ORIGINAL ARTICLE

# Formulation and development of industry feasible proniosomal transdermal drug delivery system of granisetron hydrochloride

Bhushan Arun Patil, Prashant Keshav Puranik, Shankar Dadasaheb Pol, Prajakta Kalidas Khobragade, Pritee Shamrao Ramteke, Rajashree Gopal Palasakar, Nitiraj Ransing-Patil

Department of Pharmaceutics, Government College of Pharmacy, Aurangabad, Maharashtra, India

Proniosomes gel is semisolid liquid crystal products of nonionic surfactants, which converted into niosomes upon hydration. A proniosome based transdermal drug delivery system of granisetron hydrochloride (GRA HCL) developed by coacervation phase separation method. Formulation optimized by use of $3^2$ full factorial design. Span 60 and cholesterol selected as independent variables, while entrapment efficiency (EE) and flux selected as dependent variables. Proniosomes evaluated for EE, *in vitro* permeation study, stability study, microscopial examination by photomicroscopy, scanning electron microscopy, particle size analysis. F5 batch containing 90 mg span 60, and 10 mg cholesterol show maximum entrapment (66.57 ± 0.20%) and flux (7.94 ± 0390 μg/cm$^2$/h). Comparative *in vitro* drug release study of plain drug solution and drug in proniosomal gel form was carried out for 48 h on guinea pig skin. It was found that cumulative release and flux of proniosomal gel was nearly two times more than drug solution containing same drug concentration. The study demonstrated the effectiveness of proniosomal transdermal patch containing GRA HCL for effective management of chemotherapy induced nausea and vomiting.

***Key words:*** *Factorial design, industry feasible, niosomes, proniosomes, stability, transdermal drug delivery*

## INTRODUCTION

Chemotherapy induced nausea and vomiting (CINV) is a most severe side effect of anticancer drugs. It was found that Patients receiving chemotherapy have nausea and vomiting as the first and second most severe side effects respectively.[1,2] Nausea is a sensation of discomfort and feeling the urge to vomit.[3] Vomiting (emesis) is the forcible ejection of stomach contents through the mouth.[4] Conventionally antiemetic agents are administered by the oral or intravenous (IV) route. Granisetron hydrochloride (GRA HCl) has short half-life (3-4 h), so oral or IV routes have a disadvantage that need of frequent administration of the drug. Particularly, in any situation where a patient is suffering from nausea and vomiting, oral administration of an antiemetic agent is challenging and creates more discomfort for the patient. Nausea and vomiting may make it difficult for patients to take oral medications or keep them in the gastrointestinal tract long enough to be absorbed properly. For patients unable to swallow tablets because of emesis, IV anti-emetics are required.[5] However, IV or intramuscular administration is generally impracticable for home use. Hence, need alternative routes of administration like transdermal administration are needed as an alternative to conventional route.[6] Transdermal drug delivery system (TDDS) have therapeutic benefits such as sustained drug delivery for drugs with short half-lives, maintain steady plasma profile, so reduced systemic side-effects in potent drugs, reducing the typical dosing schedule to once or twice weekly also so improved patient compliance; and avoidance of the first-pass metabolism effect for drugs with poor oral bioavailability.[7] Alternatively TDD can be used in situations requiring minimal patient cooperation.[8] The noninvasive character of TDD makes it accessible to a wide range of patient populations and a highly acceptable option for drug dosing.[9] Nonpolymeric

**Address for correspondence:**
*Prof. Bhushan Arun Patil,*
*Master of Pharmacy (Pharmaceutics), Department of pharmaceutics*
*Government College of Pharmacy, Aurangabad - 431 005,*
*Maharashtra, India.*
*E-mail: patilbhushan19@gmail.com*

**Access this article online**

**Quick Response Code:**

**Website:** www.asiapharmaceutics.info

**DOI:** 10.4103/0973-8398.154707

nanoparticle or vesicular systems (niosomes and liposomes) are promising carrier systems to cross stratum corneum of skin which is main permeation barrier.[10,11] They may act as vehicles or as permeation enhancer for bioactive materials to enhance their penetration via stratum corneum, but their major drawback is their instability, which can be overcome by utilizing provesicular drug delivery approaches like proniosomes.[12] Proniosomes gel is semisolid liquid crystal products of nonionic surfactants. These gel are easily prepared by dissolving the surfactant in a smallest amount of alcohol and the least amount of aqueous phase, due to the limited amount of water present, these systems behave as viscous preparation.[13] Proniosomes can be converted into the niosomes *in situ* by absorbing water from the skin.[14] Proniosomes provide additional convenience of transportation, distribution, storage and dosing as well as avoid many of the problems associated with the aqueous niosome dispersion like physical stability (aggregation, fusion, leaking), its high cost, and difficulties in sterilization. Proniosomes have simple formulation procedure, low cost of production and capable to large scale production (Industry feasible) with adequate physical and chemical stability.[15,16]

Hence, objective of this study was to develop a more promising, controlled proniosomal TDDS was developed, which may have a faster onset of action that last for a longer period of time so, better control on CINV. To achieve this objective proniosomes of GRA HCL was prepared by coacervation phase separation method. In this study, span 60 use as nonionic surfactant, soya lecithin as a penetration enhancer, cholesterol essential for vesicles preparation and their stability. Preparation optimized by full $3^2$ factorial designs.

## MATERIALS AND METHODS

### Materials

Granisetron hydrochloride was obtained as a gift sample from Sun Pharma Limited (Halol, India). Soya lecithin was provided by Perfect Biotech (Nagpur, India). Span 60 and cholesterol were obtained from Loba Chemie (Thane, India). Cotran 9720 polyethylene film and scotchpack 9741 SBOPP film were provided by 3M (USA). Durotak 387-2287 acrylate-vinylacetate noncuring pressure sensitive adhesive procured from National Starch and Co. Limited (USA). Other excipients used to prepare proniosomes were of standard pharmaceutical grade and all chemical reagents of analytical grade.

### Preparation and optimization of proniosomes

Proniosomes were prepared by a coacervation and phase separation method. GRA HCl, span 60, cholesterol, soya lecithin were taken in a clean, dry wide mouth glass vial as per Table 1 and 250 µl alcohol added to it. Open end of the glass bottle was covered with a lid to prevent the loss of solvent from it and warmed over a water bath at 60-70°C for about 5 min until the surfactant mixture was dissolved completely. Then added 160 µl pH 7.4 phosphate buffer and warmed on the water bath for about 2 min till the clear solution observed. Later, mixture was allowed to cool down at room temperature till the dispersion was converted to proniosomal gel. Excess solvent was removed by vacuum evaporation of the solvent.[17]

A $3^2$ full factorial design was used for the process optimization. Span 60 and cholesterol were considered as an independent factor, while flux and entrapment efficiency (EE) were selected as dependent factor. Summary of factorial design is given in Table 2 and full factorial design formula is shown in Table 1.[18]

### Evaluation of proniosomal gel

*Entrapment efficiency determination*

To 0.2 g of proniosome gel was weighed in a glass vial, and then added to 10 ml of the aqueous phase (phosphate buffer pH 7.4). Then, this aqueous suspension was then sonicated. Niosomes containing GRA HCl was separated from untrapped drug by centrifugation at 25,000 rpm for 25 min at 4°C. Supernatant was recovered and assayed by spectrophotometrically (Shimadzu ultraviolet [UV]-1601 PC Double Beam, Kyoto, Japan) at 302 nm. The EE was calculated by the following equation,

$$EE = ([Q_t - Q_s]/Q_t)\times 100 \quad (1)$$

Where,

EE is the entrapment efficiency,
$Q_t$ is the theoretical amount of GRA HCl that was added,
$Q_s$ is the amount of GRA HCl detected only in the supernatant.

*In vitro permeation study*

The permeation of GRA HCl proniosome formulation was

**Table 1: Summary of factorial design**

| Coded values | Actual values (%) | | Responses | |
|---|---|---|---|---|
| | $X_1$ (Span 60) | $X_2$ (Cholesterol) | $Y_1$ | $Y_2$ |
| −1 | 80 | 7.5 | Entrapment efficiency | Flux |
| 0 | 90 | 10 | | |
| +1 | 100 | 12.5 | | |

**Table 2: Full factorial design formula**

| Formulation code | GRA HCl (mg) | Soya lecithin (mg) | Span 60 (mg) | Cholesterol (mg) |
|---|---|---|---|---|
| F1 | 5 | 90 | 80 | 7.5 |
| F2 | 5 | 90 | 90 | 7.5 |
| F3 | 5 | 90 | 100 | 7.5 |
| F4 | 5 | 90 | 80 | 10 |
| F5 | 5 | 90 | 90 | 10 |
| F6 | 5 | 90 | 100 | 10 |
| F7 | 5 | 90 | 80 | 12.5 |
| F8 | 5 | 90 | 90 | 12.5 |
| F9 | 5 | 90 | 100 | 12.5 |

determined by using modified K-C diffusion cell. The guinea pig skin was mounted on modified K-C diffusion cell. Skin was mounted on the receptor compartment with the stratum corneum side facing upwards into the donor compartment. Excessive skin at the sides was trimmed off to minimize lateral diffusion. The receptor compartment was filled with receptor media of composition PEG 400:water:20:80 medium to maintain a sink condition. The available diffusion area of the cell was 4.52 $cm^2$ with radius 1.2 cm. Skin was allowed to equilibrate with receptor fluid for 60 min, then donor compartment was filled with the proniosome formulation as shown in Table 1 subsequently drug solution containing 5 mg/5 ml in water was prepared and added to the donor side of the diffusion cell as a control. The top of the diffusion cell was covered with paraffin paper. The receptor solution was stirred by a star-head magnetic bar (size 10 × 10 mm) (Himedia) rotating at a constant speed of 600 rpm by motorless magnetic mega stirrer (WHIRLMATIC-MEGA, Spectralab). The temperature in the bulk of the solution was maintained at a constant level of 37°C ± 1°C using constant temperature water circulating bath (deep engineering), which circulates thermostated water through the water jacket surrounding the receptor compartment. At appropriate intervals, 2 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh receptor solution. The drugs concentrations were measured by UV spectrophotometric method at $\lambda_{max}$ 302 nm. Permeation study was performed for 48 h. Each experiment was performed in triplicate. All data were presented as mean ± standard deviation.[19]

**Microscopical and morphological examination**

*Light microscopy*

A thin layer of proniosomal gel was spread in a cavity slide, and then a cover slip was placed. Slide was observed under the microscope with and without polarized light (OLYMPUS Photo Microscope, Japan). A drop of water was added through the side cover slip into the cavity slide while under the microscope and observed again. Photomicrographs were taken at suitable magnifications as ×4, ×40, ×100 after addition of water.

*Scanning electron microscopy*

In a glass tube 0.2 g proniosome gel was diluted with 10 ml of pH 7.4 phosphate buffer; then dispersion was sprinkled and fixed on a scanning electron microscopy (SEM) holder with double sided adhesive tape and coated with a layer of gold for 3 min using a sputter coater. Niosome prepared after hydration of proniosomes were evaluated for their surface morphology, shape, size. The samples were examined using a SEM (Jeol JSM-6350, Tokyo, Japan) at 15 kV accelerating voltage.[20]

*Vesicle size and size distribution*

Vesicle size and polydispersity index (PI) was determined by Zeta sizer (Beckman coulter counter, Germany). This technique is ideal for measuring the nanoparticle size, diffusion coefficient, and molecular weight of polymers in solutions. A diluted (0.2 g of proniosomal gel in 10 ml of pH 7.4 phosphate buffer) suspensions of niosomes (hydrated proniosome) that became a colloidal solution after sonication was used to determine the size and size distribution. The vesicle measurements were done at a temperature 25°C ± 0.5°C.

**Differential scanning calorimetry**

To study the possible interactions between GRA HCl and vesicle ingredients of F5 batch of highest EE% was selected and samples of 5.2 mg of each empty and drug loaded proniosomes were submitted to differential scanning calorimetry (DSC) analysis using differential scanning calorimeter (Shimadzu DSC-60, Japan). Each sample was sealed in a standard aluminum pan and scanned between 0°C and 35°C, while another empty pan was used as a reference. The thermograms were obtained at 10°C/min. The heat flow calibration was performed with indium.

**Stability study**

The optimized proniosomal formulae F5 were sealed in 30 ml clear glass vials and stored at refrigeration temperature (4°C ± 2°C), room temperature (25°C ± 2°C), and hot condition in oven (45°C ± 2°C) for stability study. After 7, 15, 30, 60, 90 days, hydration step was carried out and the EE of each sample was determined and compared with the freshly prepared proniosomes derived niosomes.

**Preparation of reservoir type patch**

Circular "O" ring shaped spacer was used to hold the gel in the device. A spacer was obtained by cutting the plastic sheets (1 mm thickness and diameter 1.3 cm) of high density polyethylene. The spacer was adhered to the protective impermeable backing membrane using an adhesive to obtain an empty device. The spacer was filled with proniosomal gel (F5 batch). Cotran 9720 Polyethylene film (3M, USA) and Scotchpack 9741 SBOPP film (3M, USA) were used as backing membrane and release liner, respectively. Nylon mesh was used to hold gel. Durotak 387-2287 acrylate-vinylacetate noncuring pressure sensitive adhesive (National starch and Co., USA) was used as an adhesive.[12]

**Statistical analysis of data**

Response surface quadratic model was used to evaluate the effect of process variables, that is, span 60 and cholesterol were selected as independent parameters, while flux and EE as dependent factors. The following second order polynomial equation was applied as a tool of mathematical modeling:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (2)$$

Where, Y is the dependent variable, $b_0$ is the arithmetic mean response of the nine runs and $b_i$ ($b_1$, $b_2$, $b_{12}$, $b_{11}$ and $b_{22}$) is the estimated coefficient for corresponding factor $X_i$ ($X_1$, $X_2$, $X_{12}$, $X_{11}$ and $X_{22}$), which represents the average results of changing one factor at a time from its low to high value. The interaction term ($X_1X_2$) depicts the changes in the response when two factors are

simultaneously changed. The polynomial terms ($X_1^2$ and $X_2^2$) are included to investigate nonlinearity. The statistical data analysis was carried out using Design-Expert version 7.1.6 software (Minneapolis, MN, USA).[21]

## RESULTS AND DISCUSSION

Proniosomal TDD of GRA HCl is a good alternative to conventional oral and IV route as well as provides longer duration and controlled drug release of drug. In this study, proniosomes were prepared by coacervation phase separation method. This method is simple and less time consuming, economic.[22] Proniosomal gel was a coacervate of span 60, soya lecithin, cholesterol and drug at 60-70°C. In proniosome gel span 60 act as vesicle forming agent, soya lecithin as permeation enhancer, while cholesterol as a stabilizer for vesicles. Proniosomes converted in to niosomes after hydration with phosphate buffer 7.4. Optimization was done by $3^2$ factorial design. Span 60 and cholesterol were selected as independent parameters, while flux and EE as dependent factors. The factorial design batches were formulated according to Table 1.

### Entrapment efficiency determination

Entrapment efficiency of all factorial batches were determined and shown in Table 3. F5 batch containing 90 mg soya lecithin, 10 mg cholesterol, 90 mg span 60 showed maximum entrapment (66.57% ± 0.20%). Concentration of span 60 increases then entrapment also increases up to 90 mg, but latter decreases because higher amounts of span 60 may compete with the drug for packing space within the bilayer, hence excluding the drug from vesicles.[23] While, decreasing the EE with increasing cholesterol ratio above a certain limit may be due to the fact that increasing cholesterol beyond a certain concentration can disrupt the regular linear structure of vesicular membranes.[18]

### *In vitro* permeation study

Permeation (flux) of all factorial batches were determined and shown in Table 3. F5 batch containing 90 mg soya lecithin, 10 mg cholesterol, 90 mg span 60 showed maximum flux (7.94 ± 0.390 μg/cm²/h) and permeability coefficient (1.58 ±0.078 cm²/h). EE increases then permeation (flux) also increases. Flux of drug solution (control) was found to be (3.53 ± 0.07 μg/cm²/h) and permeability coefficient (0.70 ± 0.01 cm²/h). Flux of optimized batch F5 has near about twice flux of control [Figure 1 and Table 4].

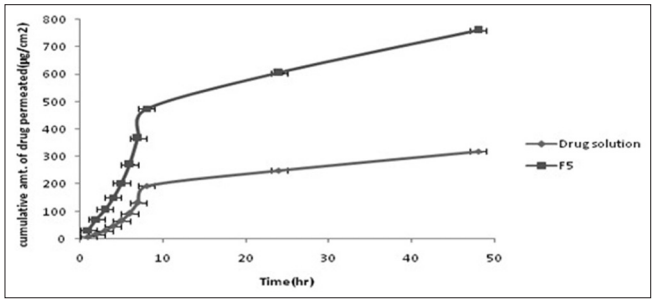


**Figure 1:** Flux of F5 batch and plain drug solution

### Microscopical examination

*Light microscopy*

After adding water to the F5 batch sample, the microscopic examination of the prepared proniosome gel formulations revealed the formation of niosomal vesicular structure with entrapped GRA HCl [Figure 2]. It showed that proniosomal gel form niosome after hydration.

*Scanning electron microscopy*

Scanning electron micrographs revealed the formation of well-identified spherical niosomal vesicles with sharp boundaries after hydration of proniosomes. Niosome formed after hydration of proniosomes have size below 1000 nm. Scanning electron micrographs of proniosome (F5), batch is shown in Figure 3.

*Vesicle size and size distribution*

Vesicle size was determined using Zeta Sizer (Beckmann coulter counter, Germany). It was found in nano range 536.8 nm and PI was found to be 0.250 [Table 5]. PI values > 0.3

**Table 3: Entrapment efficiency and permeation (Flux) of experimental batches**

| Formulation code | Entrapment (%) | Flux (μg/cm²/hr) | Permeability coefficient (×10⁻³) (cm²/hr) |
|---|---|---|---|
| F1 | 59.76±0.11 | 4.94±0.082 | 0.98±0.016 |
| F2 | 62.45±0.21 | 5.97±0.080 | 1.19±0.015 |
| F3 | 60.55±0.13 | 5.30±0.008 | 1.06±0.001 |
| F4 | 61.55±0.12 | 5.60±0.054 | 1.12±0.011 |
| F5 | 66.57±0.20 | 7.94±0.390 | 1.58±0.078 |
| F6 | 64.27±0.10 | 6.82±0.075 | 1.36±0.015 |
| F7 | 60.81±0.18 | 5.38±0.056 | 1.07±0.011 |
| F8 | 64.86±0.23 | 7.02±0.089 | 1.40±0.017 |
| F9 | 62.19±0.28 | 5.84±0.027 | 1.16±0.004 |

**Table 4: *In vitro* permeation rate profiles of F5 and plain drug solution through guinea pig skin**

| Formulation | Cumulative drug release | Flux (μg/cm²/hr) | Permeability coefficient (×10⁻³) (cm/hr) |
|---|---|---|---|
| Proniosomal gel (F5) | 760.53±0.72 | 7.94±0.39 | 1.58±0.07 |
| Drug solution | 319.35±1.68 | 3.53±0.07 | 0.70±0.01 |

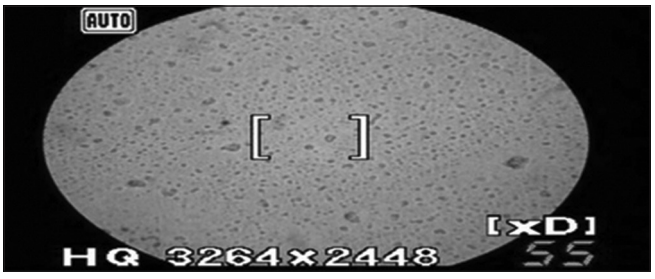


**Figure 2:** Photomicroscope of hydrated proniosome formulation (F5) under ×40

indicate heterogeneity so; vesicles can be considered as monodisperse (homogeneous).[17]

**Differential scanning calorimetry**

Differential scanning calorimetry thermograms of GRA HCl, span 60, empty and drug loaded niosomes are illustrated in Figures 4-7, respectively. GRA HCl, span 60 showed endothermic peak at 311.74, 58.64°C respectively, corresponding to their near melting temperatures. DSC thermogram of drug free niosomes showed the appearance of a new broad endothermic peak at 133.46°C indicating the inter-action between the molecules of span 60, cholesterol and soya lecithin. However, thermogram of GRA HCl loaded niosomes revealed a disappearance of the characteristic endothermic peak, and the endotherm of the niosome was shifted from 133.46°C to a new peak at 130.67°C and 110.24°C. These results suggest the dispersion and entrapment of GRA HCl into the bilayers of niosomal vesicles.[17]

**Table 5: Vesicle size analysis of proniosomes (F5)**

| Parameter | Result |
|---|---|
| Diameter (d) | 536.8 nm |
| Polydispersity index (P. I.) | 0.250 |
| Diffusion cont. (D) | 9.163e-009 $cm^2$/sec |

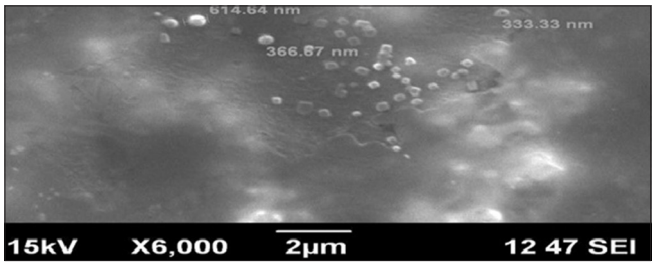


**Figure 3:** Scanning electron micrographs of niosomes after hydration of proniosome (F5)

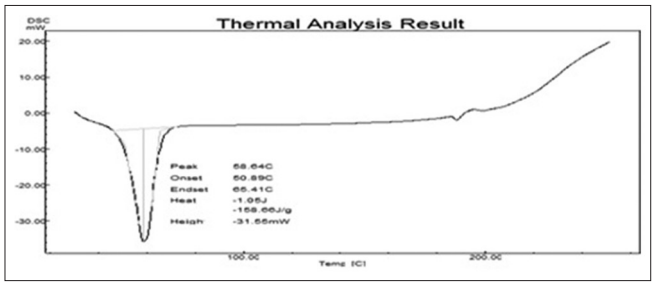


**Figure 5:** Differential scanning calorimetry thermogram of span 60

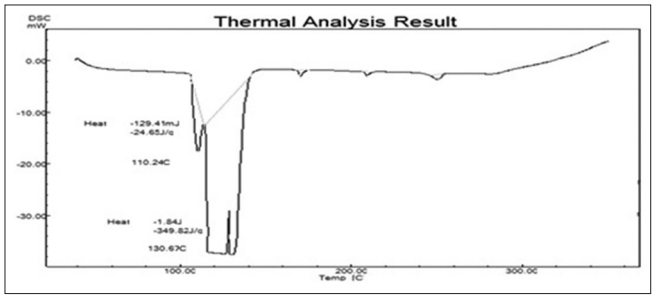


**Figure 7:** Differential scanning calorimetry thermogram of proniosomal gel with drug (F5 batch)

**Stability study**

The optimized proniosomal formulae F5 were sealed in 30 ml clear glass vials and kept for stability study at refrigeration temperature (4°C ± 2°C), room temperature (25°C ± 2°C), and hot condition (45°C ± 2°C). After 7, 15, 30, 60, 90 days, hydration step was carried out and the EE of each sample was determined and compared to the freshly prepared proniosomes derived niosomes [Table 6 and Figure 8]. The stability study indicates that the formulations are most stable at 4°C and with minimum leakage.

**Statistical analysis of data**

The $3^2$ full factorial design was selected to study the effect of independent variables span 60 (X1) and cholesterol (X2)

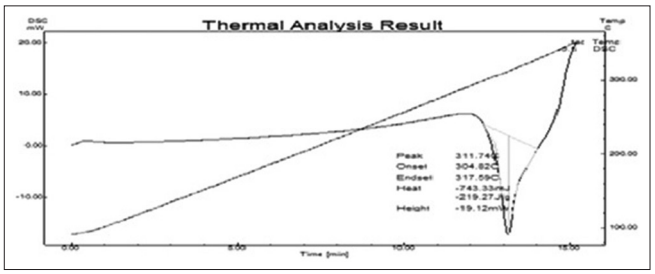


**Figure 4:** Differential scanning calorimetry thermogram of granisetron hydrochloride

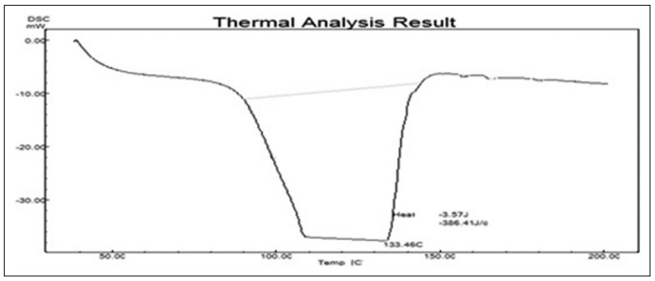


**Figure 6:** Differential scanning calorimetry thermogram of proniosomal gel without drug (F5 batch)

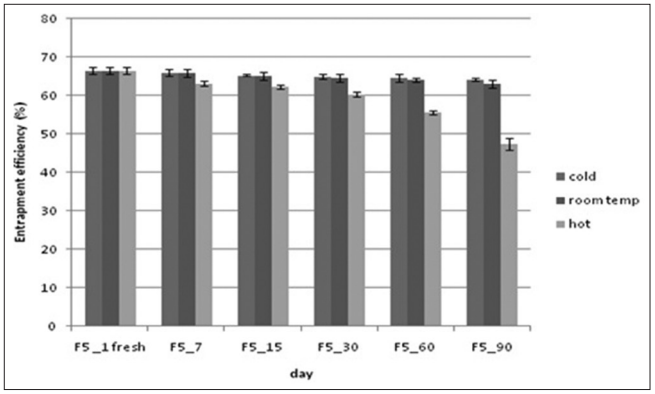


**Figure 8:** Stability study

on dependent variables EE and flux. The response data was analyzed by using Stat Ease Design Expert 7.1.6 software (Minneapolis, MN, USA). Summary of statistical design and responses shown in Tables 7 and 8, respectively. The results were shown in the Tables 9 and 10.

$P < 0.05$ indicated significance of the model terms. Analysis of variance indicated that the developed models were significant for each considered response.

The three-dimensional response plots were constructed from quadratic model obtained through Design Expert software in which the responses were represented by bars as a function of independent variables as shown in the Figures 9 and 10. The relationship between the response and independent variables can be directly visualized from the response plots.[21]

**Table 6: Stability study analysis**

| Days | Cold | Room temp | Hot |
|---|---|---|---|
| F5_1 fresh | 66.50±0.09 | 66.5±0.09 | 66.50±0.09 |
| F5_7 | 65.96±0.22 | 65.83±0.19 | 63.13±0.06 |
| F5_15 | 65.22±0.02 | 65.07±0.09 | 62.22±0.11 |
| F5_30 | 64.93±0.06 | 64.52±0.10 | 60.36±0.20 |
| F5_60 | 64.55±0.09 | 64.08±0.05 | 55.68±0.05 |
| F5_90 | 64.20±0.03 | 63.04±0.14 | 47.38±0.44 |

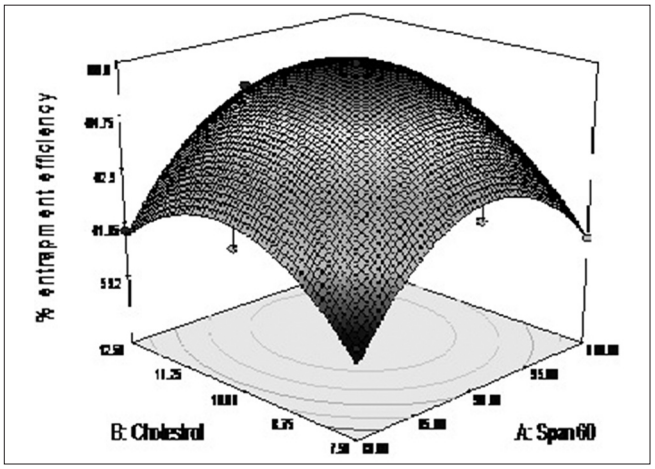


**Figure 9:** Three-dimensional response plots for drug entrapment efficacy

**Table 7: Summary of statistical design**

| Factor | Name | Units | Type | Actual values | | Coded values | |
|---|---|---|---|---|---|---|---|
| | | | | Lowest | Highest | Lowest | Highest |
| A | Span 60 | Mg | Numerical | 80 | 100 | −1 | +1 |
| B | Cholesterol | Mg | Numerical | 7.5 | 12.5 | −1 | +1 |

**Table 8: Summary of responses**

| Response | Description | Units | Obs. | Analysis | Min | Max | Mean |
|---|---|---|---|---|---|---|---|
| Y1 | Entrapment | % | 9 | Polynomial | 59.76 | 66.57 | 63.165 |
| Y2 | Flux | (μg/cm²/hr) | 9 | Polynomial | 4.94 | 7.94 | 6.44 |

**Table 9: Analysis of variance for drug entrapment**

| Source | Sum of squares | Degrees of freedom | Mean square | *F* value | *P* value | Significance |
|---|---|---|---|---|---|---|
| Model | 38.83 | 5 | 7.77 | 14.77 | 0.0283 | Significant |
| A-span-60 | 3.99 | 1 | 3.99 | 7.58 | 0.0705 | |
| B-Cholesterol | 4.33 | 1 | 4.33 | 8.25 | 0.0640 | |
| AB | 0.087 | 1 | 0.087 | 0.17 | 0.7114 | |
| $A^2$ | 19.28 | 1 | 19.28 | 36.68 | 0.0090 | |
| $B^2$ | 11.14 | 1 | 11.14 | 21.19 | 0.0193 | |
| Residual | 1.58 | 3 | 0.53 | | | |
| Cor total | 40.41 | 8 | | | | |

**Table 10: Analysis of variance for drug permeation (Flux)**

| Source | Sum of squares | Degrees of freedom | Mean square | *F* value | *P* value | Significance |
|---|---|---|---|---|---|---|
| Model | 7.10 | 5 | 1.42 | 9.59 | 0.0460 | Significant |
| A-span-60 | 0.66 | 1 | 0.66 | 4.45 | 0.1252 | |
| B-Cholesterol | 0.69 | 1 | 0.69 | 4.64 | 0.1202 | |
| AB | 0.0025 | 1 | 0.0025 | 0.017 | 0.9048 | |
| $A^2$ | 3.49 | 1 | 3.49 | 23.60 | 0.0166 | |
| $B^2$ | 2.25 | 1 | 2.25 | 15.23 | 0.0299 | |
| Residual | 0.44 | 3 | 0.15 | | | |
| Cor total | 7.54 | 8 | | | | |

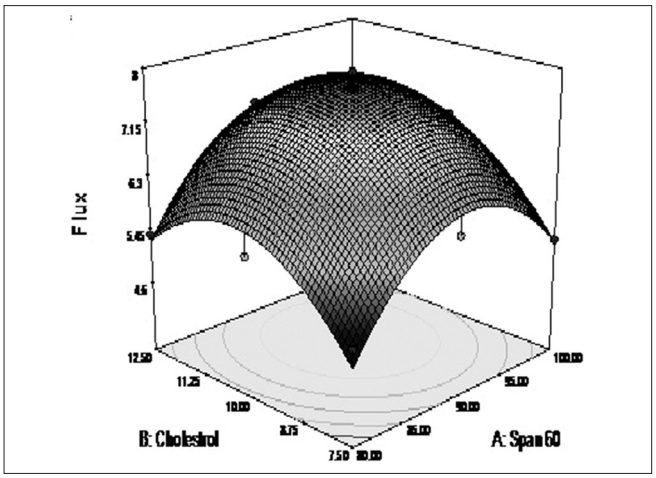


**Figure 10:** Three-dimensional response plot for flux

## CONCLUSION

Proniosomal TDD of GRA HCl was prepared. Formulation was optimized by use of $3^2$ factorial design. Two independent variables span 60, cholesterol were selected for study, while EE and flux as dependent variables. F5 batch show maximum entrapment (66.57% ± 0.20%) and flux (7.94 ± 0390 μg/cm$^2$/h). Comparative *in vitro* drug release study of plain drug solution and drug in proniosomal gel form (F5 batch) was carried out for 48 h on guinea pig skin. It was found that cumulative release and flux of proniosomal gel was nearly two times more than drug solution containing same drug concentration. Finally, it was concluded that GRA HCl can be successfully formulated in proniosomal TDDS, which achieve prolonged controlled drug release.

## ACKNOWLEDGMENTS

The authors are thankful to Sun Pharma Limited (Halol, India) for providing gift sample of GRA HCl. Gratitude is also extended to Perfect biotech (Nagpur, India) for the donation of soya lecithin sample.

## REFERENCES

1. Gill P, Grothey A, Loprinzi C. Nausea and vomiting in the cancer patient. Oncology 2006;7:1482-96.
2. Morrow GR. Chemotherapy-related nausea and vomiting: Etiology and management. CA Cancer J Clin 1989;39:89-104.
3. Scorza K, Williams A, Phillips JD, Shaw J. Evaluation of nausea and vomiting. Am Fam Physician 2007;76:76-84.
4. Andrykowski MA. Defining anticipatory nausea and vomiting: Differences among cancer chemotherapy patients who report pretreatment nausea. J Behav Med 1988;11:59-69.
5. Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW, *et al*. Recommendations for the use of antiemetics: Evidence-based, clinical practice guidelines. American Society of Clinical Oncology. J Clin Oncol 1999;17:2971-94.
6. Phillips RS, Gopaul S, Gibson F, Houghton E, Craig JV, Light K, *et al*. Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. Cochrane Libr 2010;9:1-87.
7. Thomas BJ, Finnin BC. The transdermal revolution. Drug Discov Today 2004;9:697-703.
8. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol 2008;26:1261-8.
9. Shin SC, Kim HJ, Oh IJ, Cho CW, Yang KH. Development of tretinoin gels for enhanced transdermal delivery. Eur J Pharm Biopharm 2005;60:67-71.
10. Jain NK. Controlled and Novel Drug Delivery. 1st ed. New Delhi: CBC Publishers and Distributers; 1997. p. 100-20.
11. Elsayed MM, Abdallah OY, Naggar VF, Khalafallah NM. Deformable liposomes and ethosomes: Mechanism of enhanced skin delivery. Int J Pharm 2006;322:60-6.
12. Vora B, Khopade AJ, Jain NK. Proniosome based transdermal delivery of levonorgestrel for effective contraception. J Control Release 1998;54:149-65.
13. Fang JY, Yu SY, Wu PC, Huang YB, Tsai YH. *In vitro* skin permeation of estradiol from various proniosome formulations. Int J Pharm 2001;215:91-9.
14. Alsarra IA, Bosela AA, Ahmed SM, Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur J Pharm Biopharm 2005;59:485-90.
15. Ammar HO, Ghorab M, El-Nahhas SA, Higazy IM. Proniosomes as a carrier system for transdermal delivery of tenoxicam. Int J Pharm 2011;405:142-52.
16. Gupta A, Prajapati SK, Balamurugan M, Singh M, Bhatia D. Design and development of a proniosomal transdermal drug delivery system for captopril. Trop J Pharm Res 2007;6:687-93.
17. El-Laithy HM, Shoukry O, Mahran LG. Novel sugar esters proniosomes for transdermal delivery of vinpocetine: Preclinical and clinical studies. Eur J Pharm Biopharm 2011;77:43-55.
18. El-Samaligy MS, Afifi NN, Mahmoud EA. Increasing bioavailability of silymarin using a buccal liposomal delivery system: Preparation and experimental design investigation. Int J Pharm 2006;308:140-8.
19. Sarpotdar PP, Gaskill JL, Giannini RP. Effect of polyethylene glycol 400 on the penetration of drugs through human cadaver skin *in vitro*. J Pharm Sci 1986;75:26-8.
20. Azarbayjani AF, Tan EH, Chan YW, Chan SY. Transdermal delivery of haloperidol by proniosomal formulations with non-ionic surfactants. Biol Pharm Bull 2009;32:1453-8.
21. Lewis GA, Mathieu D, Phan-Tan-Luu R. Pharmaceutical Experimental Design. New york: Marcel Dekker Inc.; 1999. p. 1-86.
22. Kakar R, Rao R, Goswami A, Nanda S, Saroha K. Proniosomes: An emerging vesicular system in drug delivery and cosmetics. Der Pharma Lett 2010;2:227-39.
23. Mokhtar M, Sammour OA, Hammad MA, Megrab NA. Effect of some formulation parameters on flurbiprofen encapsulation and release rates of niosomes prepared from proniosomes. Int J Pharm 2008;361:104-11.

**How to cite this article:** Patil BA, Puranik PK, Pol SD, Khobragade PK, Ramteke PS, Palasakar RG, *et al*. Formulation and development of industry feasible proniosomal transdermal drug delivery system of granisetron hydrochloride. Asian J Pharm 2015;9:113-9.

**Source of Support:** Nil. **Conflict of Interest:** None declared.