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# PRO VESICULAR BASED COLLOIDAL CARRIERS FOR TRANSDERMAL DRUG DELIVERY

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**Abstract**

The present investigation aimed at formulation development and performance evaluation of proniosomal gel as a vesicular drug carrier system. Domperidone (DOM) is a dopamine- receptor (D2) antagonist, which is widely used in the treatment of motion-sickness. The pharmacokinetic parameters (absolute bioavailability about 10-20 % and log P, 3.11) make DOM a suitable candidate for transdermal delivery. The purpose of the present investigation was to develop transdermal delivery systems for DOM and to evaluate their physicochemical characteristics, in vitro release an ex vivo permeation through rat abdominal skin. Proniosome drug delivery was preferred due to improved stability of the system than niosomes. A proniosome based transdermal drug delivery system of domperidone was developed and extensively characterized both in-vitro and ex-vivo. Proniosomal gel formulations of domperidone were characterized for vesicular shape & size, entrapment efficiency, permeation study. The effects of cholesterol, lecithin and different non-ionic surfactants on transdermal permeability profile of domperidone were performed. The stability studies were performed at 2°C and at room temperature. Optimized formulation showed maximum cumulative percentage of drug release (96.551%), permeation (4.119 mg) in 24 hrs, flux (0.173 µg / $cm^2$/ hr), and permeation coefficient of 0.029 $cm^2$/hr and enhancement ratio 2.351. FTIR studies showed no evidence of interaction between the drug and polymers. Penetration enhancers, non-ionic surfactants and vesicle-skin interaction may contribute to the enhanced domperidone permeation. Thus Proniosome was found to be a promising carrier system for domperidone because of ease in preparation and stability for prolonged period. The study demonstrated the utility of proniosomal transdermal patch bearing domperidone for emesis.

**Keywords:** Transdermal, Domperidone, Proniosomes, Permeation, Span 60, Lecithin.

**Introduction**

The transdermal route is widely used as it is convenient, safe and offers numerous advantages over conventional ones that includes evading GI incompatibility, variable GI absorption, bypassing first pass metabolism, enhanced bioavailability, decreased frequency of administration, improved patient compliance, rapid cessation of drug input and can maintain a suitable plasma concentration. One of the major disadvantages in transdermal drug delivery is the low penetration rate of substances through the skin (Schreier and Bouwstra, 1994). Several techniques have been explored to increase the drug penetration rate across skin including iontophoresis and penetration enhancement, particularly for the delivery of peptides and proteins. Third alternative method, the encapsulation of drugs in lipid vesicles prepared from phospholipids (liposomes) or nonionic surfactants (niosomes) which have been shown to facilitate transport of drugs into and across skin. Niosomes have a problem of degradation by hydrolysis or oxidation, demands special storage and handling shows sedimentation, aggregation or fusion on storage.

Proniosomes a versatile delivery system is their potential of entrapping a wide range of active compounds without showing any problems of physical stability (aggregation, fusion, leaking). Proniosomes provide the convenience of the transportation, distribution, storage, and dosing. Proniosomes upon hydration with water from skin after topical application get readily converted into niosomes of uniform size. Proniosomes exists in two forms, i.e. semi solid liquid crystal gel and dry granular powder, depending on their method of preparation. Out of these two forms, the proniosome gel is mainly used for topical/transdermal applications. Proniosomal gel is a compact semi-solid liquid crystaline (gel) product of non-ionic surfactants easily formed on dissolving the surfactant in minimal amount of acceptable solvent and the least amount of aqueous phase. This compact liquid crystalline gel can be readily converted into niosomes on hydration. Proniosomal gel offers a great potential to reduce the side effects of drugs and increased therapeutic effectiveness.

Proniosomes can entrap both hydrophilic and hydrophobic drugs. Domperidone is a dopamine- receptor (D2) antagonist, widely used in the treatment of motion-sickness. In humans, peak plasma levels of domperidone occur within 10 to 30 min following intra-muscular injection and 30 min after oral (fasted) administration. It has been reported that it is rapidly absorbed after oral administration, but undergoes extensive first pass metabolism; leading to poor bioavailability of 15%. From both, physicochemical (low molecular weight 425.9g/mol, low dose 10 mg) and pharmacokinetic (absolute bioavailability about 10-20 % and log P, 3.11) perspective, DOM was considered to be a suitable candidate for transdermal delivery (Madishetti *et al., 2010*).

**Materials and Methods**

Span 20 (Ozone chemicals), 40 (Central Drug House pvt Ltd., New Delhi), Span 60, Span 80, phospholipoid (Germany), cholesterol (S.D. fine chemicals), Ethanol (Changshu yangyuan chemical, china), Methanol, Isopropyl alcohol, 0.1% Glycerol (Merck, Mumbai), other chemicals were of analytical grade. Distilled water was used for all experiments.

**Preparation of proniosomes**

Proniosomes were prepared by the method reported by Perrett et al 1991. Precisely, surfactants: alcohol (1:1) (total surfactant 100 mg) and drug were taken in a clean and dry, wide mouth small glass tube. The compositions of surfactants are given in Table 1. After mixing all the ingredients, the open end of the glass tube was covered with a lid to prevent loss of solvent from it and warmed on a water bath at 60–70C for about 5 min, until the surfactants were dissolved completely. The aqueous phase (0.1% glycerol solution) was added and warmed on a water bath till clear solution is formed which on cooling converts into a proniosomal gel. The final ratio of surfactant: alcohol: aqueous phase was 5:5:4 w/w/w. The gel obtained was preserved in same glass tube in dark for characterization (Vora *et al* 1998). A thin layer of proniosomal gel was spread in a cavity slide and after placing the cover slip observed under microscope with and without polarized light. A drop of water was added through the side of the cover slip into the cavity slide while under microscope and again observed. Photomicrographs were taken at suitable magnifications before and after addition of water for the formulation S40L.

**Table 1: Formulations of Microscopic evaluation.**

| Code | Span 20 (mg) | Span 40 (mg) | Span 60 (mg) | Span 80 (mg) | Cholesterol (mg) | Lecithin (mg) |
|---|---|---|---|---|---|---|
| **S20** | 360 | | | | 40 | |
| **S40** | | 360 | | | 40 | |
| **S60** | | | 360 | | 40 | |
| **S80** | | | | 360 | 40 | |
| **S20L** | 180 | | | | 40 | 180 |
| **S40L** | | 180 | | | 40 | 180 |
| **S60L** | | | 180 | | 40 | 180 |
| **S80L** | | | | 180 | 40 | 180 |

**Size and size distribution**

Size and size distribution studies were done for niosomes prepared from proniosomes hydration. The proniosomal gel (100 mg) was hydrated in a small glass test tube using 10 ml of pH 7.4 phosphate buffer solution. The dispersion was observed under optical microscope at 40X magnification. Size and size distribution of 200–300 niosomes were noted using calibrated stage and ocular micrometers (Elico Instruments, Hyderabad). Similarly, size was noted for niosomes formed spontaneously from proniosomes after hydration without agitation in a cavity slide [4].

**Entrapment efficiency**

To 0.2 g of proniosome gel, weighed in a glass tube, 10 ml phosphate buffer pH 7.4 were added. The aqueous suspension was then sonicated.

Niosomes containing domperidone were separated from untrapped drug by centrifugation at 9000rpm for 45 min at 4 ◦C. The supernatant was recovered and assayed spectrophotometrically using UVspectrophotometer (UV-1800 Shimadzu, Japan), at 283nm Ammara *et al.*, 2011). The encapsulation percentage of drug (EP) was calculated by the following equation Alsarra *et al., 2005*).

$$\mathbf{EP = [(C_t - C_r)/ C_t] * 100}$$

Where, Ct, concentration of total domperidone, Cr, concentration of free domperidone.

**Vesicle physical analysis**

The shape, surface characteristics, and size of the niosomes were observed by scanning electron microscopy. Once again, 0.2 g 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.

**Fourier transform infrared spectroscopy**

Fourier transform IR spectra were obtained on Shimadzu FT-IR spectrometer. Samples were prepared in KBr disks (2mg sample in 200mg KBr). The scanning range was 450-4000 $cm^{-1}$ and the resolution was 4 $cm^{-1}$.

**Fabrication of transdermal patch:**

The circular aluminium foil of diameter 2.5 cm was used as backing membrane. On this backing membrane a plastic sheet of same size with 1.0 mm thickness was stuck with adhesive. The circle of diameter 1.32 cm (corresponding to 1.369$cm^2$ area) was cut centrally on a plastic sheet of the same size and thickness used previously and stuck with

adhesive. The proniosomal gel was evenly spread over this area and covered with the fine nylon mesh. The liquid crystalline proniosomal gel acts as a reservoir for the transdermal delivery of domperidone.

***In Vitro* Release Study**

*In vitro* release studies were carried out using unjacketed vertical franz diffusion cells with a diffusional surface area of 6.154 $cm^2$ and 20 mL of receptor cell volume. Prior to the study, the dialysis membrane (Himedia laboratories Pvt Ltd., Mumbai) was soaked in phosphate buffer pH 7.4 Formulation equivalent to 5mg of Domperidone was placed in the donor compartment.

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 upto 24 hrs . 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 (0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hrs) and replaced with equal volume to maintain constant receptor phase volume. At the end of the study, the samples were suitably diluted and the amount of drug was determined spectrophotometrically at 283 nm.

***In Vitro* Permeation Study Using Excised Rat Abdominal Skin**

**Preparation of Rat Abdominal Skin**

Male albino rats (150-200 g) were used for the experiment. The rats were sacrificed by using excess amount of anesthetic 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, 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 (used within 2 weeks of preparation [6].

**Permeation Study**

In vitro permeation studies were carried out using unjacketed vertical franz diffusion cells with a diffusional surface area of 6.154 $cm^2$ 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 0.5 g of gel formulation/reference formulation equivalent to 5 mg of domperidone was placed in the donor compartment. 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 upto 24 hrs. 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 (0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hrs) and replaced with equal volume to maintain constant receptor phase volume. At the end of the study, the samples were suitably diluted and the amount of drug was determined spectrophotometrically at 283 nm.

**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=Flux(µg/cm$^2$/hr), A=Surface area, dQ/dt = Cummulative 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 [6].

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

where, Kp=Permeability co efficient (cm/hr); J= transdermal flux; C= Initial concentration of acyclovir sodium in the d compartment.

**Enhancement Ratio**

The penetration enhancing effect of various formulations containing acyclovir sodium gels were calculated in terms of Enhancement Ratio (ER) by using the following equation.

**ER = Jss of formulation/ Jss of reference**

**Evaluation of Optimised Formulation**

Formulation F4 was optimised on the basis of permeation studies and evaluated for following parameters

**Stability studies**

Stability studies were carried out by storing the optimized formulation (F4) at various temperature conditions as per ICH guidelines i.e. at refrigeration temperature (2°-8°C), room temperature (25°± 0.5°C) for a period of two months. Drug content and variation in the average vesicle diameter were determined before and after the completion of 2

months. Surface morphology of optimized formulation (F4) by SEM image is shown in Figure 9&10. and the results are reported in Table 5 ( Raju Jukanti *et al., 2011*).

**Skin irritancy test**

The skin irritancy potential of the proniosome formulations was evaluated in 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 1 week.

**Statistical Analysis**

Significance of difference between formulations was calculated by one way analysis of variance using Newman Keuls (compare all pairs) with Instant Graph Pad Prism software. The difference was considered to be statistically significant at $p<0.05$.

**Results and discussion**

**Microscopic examination**

A thin layer of proniosomal gel was spread in a cavity slide and after placing the cover slip observed under microscope. A drop of water was added through the side of the cover slip into the cavity slide while under microscope and again observed. Photomicrographs were taken at suitable magnifications before and after addition of water for formulation S40L. (Figure 1a and1b).

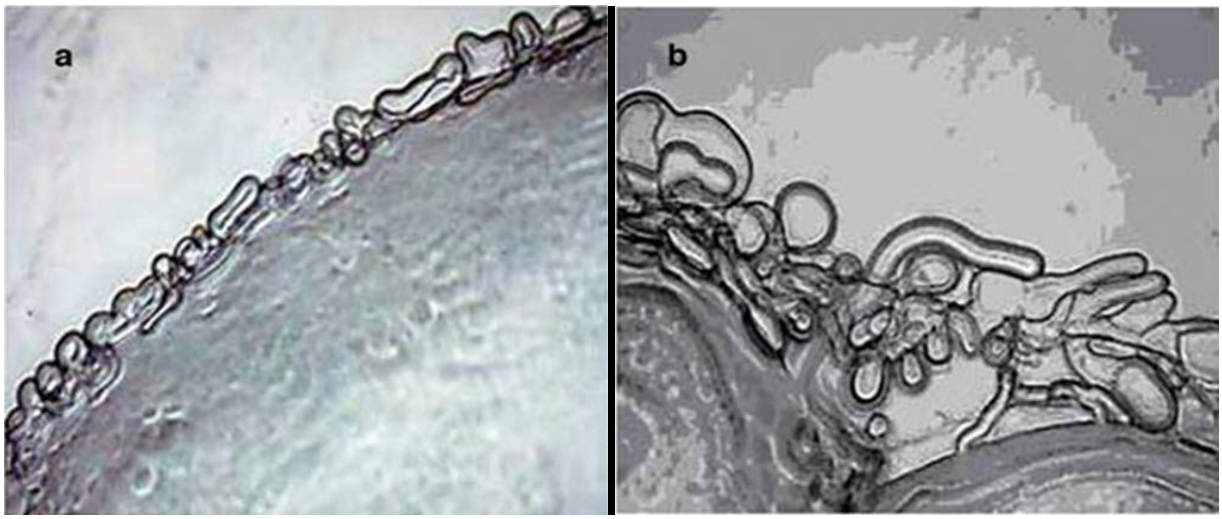


**Figure 1 a) Photomicrograph of proniosomes (X40) b) Niosomes separating from proniosomes upon hydration (X40).**

**Drug Content**

Domperidone contents in the proniosome gel of different non ionic-surfactant, lecithin ratio (9:1), non-ionic surfactant, lecithin, cholesterol ratio (4.5:4.5:1) respectively. The order of drug content or percentage yield was

S40L>S20L>S60L>S80L>S20>S40>S60>S80. Uniformity of content present in proniosomal gel confirmed to assure uniformity in dosages. The results are reported in Table. 2.

**Particle size analysis**

The results were reported in Table no. 2. Size range of the all formulations was found to be is 13.84µm(S20), 15.99µm(S20L), 12.36µm(S40), 11.22µm(S40L), 13.24µm(S60), 10.14µm(S60L), 12.79µm(S80), 10.05µm(S80L) respectively. The proniosome vesicle were formed to be uniform in size 11.22±0.76µm (S40L) and 10.14µm (S60L). The differences of vesicle size among all niosomes with span were not great. The relationship observed between niosome size and span hydrophobicity has been attributed to the decrease in surface energy with increasing hydrophobicity, resulting in the small vesicles. Vesicles with small diameter are believed to better permeate through the skin. Niosomes of S60L were smaller in size than S40L. In corporation of lecithin leads to vesicles of smaller size due to increase in hydrophobicity which results in reduction of vesicles size . There is probably formation of more compact and well organized bilayers which prevents the leakage of drug (Hemant *et al., 2012*). Isopropanol results in vesicles of smallest size, may be due to branched chain present in it.

**Entrapment efficiency (EE)**

The results were reported in Table no. 2. & Figure no. 2. The entrapment efficiency was found to be (84.37% - 94.21%) for formulations. Encapsulation studies were carried out on all formulations. In these studies the higher entrapment efficiency is for S40L formulation 94.21%. Incorporation of lecithin is also justified as it acts as permeation enhancers. Incorporation of lecithin further enhanced the percent drug entrapment to 94.21%. Entrapment efficiencies in span 40 and span 60 formulations were higher than those in other span formulations. Span 40 and Span 60 are solid at room temperature and showed the higher phase transition temperature (Tc). This result was consistent of Levonorgestrel in proniosomes incorporated with span 40.

**Table 2: % of drug content, entrapment efficiency, particle size of domperidone proniosome gel, mean ± S.D. (n=3).**

| **Formulation code** | **% Drug content** | **Entrapment Efficiency (%)** | **Particle Size (µm)** |
|---|---|---|---|
| **S20** | 93.37±2.74 | 87.41±3.35 | 13.84±0.68 |
| **S40** | 92.43±3.02 | 90.75±1.04 | 12.36±0.54 |
| **S60** | 91.73±2.15 | 89.84±2.74 | 13.24±0.37 |
| **S80** | 90.32±3.26 | 84.37±2.42 | 12.79±0.47 |

| | | | |
|---|---|---|---|
| **S20L** | 94.77±3.31 | 87.49±7.79 | 15.99±0.74 |
| **S40L** | 97.22±1.78 | 94.21±1.33 | 11.22±0.76 |
| **S60L** | 93.61±2.19 | 92.66±6.89 | 10.14±0.72 |
| **S80L** | 93.42±4.26 | 89.69±1.53 | 10.05±0.82 |

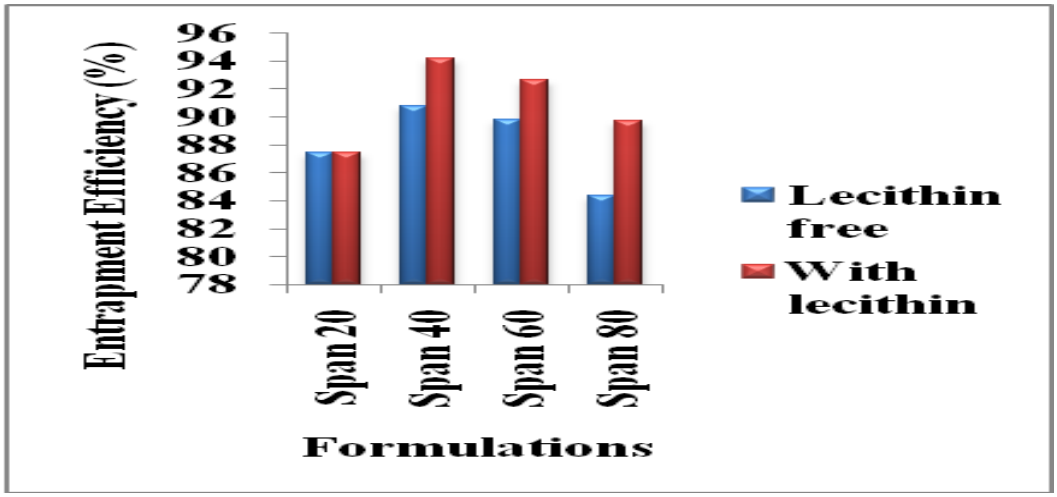


**Figure 2: Entrapment efficiency of proniosomal formulations.**

**In-vitro release of proniosomal formulations**

The results were shown in figure no. 3. Formulation Release: According to the release study formulations are given a better drug release in the range of 53.501% to 96.551% .Formulation S40L given the high release rate compared to the other formulations. This formulation has given 96.551% release up to 24hr. Drug release has been maximum for formulation S40L than other formulations. Soya lecithins have been reported to contain unsaturated fatty acids, oleic and linoleic acid, which have penetration enhancing properties of their own as compared to egg lecithin which contain saturated fatty acids [9]. Effect of different spans on drug permeation profile showed that flux value was highest for Span 40 and lowest for span 80. No significant difference observed in skin permeation profile of formulations containing Span 40 and Span 60.

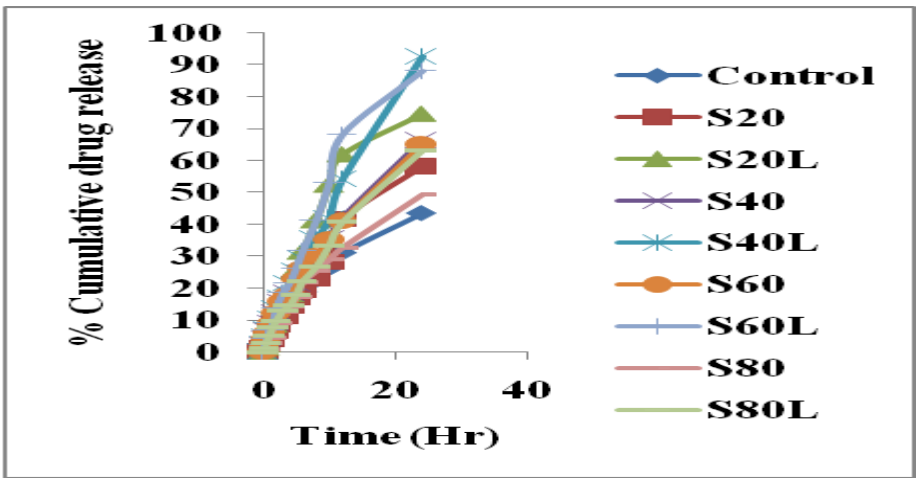


**Figure 3: In-vitro drug release from proniosomal formulations.**

Formulation containing isopropanol gives highest drug permeation among the different alcohols. Permeation increases as the chain length increase from $C_2$ to $C_4$ (ethanol to butanol). But, drug permeation was maximum for isopropanol formulation which is not in agreement with the above finding possibly due to branched chain structure of isopropanol which acts as co-surfactant and might loosen the bilayers packing resulting into the increased release of drug[10]. The enhancement in permeation may also be due to mixed action involving the effect of lecithin, surfactants and alcohol.

**In-vitro permeation release of Formulation**

The proniosomal gel formulations were characterized for their drug permeation and results were reported in Table 3. The drug permeation was maximum form formulation containing Span 40 (S40L) among all tested formulations. From the permeation profile it was clear that the gel showed optimum drug release up to 12 hrs. From the formulation S40L which was 96.551% results shown in figure no. 4.

**Table 3: Results of Flux, permeability coefficient, Enhancement of formulations**

| Code | Flux ($mg/cm^2$) | Kp ($cm^2/hr$) | ER |
|---|---|---|---|
| **S20** | 0.1 | 0.019 | 1.508 |
| **S20L** | 0.144 | 0.025 | 1.984 |
| **S40** | 0.097 | 0.020 | 1.601 |
| **S40L** | 0.173 | 0.029 | 2.351 |
| **S60** | 0.09 | 0.19 | 1.539 |
| **S60L** | 0.143 | 0.029 | 2.286 |
| **S80** | 0.07 | 0.015 | 1.209 |
| **S80L** | 0.122 | 0.0207 | 1.642 |

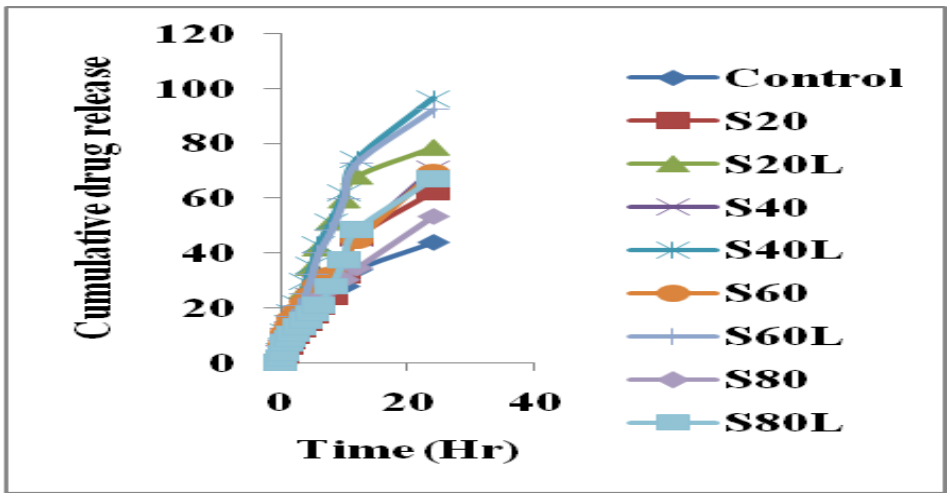


**Figure 4: Ex-vivo release of proniosomal formulations.**

Permeation release study is performed on all formulations. Permeation study is needed for flux, enhancement ratio. The range of flux is (0.07µg/cm$^2$/hr - 0.173µg/cm$^2$/hr). Formulation S40L has given high flux value. According to this study we considered that S40L is best formulation. The permeation data fitted in first order drug release. It was but obvious that the smaller vesicular size of S40L enabled it to penetrate easily through the skin as smaller vesicles tend to fuse readily with the skin. Thus proniosome gel prepared by using Span 40 exhibited better permeation and optimum entrapment efficiency.

This could also be due to the emulsification effect of the surfactant after the hydration of the proniosome by the dissolution medium and formation of elution channels within the gel structure due to loss of lipid bilayers that resulted in higher flux value [11]. The results were shown in Table 3 & 5. Hence formulation S40L had selected as optimum formulation and stability testing studies were carried out. These observations were in accordance with earlier reports saying that incorporation of cholesterol was known to influence vesicle stability, permeability and entrapment efficiency. Increase in the cholesterol content resulted in a more intact and ordered lipid bilayer as a barrier for drug release and helped as a controlled release polymer and also decreased drug leakage by improving the fluidity of the bilayer membrane and reducing its permeability [12].

**Table 5: Results of stability studies of optimized formulation (S40L)**

| S. No | Temp | Initial drug content | Initial vesicle size | After 2months drug content | After 2months vesicle size |
|---|---|---|---|---|---|
| 1 | 2°C | 97.22±1.78 | 11.22±0.76 | 96.72±1.08 | 11.89±0.68 |
| 2 | 25°C | 97.22±1.78 | 11.22±0.76 | 96.08±1.12 | 11.64±0.82 |

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 modulate drug transfer across skin [13], 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. Fusion of noisome vesicles to the surface of skin, demonstrated in a previous report, results in higher flux of the drug due to direct transfer of drug from vesicles to the skin.

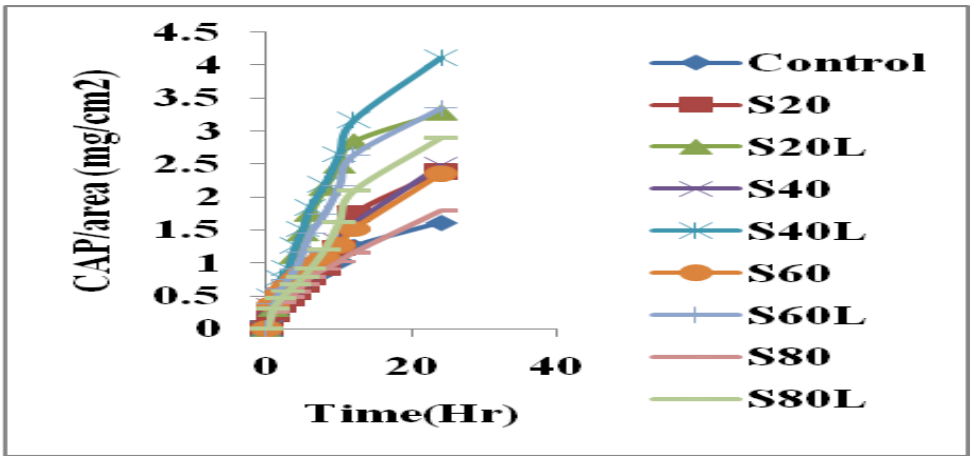


**Figure 5: Ex-vivo skin permeation of proniosomal formulations.**

**Vesicle physical analysis**

The differences in vesicle size among the niosomes prepared with span were not significant. The relationship observed between niosome size and span hydrophobicity has been attributed to the decrease in surface energy with increasing hydrophobicity, resoluting in the small vesicles. Increasing the cholesterol content or reducing the lecithin content also contributed an increase in the hydrophobicity, with a subsequent slight reduction in vesicle size. Isopropanol results in vesicles of smallest size, may be due to branched chain present in it. The scanning electron microscopy image of the best formulation is shows in the figure 6.

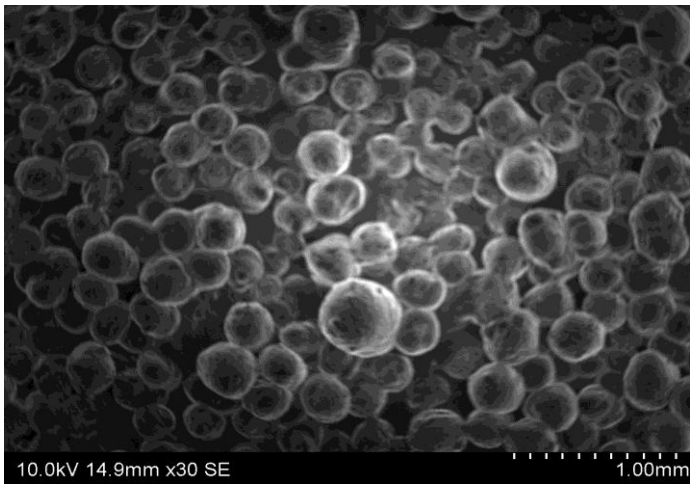


**Figure 6: SEM of optimized formulation S40L**

**FTIR Studies**

Fourier transforms infrared spectroscopy studies was carried out for domperidone pure drug & best formulation, The proniosomal gel are spread on the KBr disk and keep aside for 30 min, at room temperature after that FTIR studies of the pure drug and formulation are carried out. Results were shown in figure 7.

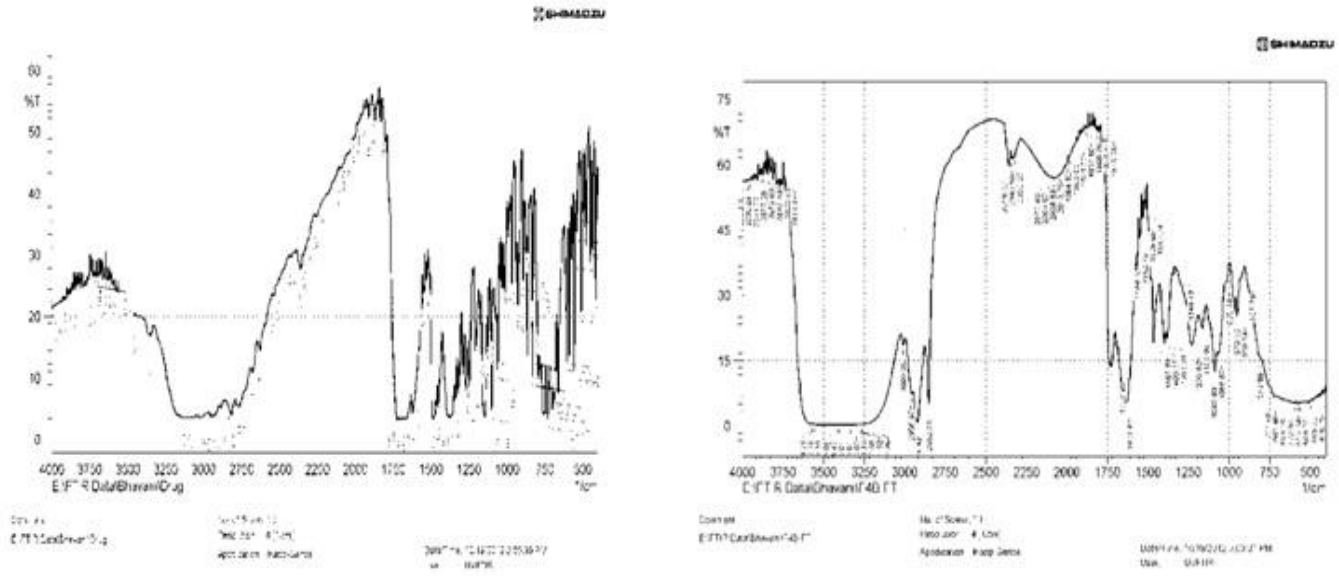

**Figure 7: FTIR spectrum of domperidone and optimized formulation.**

**Fourier transforms infrared spectroscopy**

FTIR studies were carried out for the pure drug – Domperidone, Formulation S40L. The most characteristics peaks of the pure drug – domperidone was assigned from standard literature. These included N-H amine stretching and C=O stretching and C-H stretching are as shown below.

1. 3352.39 $cm^{-1}$ : N-H Amine Stretching

2. 2818.09 $cm^{-1}$ : C-H Stretching

3. 1720.56 $cm^{-1}$ : C=O stretching

An FTIR study was carried out to ascertain as to whether there was any drug – excipient interaction in the final formulations and whether the drug was intact or not at the end of the preparative process. The results are summarized as follows.

As seen in figure 7, the spectra for domperidone exhibit a peak at 3325.39 $cm^{-1}$ due to amine (N-H) stretching, 2818.09 $cm^{-1}$ due to C-H stretching. The stretching at 1720.56 $cm^{-1}$ due to C=O stretching. FTIR studies carried out with Formulation S40L exhibited peaks at 3346.61 $cm^{-1}$ (N-H amine stretching), 2824.18 $cm^{-1}$ (C-H stretching) and 1728.28 $cm^{-1}$ (C=O stretching). The intensity and position of these characteristic peaks shows easy interpretation of any possible interaction between the drug and the excipients. The results clearly showed that there was no interaction between the drug and the excipients in the prepared Formulation S40L. The drug – Domperidone was intact and there was no sign of any degradation due to preparative processes adopted during the loading of the drug into proniosomal drug delivery system.

**Skin Irritation Test**

No obvious erythema, oedema or erosion was observed on the skins of rats after application of gels and the reference formulation.

**Stability studies**

From the results of vesicular size and shape and drug content (Table 5) of the optimised formulation (S40L) it was concluded that the formulation was stable at refrigeration and room temperature as well. Results for vesicular shape are shown in Figure 8.

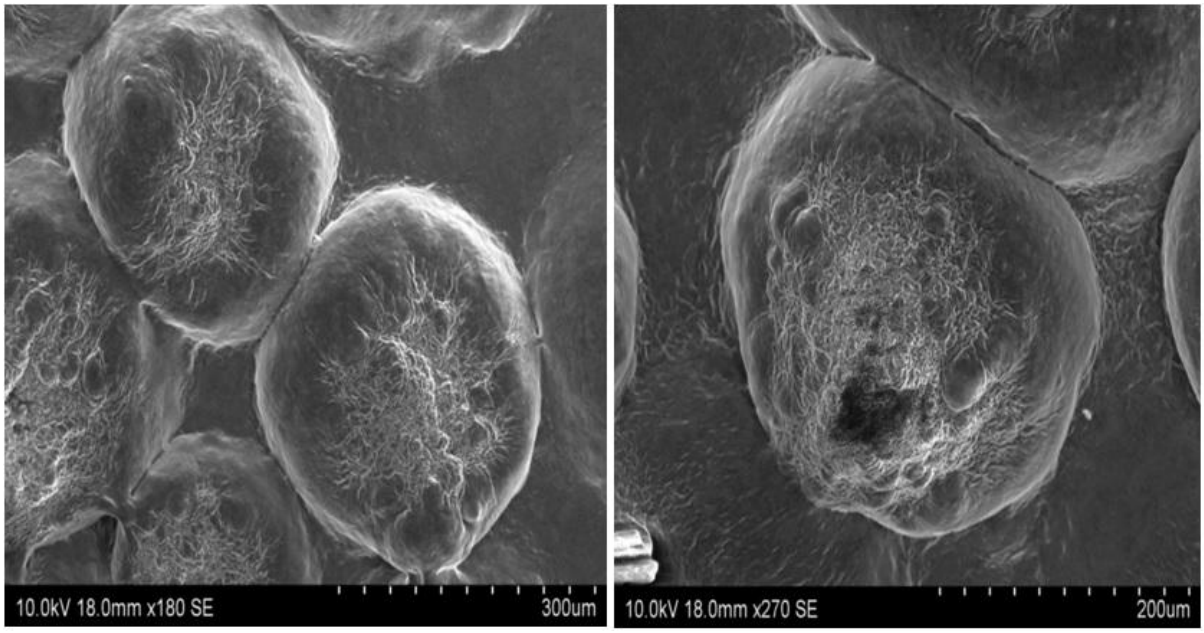


**Figure 8: SEM of optimized formulation F4 before after storage of 2 months.**

**Statistical Analysis**

Significance of difference between formulations was calculated by one way analysis of variance using Newman Keuls (compare all pairs) with Instant Graph Pad Prism software. The difference was considered to be statistically significant at $p<0.05$. Results showed statistically significant ($p<0.05$).

**Table 4: IR Peaks of Drug & Formulation**

| Group | Observed IR Peaks of Drug ($cm^{-1)}$ | Observed IR Peaks of Formulation S40L ($cm^{-1}$) |
|---|---|---|
| N-H amine stretching | 3325.39 | 3346.61 |
| C-H stretching | 2818.09 | 2824.18 |
| C=O stretching | 1720.56 | 1728.28 |

**Conclusion**

Proniosomal formulations of domperidone were prepared with different non-ionic surfactants with phosphotidyl choline and without phosphotidyl choline and evaluated. The formulation S40L is found to be the best formulation. The cumulative drug release was found to be 96.55% at the end of 24 hr study and the formulation F4 drug release followed first order kinetics with Hixon Crowell mechanism and non-fickian diffusion (n <1). From *ex-vivo* abdominal rat skin absorption studies formulation S40L showed good release of 96.55% up to 24 hr. The entrapment efficiency was between 86.66±2.89 and 94.21±1.33%. The flux was found to be 0.173µg/cm$^2$/hr. Statistical analysis showed results were significant ($p<0.05$). Scanning electron microscopy (SEM) studies revealed that the proniosome were spherical in shape with smooth surface morphology and had a mean particle diameter between 10.05±0.82 and 15.99±0.74 µm. The formulation is easy to scale up as the procedure is simple and does not involve lengthy procedures and unnecessary use of pharmaceutically unacceptable additives. Hence it offers direct fabrication of a transdermal patch and does not require dispersion of vesicles into a polymer matrix.

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