improve bioavailability by passing the first pass effect.

## REFERENCES

- Vora B., Khopade A. J., Jain N.K. Proniosome based transdermal delivery of levonorgestrel for effective contraception. *J. Cont. Rel.* 1998; 54:149–165.
- Schreier H., Bouwstra J. Liposomes and niosomes as topical drug carriers for dermal and transdermal drug delivery. *J Control Rel.* 1994; 30:1-15.
- Jia-You Fang., Song-Yih Y., Pao-Chu W., Yaw- Bin H., Yi-Hung T. *In vitro* skin permeation of estradiol from various proniosome formulations. *Int J Pharm.* 2001; 215:91–99.
- Gupta A., Prajapati S.K, Balamurugan M., Singh M., Bhatia D. Design and Development of a Proniosomal Transdermal Drug Delivery System for Captopril. *Tropical J. Pharm Res.* 2007; 6:687-693.
- Hu C., Rhodes D. G. Proniosomes: a novel drug carrier preparation. *Int J Pharm.* 1999; 185:23-35.
- Humphrey P.P., Feniuk W., Marriott A. S., Tanner R.J., Jackson M. R., Tucker M.L. Preclinical studies on antimigraine drugs. *Eur Neurol.* 1991; 31:282–290.
- Upadhyay K.K., Tiwari C., Khopade A.J., Bohidar H.B., Jain S.K. Sorbitan Ester organogels for transdermal delivery of sumatriptan. *Drug Dev Ind Pharm.* 2007; 33:617–625.
- Siegel S.J., Neill C.O., Dube L.M., Kaldewey P., Morris R., Jackson D., Sebree T. iontophoretic patch for optimal transdermal delivery of sumatriptan. *Pharm Res.* 2007; 24:1919–1926.
- Mokhtara M., Sammour O.A., Hammada M.A., Megrab N.A. Effect of some formulation parameters on flurbiprofen encapsulation and release rates of niosomes prepared from proniosomes. *Int. J. Pharm.* 2008; 361:104-111.
- Alsarra A., Bosela A.A., Ahmed S.M., Mahrous G.M. Proniosomes as a drug carrier for transdermal delivery of ketorolac. *Eur. J. Pharm.* 2005; 59:485–490.
- Rizwan M., Aqil M., Ahad A., Sultana Y., Ali M.M. Transdermal Delivery of Valsartan: I. Effect of Various Terpenes. *Drug Dev. Ind. Pharm.* 2008; 34:618-626.
- Zhao K., Singh J. *In vitro* percutaneous absorption enhancement of propranolol hydrochloride through porcine epidermis by terpenes/ ethanol. *J. Control. Rel.* 1999; 62:359-366.
- Sunil T.N., Ramesh P. Transdermal delivery of zidovudine: effect of terpenes and their mechanism of action. *J. Control. Rel.* 2004; 95:367- 379.
- Escribano E., Calpena A.C., Queralt J., Obach R., Domenech J. Assesment of diclofenac permeation with different formulations: anti-inflammatory study of selected formula. *Eur. J. Pharmsci.* 2003; 19:203-210.
- Krishnaiah Y.S.R., Bhaskar P., Sathanarayana V. Penetration enhancing effect of ethanol-water solvent system and ethenolic solution of carvone on transdermal permeability of nimodipine from HPMC gel across rat abdominal skin. *Pharm.Dev.Technol.* 9: 63-74, 2004.
- Wissing S.A., Müller R.H. The influence of solid lipid nanoparticles on skin hydration and viscoelasticity - in vivo study. *Eur. J.Pharm. Biopharm.* 56: 67- 72, 2003.
- Varshosaz J., Pardakhty A., Baharanchi S.M. Sorbitan monopalmitate-based proniosomes for transdermal delivery of Chlorpheniramine maleate. *Drug Deliv.* 12:75-82, 2005
- Ammara H.O., Ghorabb M., El-Nahhas S.A., Higazy I.M. Proniosomes as a carrier system for transdermal delivery of tenoxicam. *Int J Pharm.* 405: 142-52, 2011.
- Karthik J.Y., Raju J., Ashok V., Sharath S., Suresh B., Prabhakar K., Prabhakar Reddy V. Bioavailability enhancement of zaleplon via proliposomes: Role of surface charge. *European Journal of Pharmaceutics and Biopharmaceutics.* 80: 347–357, 2012.
- Abdallah M., Sammour O., EL-Ghamry H., Abu-Seleem M. Preparation and *in-vitro* evaluation of diclofenac sodium niosomal formulations. *IJPSR.* 4:1757-1765, 2013.
- El-Laithy H.M., Shoukry O., Mahran L.G. Novel sugar esters proniosomes for transdermal delivery of vinpocetine: Preclinical and clinical studies. *Eur J Pharm Biopharm.* 77: 43-55, 2011.



22. HaoY., Zhao F., Li N., Yang Y., Li K. Studies on a high encapsulation of colchicine by niosome system. *Int. J. Pharm.* 244: 73- 80, 2002.
23. Hwang, B.Y., Jung B.H., Chung S .J., Lee M., Shim C. *In vitro* skin permeation of nicotine from proliposomes. *J. Cont. Rel.*; 49: 177- 184, 1997.
24. Mahjour M., Mauser B., Rashidbaigi Z., Fawzi M.B. Effect of yolk lecithin and commercial soyabean lecithin on *in vitro* skin permeation of drugs. *J.Control.Rel.*; 14:243-252, 1990.

**\*Corresponding Author:**

**Raju Jukanti**

Email: [drjukanti@gmail.com](mailto:drjukanti@gmail.com)