

## Formulation and Evaluation of Domperidone Oral Proliposomal Powders

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**Abstract:** The main objective of research work was to develop and characterize proliposomal powders of domperidone for improved solubility and oral bioavailability. Domperidone is a specific 5HT<sub>3</sub> receptor antagonist used in the treatment of nausea and vomiting. It has low aqueous solubility and moreover after oral administration it undergoes extensive gastric and hepatic first pass metabolism. This results in very low oral bioavailability which may not decrease rate of vomiting. Proliposomal powders were developed using various ratios of hydrogenated soyphosphatidylcholine, cholesterol, and sodium cholate. The mean size of the vesicles was in the range of 390 to 520 nm. The entrapment efficiency of domperidone was found to be 44 to 90%. Values of Q<sub>60</sub> observed for proliposome formulations were ranging from 69% to 92%. Photomicrographs obtained by SEM shows the transformation to amorphous state. XRD studies showed decrease in intensity of peak due to formation of some amorphous state. Ex- vivo studies data depicts increased permeation of formulation. The peak serum concentration of domperidone obtained from domperidone proliposomal powders with charge inducers (DOMPL-SC) was significantly higher in contrast to control (p<0.001) whereas the time to reach the peak concentration (T<sub>max</sub>) remained same. The extent of absorption assessed from AUC following oral administration of DOMPL-SC was significantly higher compared to control (p<0.001). There were no signs of instability such as agglomeration, crystallization seen even after 90 days of stability studies.

### Introduction:

A number of novel drug delivery systems have been developed to achieve controlled and targeted drug delivery. Among them encapsulation of the drug in vesicular structures is expected to prolong the duration of the drug in systemic circulation and reduce the toxicity by selective uptake. Similarly a number of vesicular drug delivery systems such as liposomes, niosomes, transferosomes, pharmacosomes and provesicular systems like proliposomes and proniosomes have been developed<sup>1</sup>.

Liposomes are unilamellar or multilamellar spheroid structures composed of lipid molecules, often phospholipids, assembled into bilayers. Because of their ability to carry a variety of drugs, liposomes have been extensively investigated for their potential application in drug delivery for drug targeting for controlled release or for increasing solubility<sup>2</sup>.

Apart from the advantages, the limited success of liposomes in oral delivery is because of its physico-chemical stability issues such as sedimentation, aggregation, fusion, phospholipid hydrolysis, and/or oxidation<sup>3</sup>.

In order to improve stability of liposomes, proliposomes are developed. Proliposomes are dry free flowing which up on hydration, forms liposomal dispersion that are similar to conventional liposomes. Due to its solid properties most of the stability issues associated with conventional liposomes are reduced. Reports on proliposomal formulations suggest increases solubility and bioavailability of some poorly soluble drugs<sup>4</sup>.

Domperidone, is 5-chloro-1-(1-[3-(2-oxo-2, 3-dihydro-1*H*-benzo[*d*]imidazol-1-yl) propyl] piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one. It is a specific 5HT<sub>3</sub> receptor antagonist used in the treatment of nausea and vomiting. Domperidone has low aqueous solubility and moreover after oral administration it undergoes extensive gastric and hepatic first pass metabolism. This results in very low oral bioavailability which may not decrease rate of vomiting. In the present work attempts were made to develop proliposomes of domperidone with an aim to improve bioavailability by increasing intestinal permeability which would transport drug through lymphatic transport system bypassing first pass metabolism.

## Materials and Method:

Domperidone was obtained as gift sample from Unichem Laboratories Ltd., Raigad India, Phospholipon 80H (Highly purified hydrogenated soybean phosphatidylcholine, (90% purity, HSPC) Lipoid, GmbH Germany, Pearlitol SD 200, Sodium cholate was kind gift from Dr. Reddy's Laboratories Ltd. Hyderabad, India. Cholesterol was purchased from Sigma Aldrich, India. All other chemicals used were of analytical grade and solvents were of HPLC grade. Freshly collected double distilled water was used throughout the experiment.

### Preparation of domperidone proliposome powders

**Table 1: Composition and appearance of Domperidone encapsulated proliposome powders**

Formulation	Molar ratio(HSPC:CHOL)	HSPC (mg)	CHOL (mg)	SC (mg)	Appearance
DOM-PL0	1:0	187.5	-	-	Yellowish
DOM-PL1	3:1	140.5	24.1	-	Yellowish
DOM-PL2	2:1	125	32.5	-	Yellowish
DOM-PL3	1:1	94	49	-	Yellowish
DOM-PL4	1:2	62.5	64.5	-	Yellowish
DOM-PLSC	1:1	94	49	8.6	Yellowish

HSPC, CHOL and SC indicate hydrogenated soybeanphosphatidylcholine, cholesterol and sodium cholate. Lipid mixture used in all the preparations was 250  $\mu$ M

Each formulation contains 10 mg and 250 mg of domperidone and spray dried mannitol respectively.

Film deposition method<sup>4</sup> was adopted for the preparation of proliposome powders, and the composition was represented in table no. 1. Accurately weighed amounts of lipid mixture (250  $\mu$ M) consisting of Phospholipon 80H and cholesterol at various molar ratios, domperidone (10 mg) and sodium cholate, a charge inducer was dissolved in 20 mL of solvent mixture containing chloroform and methanol (9:1). The above solution was transferred into a 250 mL round bottomed flask; to it 250 mg of spray dried mannitol was added to form slurry. The flask was fixed to a rotary flash evaporator (Laborota 4000, Heidolph, Germany), with the help of a clamp and the organic solvent was allowed to evaporate under reduced pressure at a temperature of  $45 \pm 2$  °C. After the complete evaporation of solvent, the formed powders were further dried overnight in a vacuum oven at room temperature so as to obtain dry, free-flowing product. The obtained proliposome powders were sieved with a US 60 mesh screen (250  $\mu$ m) to form uniform sized free flowing powders and stored in a tightly closed container at 4°C for further evaluation.

## Characterization of Proliposome Powders

### Formation of vesicular structures from proliposome powders

Little quantity of proliposomal powder was taken and placed on a glass slide and to it few  $\mu$ L of distilled water was added drop wise and a cover slip was placed over it<sup>5</sup>. The slide was placed under an optical microscope, observed at a magnification of 450X formation of vesicular structures were seen (Coslabs micro, India) and photomicrographs of the formed liposomes were taken. For the morphological evaluation, the proliposome powder was hydrated with distilled water and agitated manually for 2 min, and the scanning electron microscope observations were performed to know the morphology of formed liposomes.

### Flow properties of proliposome powders

The flow properties of proliposomal powders were determined mainly by angle of repose, Carr's compressibility index and Hausner's ratio. Fixed funnel method was used to determine angle of repose. The bulk and tapped density of the proliposomal powders were used to calculate Carr's compressibility index and Hausner's ratio<sup>6</sup>.

### Number of vesicles per mm<sup>3</sup>

Number of vesicles formed is an important parameter in optimizing the formulation. The vesicular structures formed on contact with water were counted in a haemocytometer under an optical microscope and the number of vesicles per cubic mm was calculated by using the following formula<sup>7</sup>.

$$\text{Total no. of liposomes per cubic mm} = \frac{\text{Total no. of liposomes counted} \times \text{dilution factor} \times 4000}{\text{Total number of squares counted}}$$

### Measurement of vesicle size and zeta potential of liposomes

The proliposomal powders upon contact with water when shaken well forms a dispersion which was subjected to bath sonication (Sonica, Italy) for about 2 minutes. The formed dispersion was used for the determination of size and zeta potential measurements. The photon correlation spectroscopy using Nano ZS (Malvern Instruments, Malvern, UK) was used to determine the mean size and zeta potential of liposomes formed. Each sample was suitably diluted and size analysis was performed at 25°C with an angle of detection of 90°C. Size, polydispersity index and mean zeta potential of liposomes were obtained from the Zetasizer.

### Determination of entrapment efficiency and drug content

Entrapment efficiency was determined by dialysis membrane method<sup>8</sup> where accurately weighed amount of proliposomal powders were taken in to a test tube to that 2 mL of water was added. A boiling tube was taken and fixed to a stand, one end of which was closed with cellophane membrane. Prepared dispersion was poured in to the test tube. The entire set up was placed in a 50ml beaker containing 0.1N HCl. The untrapped drug passes through the membrane in to the beaker. At periodic intervals 1ml of solution from beaker was withdrawn and analysed in a UV spectrophotometer<sup>9</sup>.

$$\text{Entrapment efficiency (\%)} = \frac{\text{Total drug} - \text{Untrapped drug}}{\text{Total drug}} \times 100$$

Drug content was estimated as follows one dose of formulation was taken in a 100 mL volumetric flask, to it add small volume of methanol which solubilizes the lipid then finally make up to 100 mL with 0.1N HCl. Shake it well for about 1h in a shaker followed by centrifugation then analysed in HPLC.

### *In vitro* dissolution study

*In vitro* dissolution study of proliposome powders and control formulation was performed using USP type II (paddle) apparatus (Electrolab, TD L8, Mumbai, India). The temperature was maintained at 37±0.5°C, with paddle speed set at 50 rpm throughout the experiment. Here 0.1NHCl was used as a dissolution medium and volume of dissolution medium used was 500ml. At predetermined time intervals a volume of 5 mL was withdrawn and replaced with fresh dissolution medium to maintain the volume constant. The samples were analysed spectrophotometrically at 283 nm.

### Solid state characterization

#### Scanning Electron Microscopy (SEM)

The surface morphology of the pure drug, spray dried mannitol and optimized proliposome powder (DOM-PL) was determined by scanning electron microscope (SEM) (S-4100, Hitachi, Japan). Samples were fixed on a brass stub using double sided adhesive tape and were made electrically conductive by coating with a thin layer of gold and SEM images were recorded at 15 keV accelerating voltage.

#### Differential Scanning Calorimetry (DSC)

DSC analysis was used to evaluate the physical state of pure drug, mannitol and proliposome powder by using differential scanning calorimeter (Mettler DSC 823e, Mettler-Toledo, Germany) over a temperature range of 20°C to 300°C under a constant nitrogen gas flow of 30 mL/min at a heating rate of 10°C/min.

#### Fourier Transform Infrared (FT-IR) spectroscopy

The infrared spectra of domperidone, mannitol and optimized proliposome powder formulation were obtained using FT-IR spectrophotometer (Paragon 1000, Perkin Elmer, USA) by the conventional KBr pellet method at a scanning range of 4000–500  $\text{cm}^{-1}$  were performed at a resolution of 4  $\text{cm}^{-1}$ .

### **Powder X-ray Diffractometry (PXRD)**

The PXRD patterns of domperidone, mannitol and optimized proliposome powder formulation were obtained using X-ray diffractometer (X' Pert PROPANalytical, Netherlands). The measuring conditions were as follows:  $\text{CuK}\alpha$  radiation, nickel filtered; graphite monochromator; 45 kV voltages; and 40 mA current with X'celerator detector. All samples were run at 1° ( $2\theta$ )  $\text{min}^{-1}$  from 3° to 45° ( $2\theta$ ).

### **Ex Vivo Permeation Studies**

*Ex vivo* studies were conducted using isolated male Wistar albino rat intestine. Initially rat intestine was carefully isolated and approximately 10 cm length was cut and washed thoroughly using syringe to empty residual intestinal contents. One end of the intestine was closed by tying with thread. From the other open end of intestine, 1ml drug in 0.1N HCL was filled with oral feeding syringe. Similarly into another intestine of same length, 1ml emulsion was added after reconstitution of optimized proliposomal formulation with 0.1N HCL equivalent to single dose. Both were placed separately in 50 ml beaker containing 50ml SGF and placed on magnetic stirrer and rpm was fixed at 100. The amount of drug diffused through the membrane was calculated by collecting 2 ml samples at regular time intervals for 2 h and replaced with equal volume of fresh medium to maintain sink condition as well as constant volume.

### **Bioavailability Study**

Male albino Wistar rats of weight (180-200 g) which are in a healthy condition were used in the study. Before starting the study, the approval was taken from the Institutional Animal Ethical Committee. Before commencement of dosing, the animals were kept fasting for overnight. Animals were divided into two groups containing three in each and were randomly administered with each treatment. One group received an oral suspension of standard solution and the other group was treated with the optimized proliposomal dispersion at a dose of 20 mg/kg body weight. Blood samples (500  $\mu\text{l}$ ) were collected at predetermined time intervals from retro orbital plexus via capillary tubes and poured into micro-centrifuge tubes. From that after centrifugation (10,000 rpm for 10 min) serum was separated and was stored.

Domperidone concentration was determined in serum by HPLC using 60:30:10 buffer, acetonitrile and methanol containing 0.25 % (v/v) triethylamine and pH adjusted to 3 with orthophosphoric acid. Flow of mobile phase was at a rate of 1.0 mL/min. An octadecylsilane ( $\text{C}_{18}$ ) reverse phase stainless steel analytical column (250 x 4.6mm) with 5  $\mu\text{m}$  particle size was used for chromatographic separation (Lichrospher, Merck, Germany), which was monitored at a wavelength of 220  $\text{nm}^{10}$ . Accurately, 100  $\mu\text{L}$  of serum sample was added 100 $\mu\text{l}$  of 0.1N NaOH and 3ml of dichloromethane was added followed by vortex in a cyclomixer for a time period of 10min. The organic phase was collected carefully and was allowed to dry completely. The dried samples were then reconstituted with 100 $\mu\text{l}$  of mobile phase. From this solution 20 $\mu\text{l}$  was withdrawn from the syringe and injected into HPLC.

### **Pharmacokinetic parameters**

The peak plasma concentration ( $C_{\text{max}}$ ) and its time ( $T_{\text{max}}$ ) were obtained directly from the serum concentration vs. time profile. The area under the curve ( $\text{AUC}_{0-t}$ ) was calculated by using trapezoidal rule method. The  $\text{AUC}_{t-\infty}$  was determined by dividing the plasma concentration at last time point with elimination rate constant (K). Mean residence time (MRT) was obtained by dividing the area under first moment curve with area under curve. The relative bioavailability (F) was estimated by dividing the  $\text{AUC}_{0-\infty}$  of proliposome formulation with control oral suspension.

### **Statistical Analysis**

Statistical analysis was carried out by using one way analysis of variance (ANOVA) for various formulations was calculated using different softwares such as student-Newman-Keuls (compare all pairs) with Instat Graph pad prism software (version 4.00; GraphPad Software, San Diego California). It was found significant with ( $P < 0.05$ ).

### **Stability Studies**

Stability studies were carried out over a period of 90 days. The prepared formulations were poured in glass vials which were covered tightly with aluminium foil and kept at room temperature. At various time intervals i.e., (0, 30, 60 and 90 days), samples were observed. Upon observation any changes in the physical appearance and sign of drug crystallization will be noticed under optical microscope.

## Results and Discussion

### Preparation of domperidone proliposomal powders

Although liposomes are considered as a potential drug delivery carriers, the usage of liposomes is limited because of the degradation in the acidic media. Apart from the advantages, the limited success of liposomes in oral delivery is because of its physico-chemical stability issues such as sedimentation, aggregation, fusion, phospholipid hydrolysis, and/or oxidation. In addition, large scale production of liposome remains difficult.

Therefore proliposomes offer an elegant alternative to conventional liposomal formulations. Here, lipid and drug are coated onto a soluble carrier to form a free-flowing granular material which, on hydration, forms liposomal dispersion. Problems with the physical stability of aqueous suspensions of liposomes have been resolved by proliposomes<sup>11</sup>.

In the formulation of proliposomes carrier plays a major role, selection of carrier is important. Various types of carriers are used which includes maltodextrin, sorbitol and mannitol. Among all those spray dried mannitol was used because of its features like porous structure, high specific surface area, controlled particle size and distribution<sup>7</sup>. It is non hygroscopic having good compatibility and improves the palatability of the formulation, apart from this selection of phospholipid is important because it dictate the stability of the liposomes formed as it is susceptible to oxidation due to the presence of unsaturated bonds in the fatty acid tails<sup>12</sup>. The hydrogenated soyaphosphatidylcholine overcomes the limitations of pure phospholipid; hence it is used in our research. Entrapment efficiency is an important parameter to optimize proliposomal formulations. Cholesterol was added to improve the stability of liposomes formed. Phospholipids help in the formation of bilayer. Thus both cholesterol and phospholipids play an important role in maintaining the stability of liposomes. Here surface charge is a key factor for the increased vesicle interaction with the cell surface.

### Flow properties of Proliposomes

Flow property is an important evaluation parameter for powders. Improper flow may lead to problems in various operations. The acceptable range for angle of repose is ( $<30$ )<sup>0</sup>, Carr's index is ( $< 21$ ), Hausner's ratio is ( $<1.25$ ). The optimized formulation flow property values like angle of repose ( $23.74\pm 0.14$ ), Carr's index ( $14.85\pm 0.14$ ) and Hausner's ratio ( $1.17\pm 0.07$ ) was in an acceptable range. DOM-PL indicates domperidone proliposomal powders and DOM-PLSC indicates domperidone proliposomal powders with a charge inducer and the flow properties are indicated in Table 2.

**Table no. 2: Flow properties of various formulations**

Formulation	Angle of repose	Compressability index	Hausner's ratio
DOM-PL1	19.29±0.35	11.261±0.24	1.126±0.11
DOM-PL2	20.80±0.17	12.464±0.07	1.142±0.13
DOM-PL3	21.305±0.22	14.32±0.27	1.167±0.14
DOM-PLSC	23.74±0.14	14.85±0.14	1.17±0.07

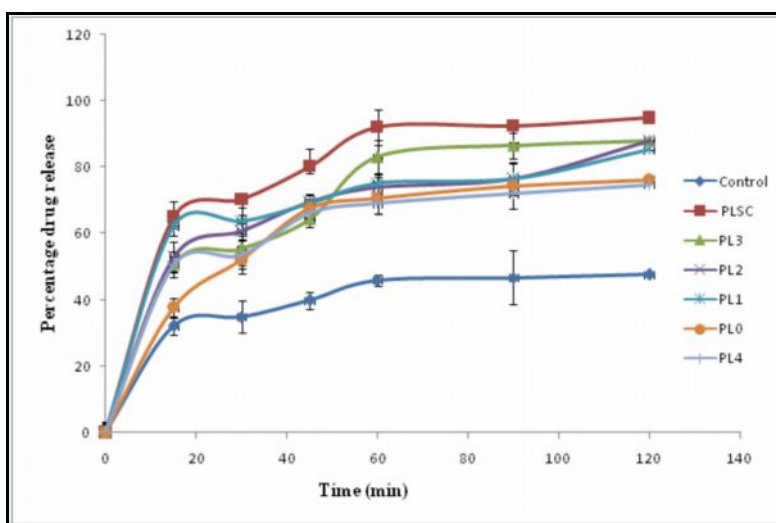
### Particle size, Zeta potential and entrapment efficiency

The size and size distribution play a significant role in the performance of vesicular systems<sup>13</sup>. The mean size of the vesicles was in the range of 390 to 520 nm (Table no. 3). As the concentration of cholesterol is increased, the size of the vesicles increased. However the PI used as a measure of a unimodal size distribution was within the acceptable limits for all the proliposome formulations. The zeta potential of the proliposome formulations (DOM-PL0 to DOM-PLSC) was found to be between -5.7 mV to -15.2 mV. The magnitude of surface charge has been increased in case of DOM-PLSC. The entrapment efficiency of domperidone was found to be 44 to 90%. The domperidone loading was increased with an increase in the cholesterol concentration which can be attributable to the hike in hydrophobicity of the bilayer and formation of stable vesicles.

**Table no. 3: Physico-chemical characterization of domperidone loaded proliposome formulations**

Formulation	Size (nm)	Polydispersity index	Zeta potential (mV)	Entrapment efficiency (%)	No. of vesicles per mm <sup>3</sup> x 10 <sup>5</sup>
DOM-PL0	503±14	0.254	-5.7±1.8	43.39±1.5	0.8
DOM-PL1	469±16	0.217	-6.7±3.4	85.19±1.1	3.6
DOM-PL2	453±9	0.167	-7.3±2.8	86.10±2.3	3.8
DOM-PL3	393±12	0.223	-8.2±1.9	86.29±1.8	3.8
DOM-PL4	483±13	0.187	-6.4±2.5	44.94±2.6	1.2
DOM-PL-SC	376±14	0.146	-15.2±2.8	90.47±3.2	3.9

### Dissolution Studies

**Figure no.1: *In vitro* release profiles of domperidone from proliposome powders**

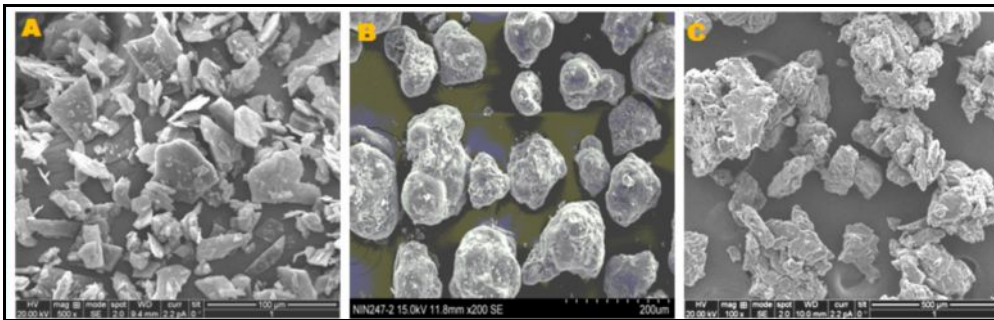
The dissolution profiles of domperidone from proliposome formulations and control was depicted in Fig no.1. The domperidone release after 60 min ( $Q_{60}$ ) was 45%. In contrary, the  $Q_{60}$  values observed for proliposome formulations was ranging from 69% to 92% and was significantly higher ( $p < 0.01$ ) (Table no. 4). Obviously, the augment in dissolution efficiency and mean dissolution rate and lower mean dissolution time for proliposome formulations indicate their potential for the improvement in the solubilization characteristics of domperidone (Table 4). The presence of phospholipid molecules in proliposome formulations result in change of physical state (crystalline to amorphous and/or molecular state) of an insoluble drug when loaded into proliposomes<sup>14</sup>.

**Table no. 4: Dissolution parameters of domperidone from proliposome powders in (pH 1.2) Each data expressed as mean±SD; n=3.**

Formulation	$Q_{15}$	$Q_{60}$	DE	MDT	MDR
Control	32.17±3.2	45.99±2.6	32.49±1.2	20.20±2.3	0.78±0.07
DOM-PL0	37.72±2.6	70.80±2.8	48.22±0.7	24.01±1.8	1.04±0.06
DOM-PL1	62.4±1.8	75.19±2.9	58.17±1.6	24.04±2.2	1.46±0.02
DOM-PL2	53.1±2.8	73.9±1.8	55.13±2.1	28.68±1.4	1.31±0.05
DOM-PL3	50.77±1.6	83.07±2.4	63.6±2.4	25.26±1.8	1.27±0.06
DOM-PL4	51.77±2.7	69.12±1.9	51.27±1.4	21.10±1.6	1.23±0.02
DOM-PLSC	64.98±3.1	92.11±2.1	65.3±1.8	19.79±2.4	1.57±0.03

## Solid State Characterization

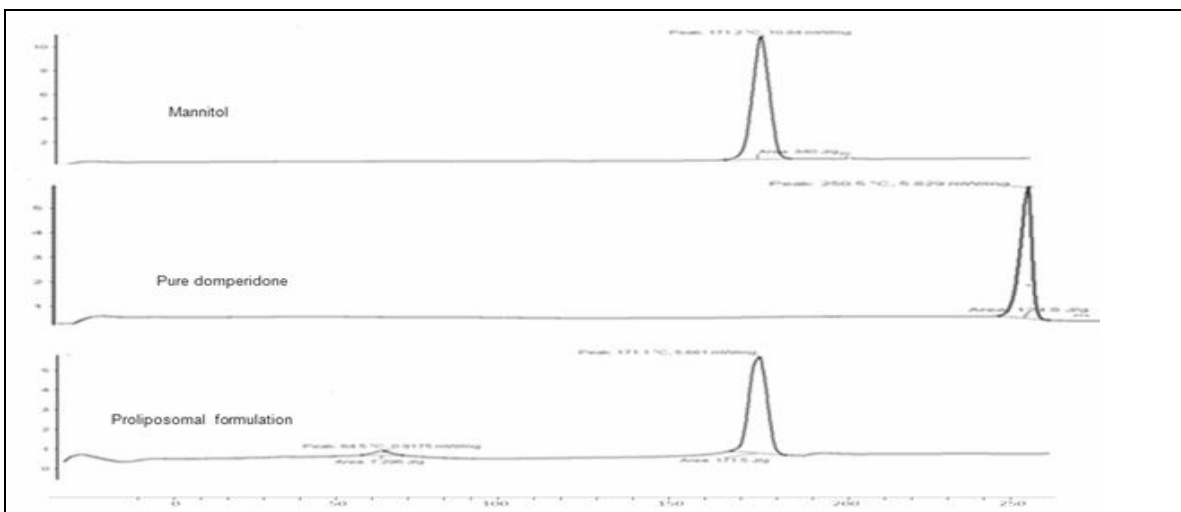
### Scanning electron microscopy (SEM)



**Figure no. 2: Scanning Electron Microscope images of A) domperidone B) Pearlitol SD200 and C) Proliposome powders (DOM-PLSC)**

The SEM images were recorded for pure drug, mannitol and proliposome powders to examine the physical state and surface characteristics (Fig no. 2). From figure it is evident that domperidone exist in typical crystalline state. The disappearance of characteristic crystals of domperidone in case of proliposome formulation confirms the transformation to amorphous and/or molecular state. Further the porous structure of mannitol was obscured in proliposome formulation because of the deposition of phospholipids on the surface of mannitol.

### Differential scanning calorimetry (DSC)

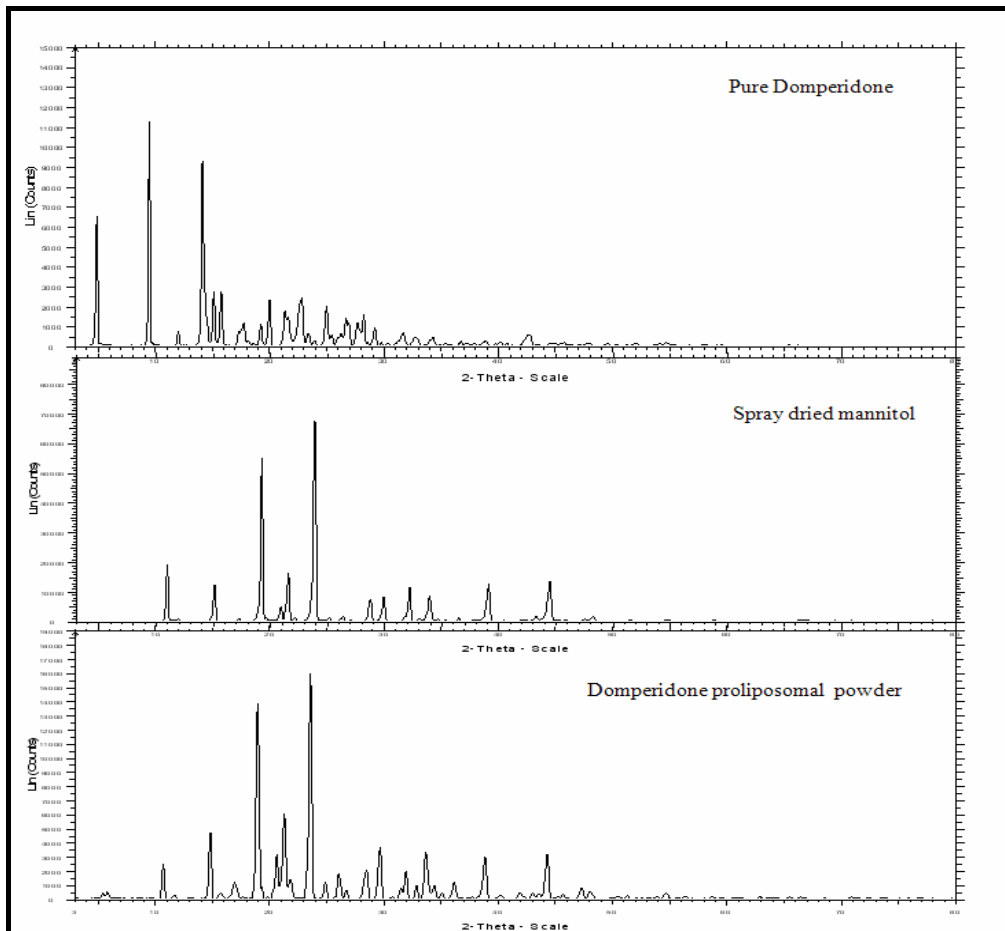


**Figure no. 3: DSC thermograms of pure domperidone and proliposomal formulation**

The DSC analysis performed to understand the thermotropic behavior and physical state of the drug in proliposome powder (Fig no. 3). The prominent endothermic peak at 250.5°C with melting enthalpy 124.8 J g<sup>-1</sup> corresponding to the melting temperature of domperidone indicates the crystalline nature of pure domperidone. The mannitol used as a carrier exhibited a prominent melting peak at 171.2°C. The absence of conspicuous peak in proliposome formulation over the melting range of domperidone unravels the transformation of the physical state of the drug (crystalline to amorphous) further supported by PXRD analysis.



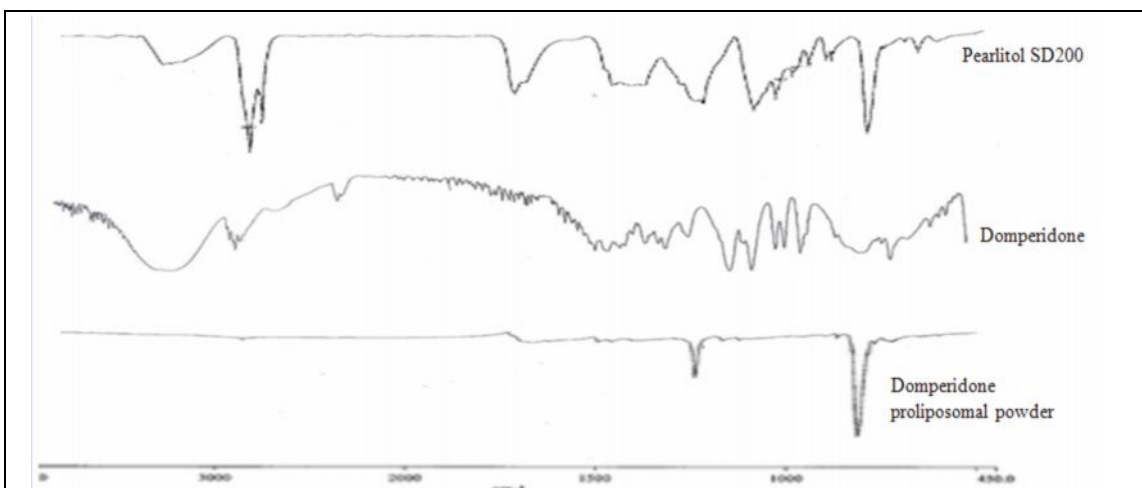
### Powdered X-Ray Diffraction studies



**Figure 4: XRD of pure drug and proliposomal powders**

Pure domperidone drug contains various peaks at regions such as 4.7, 9.3, 14.05, 15.7, 15.064, 19.935 observed in Fig no. 4 which represents the crystalline nature of drug. After interaction of drug with carrier intensity of peak is reduced which shows formation of some amorphous state but still crystallinity is observed.

### FTIR Studies



**Figure no. 5: FT-IR spectra of a) Pearlitol SD200 b) domperidone and c) Proliposome powder (DOMPL-SC)**



The FT-IR spectra of domperidone and proliposomal powders of domperidone formulation were shown in Fig no. 5. The pure drug domperidone exhibit characteristic peaks at  $3120\text{ cm}^{-1}$ ,  $1694\text{ cm}^{-1}$ , and  $1384\text{ cm}^{-1}$ . All the above characteristic peaks appear in the spectra of proliposomal powders of domperidone at same wave no. indicating no modifications or interaction between drug and excipients.

### EX-VIVO Studies

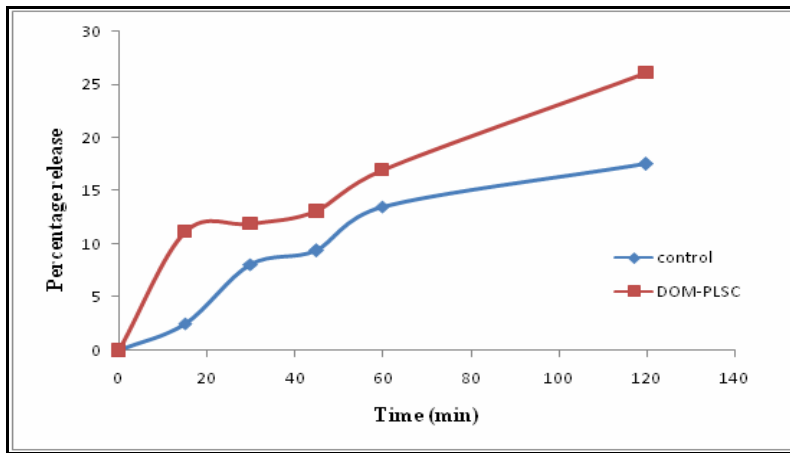


Figure no. 6: Graphical representation of ex-vivo studies

The release patterns of control and optimized formulation was shown in Fig 6. The percentage release of control at the end of 2h was 17 and the percentage release of formulation was 26. By observing the values we can conclude that the percentage release of formulation was increased depicting permeation of formulation was increased.

### Pharmacokinetic Study

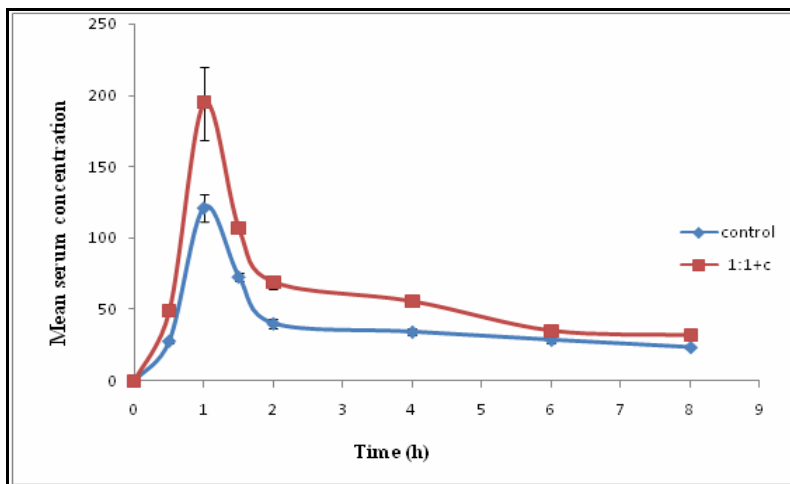


Figure no. 7: Pharmacokinetic profiles of domperidone in serum

To draw out the conclusions regarding the feasibility of proliposomes in improving the oral bioavailability of domperidone, pharmacokinetic study was conducted in rats. Earlier reports suggest that the high magnitude of surface charge increase the stability and favours the drug absorption because of efficient uptake of liposomes and increased vesicle interaction with the GI membrane. In this perspective an attempt was made to investigate the influence of surface charge by inclusion of anionic charge inducer i.e sodium cholate in the optimized proliposome formulation. Fig no. 7 envisage the mean serum concentration vs. time profiles of domperidone following peroral administration proliposomes and control and the relevant pharmacokinetic parameters were derived (Table no. 5). The peak serum concentration of domperidone obtained from DOMPL-SC was significantly higher in contrast to control ( $p < 0.001$ ) whereas the time to reach the peak concentration ( $T_{max}$ ) remained same. The extent of absorption assessed from AUC following oral administration of DOMPL-SC was significantly higher compared to control ( $p < 0.001$ ). The altered pharmacokinetic profile and an increase

in the bioavailability of domperidone from proliposomes can be explained by several facts which include, change in the permeability characteristics of GI membrane because of the surfactant property of phospholipids used in the proliposomes, efficient transfer of vesicles and endocytosis because of fusion of liposome bilayer with the cell membrane, favoured partition of domperidone into the cell membrane from GI fluids. Furthermore the increased bioavailability of domperidone from proliposome formulations might also be due to the avoidance of pre systemic metabolism because it is known fact that drugs entrapped/encapsulated in colloidal carriers are protected from enzymatic degradation within the GI tract and undergoes lymphatic transport<sup>15</sup>.

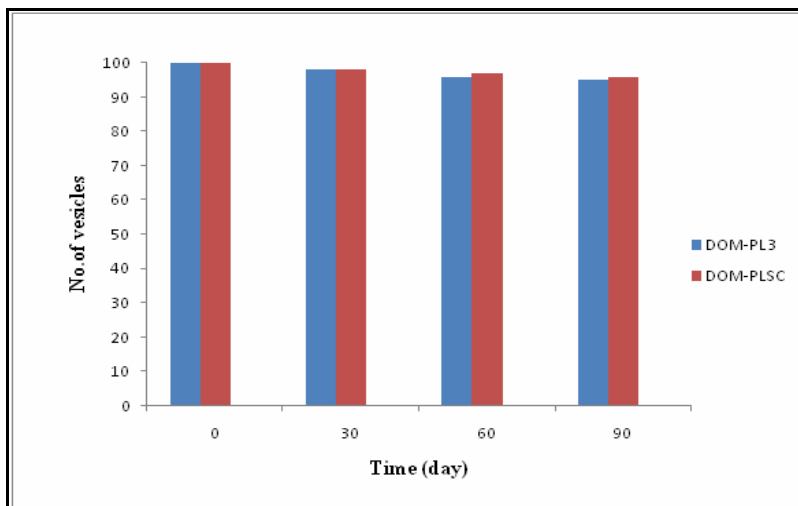
**Table no. 5: Pharmacokinetic parameters of pure drug and DOM\_PLSC in rats**

Pharmacokinetic Parameters	Formulations	
	Control	DOM-PLSC
C <sub>max</sub> (µg/mL)	121.2765	194.5966
T <sub>max</sub> (h)	1	1
T <sub>1/2</sub> (h)	7.315711	4.963083
AUC <sub>0-∞</sub> (µg mL <sup>-1</sup> )	308.0102	470.050
MRT <sub>0-∞</sub> (h)	3.36668	3.191083

Two fold of improvement in the relative bioavailability (F) ascertain the potential of proliposomes as a suitable carrier for improved oral delivery of domperidone.

### Stability Studies

Even after the storage of drug for a period of 90 days, it seems similar as that of before indicating there were no sign of instability such as agglomeration, crystallization and without any alteration in flow properties .Up on contact of powder with distilled water, huge number of liposome formation is seen when observed in optical microscope. Even though a little reduction in percentage retention of domperidone was seen which is negligible ( $p < 0.01$ ) that is evident Fig no. 8.



**Figure no. 8: Percentage retention of domperidone in proliposomal formulations upon storage mean±SD; n=3.**

### Conclusion

The present research study focused on the feasibility of neutral and charged proliposomes for the improved oral delivery of domperidone. The domperidone could be loaded into proliposome formulations with ease by film deposition method using spray dried mannitol as carrier. The effect of surface charge was studied by tailoring of optimized formulation (DOMPL-SC) with sodium cholate. The solid state characterization reveals the transformation of crystalline state of domperidone to amorphous and/or molecular state. The *ex-vivo* studies reveals about the enhancement of permeability coefficient. A 2 fold improvement in the bioavailability

of domperidone reveals the potential of proliposome formulation and the importance of surface charge on the preferential uptake across the GI barrier.

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