Formulation and Optimization of Pluronic Lecithin Organogel Containing Verapamil Hydrochloride Using Factorial Design Method

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Abstract

The purpose of the current study was to investigate the feasibility of pluronic lecithin organogel as transdermal drug delivery system of verapamil hydrochloride. Verapamil hydrochloride is an L-type calcium channel blocker of the phenylalkylamine class. Formulations were developed using 30% oil phase and 70% aqueous phase. A 3^2 factorial design was applied to check the effect of independent variables, Pluronic F-127(X_1) and Soya-Lecithin (X_2) on the dependent variable (Y) Percentage drug release in 24hr. The formulated organogels were evaluated for physicochemical properties, and *in vitro* diffusion study. It was found that the pH of all the formulations is in the range of to 6-7 that suits the skin pH, indicating skin compatibility. *Invitro* permeation study were performed using modified KC diffusion cell. Kinetic data revealed that the drug release followed Korsemeyer-Peppas model and the mechanism of release was found to be non fickian diffusion. The search for the optimized formulation composition was carried out using the desirability function approach with Design Expert™ 11.1.2.0, criterion being one having the maximum desirability value. The suggested formulation was considered as optimized batch (VOT3). Hence, Pluronic lecithin organogel is efficient carrier for transdermal drug delivery of verapamil hydrochloride, thereby sustaining the action.

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INTRODUCTION:

Transdermal drug delivery systems are self-contained discrete dosage forms that, when applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation. Transdermal delivery has many advantages over conventional modes of drug administration, it avoids hepatic first pass metabolism and improves patient compliance. [1-2] Organogels are bicontineous colloidal system that coexist as micro heterogeneous solid (i.e. Gelator) and organic liquid phase. In general, organogels formation is based in the spontaneous self-assembly of individual gelator molecules into three-dimensional networks of randomly entangled fiber like structures. This three dimensional network holds micro domains of the

liquid in a non-flowing state mainly through surface tension. Lecithin Organogels, the jelly like phases, consist of a 3-dimensional network of entangled reverse cylindrical (polymer-like) micelles, which immobilizes the continuous or macroscopic external organic phase, thus turning a liquid into a gel.[3-7] The formation of transition at the micellar level in a low viscous Newtonian liquid, consisting of lecithin reverse micelles in non-polar organic liquid. However, these systems can also be called as polymer like micelles or wormlike or threadlike micelles.[7,8]

Verapamil hydrochloride is an L-type calcium channel blocker of the phenylalkylamine class. Given orally, 90 to100% of verapamil is absorbed, but due to high first-pass metabolism, bioavailability is much poorer (10 to35%). It is 90% bound to plasma proteins and it has a volume of distribution of 3 to 5l/kg. It gets metabolized in the liver into 12 inactive metabolites. 70% of metabolites get excreted in the urine and 16% in feces; 3 to 4% is excreted unaffected in urine. Metabolism is a nonlinear dependence between plasma concentration and dosage. Onset of action is 1 to 2 hours after oral dosage. t 1/2 is 2.8 to 7.4 hours. [9,10]

Skin is a natural barrier against the penetration of most drugs, and the ability of drug to penetrate the skin epidermis, dermis, and subcutaneous fat layers depend on the properties of the drug and the carrier base. Traditional topical drug delivery systems like emulsion and suspension have various limitations such as instability and minimal systemic absorption of drug. Therefore the objective of the present study is development of a novel topical vehicle for the delivery of an antihypertensive agent in terms of effectiveness and elegance as compared to conventional drug delivery system, improved availability at the desired site by use of organogels and improved patient compliance.

MATERIALS AND METHOD:

Material

Verapamil hydrochloride was procured from Yarrow Chemicals, Mumbai, India. Poloxamer (Pluronic F127) were provided a gift samples by M/s BASF corporation, NJ, USA. Soya Lecithin and sorbic acid were procured from M/s Himedia labs Pvt. Ltd. Mumbai, India. Isopropyl myristate was a product of Central Drug House Pvt. Ltd, New Delhi, India. All other chemicals used were of analytical grade.

Methods [2, 11-14]

The various formulations of Pluronic Lecithin Organogel (Table1) were developed with different compositions. The oil phase was prepared by dispersing the specific amount of soya lecithin at room temperature in isopropyl myristate (IPM). The mixture was kept overnight at room temperature to dissolve its constituents. Then sorbic acid (SA) in appropriate quantity was added, finally, drug and plasticizer were dissolved in an oil phase. The aqueous phase was prepared by dispersing the weighed amount of Pluronic F-127 and potassium sorbate (PS) in cold water. The dispersion was stored in a refrigerator overnight for effective dissolution of Pluronic F-127. Finally, aqueous phase (70%) was slowly added in oil phase (30%) with stirring at 400 rpm using mechanical stirrer. The formulation shown in table no.1.

Experimental design

The formulation compositions are optimized by factorial design following 3^2 factorial analysis design. The formulae were developed as 9 sets varying the variables (polymer combination and Penetration enhancer) following 3^2 full factorial design (3 levels) using Design Expert™ 11.1.2.0. The two independent variables selected were the concentration of pluronic F-127(X_1) and Soya-Lecithin (X_2). The dependent variable selected for the response was drug release in 24hr. The concentration range of independent variables was selected based on the following observations from preliminary experimentation. The selected concentration range of independent variables under study with their low, medium and high levels is shown in Table 1.

Organogel Characterization

Organoleptic characteristics [15]

Each formulation was tested for color, odor, texture and phase separation as well as feels upon application (stiffness, grittiness, greasiness and tackiness).

Homogeneity test

A small quantity of each gel was pressed between the thumb and the index finger in order to notice the consistency of cream that any coarse particles being attached or detached on the finger.

Conclusiveness

Prepared gel was taken in vial and visually observed weather it is occlusive or not.

pH Determination

The pH of formulated organogels was determined using pH meter. A solution containing 1 gm of organogel in 30 ml of neutralized distilled water was prepared and subjected to pH measurement. The results are given in the table-4.

Rheological Measurement

The rheological properties of organogel were measured using a thermostatically controlled Brookfield programmable rheometer (Model DV-1+ Brookfield viscometer) by using concentric cylinder

spindle LV-4 at 100 rpm and at temperature 25ºC. The results are given in the table-4.

Spreadability [16]

Spreadability of formulations was determined by an apparatus suggested by Multimer *et al*. which was fabricated in laboratory and used for study. The apparatus consists of a wooden block, with a fixed glass slide and movable glass slide with one end tied to weight pan rolled on the pulley, which was in horizontal level with fixed slide. An excess of gel sample 2.5 g was placed between two glass slides and a 1000g weight was placed on slides for 5 minutes to compress the sample to a uniform thickness. The time (seconds) required to separate the two slides was taken as a measure of Spreadability. It was calculated using the formula,

S = ML/ T

Where, S is spreadability in gcm/sec, M is weight tied to upper slide, L is length of glass slide, T is time in seconds. The results are given in the table-4.

Drug Content[17]

The content of verapamil hydrochloride in the formulations was determined as per the method described by Willaimann et.al. For estimation verapamil hydrochloride content 1 gm of organogel was diluted to 100ml with phosphate buffer pH 7.4 and analysed spectrophotometrically at 278nm. The results are given in the table-4.

In vitro Drug Permeation Studies [18]

In-vitro diffusion study of formulated organogel was carried out on Franz diffusion cell having 2.0cm diameter and 18ml capacity. Dialysis membrane (Himedia) having a molecular weight cut-off range 12000–14000kDa was used as a diffusion membrane. The diffusion cell was filled with phosphate buffer pH 7.4; dialysis membrane was mounted on the cell. The temperature was maintained at 34±0.5ºC. At predetermined time points, 1ml samples were withdrawn from the acceptor compartment, replacing the sampled volume with phosphate buffer pH 7.4 after each sampling, for 540minutes. The samples withdrawn were filtered and used for analysis. The amount of permeated drug was determined using a UV- spectrophotometer at 278nm. The results are given in the table-4.

Kinetics of the drug release:

To know the mechanism of the drug release from the patch's, the results obtained from the in-vitro permeation studies were analysed by various kinetic models. 1. Zero order drug release: cumulative % drug release Vs time. 2. First order drug release: log cumulative% drug retained Vs time 3. Higuchi's diffusion equation: cumulative %drug release Vs square root of time 4. Peppas-korsemeyer exponential: log cumulative % drug release Vs log time. The results are given in the table-5.

Stability Studies:

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. In the present study, stability studies were carried out at 2-8^{0}C, room temperature and at 40ºC ±2ºC /75 % RH ± 5 % for a specific time period up to 3months for the optimized formulation. The evaluation parameters check periodically. The results are given in the table-6.

RESULT AND DISCUSSION:

Formulation and Characterization of Pluronic Organogel Formulations

In the present work, pluronic lecithin organogel was prepared for transdermal delivery of verapamil hydrochloride with improved therapeutic performance by their penetration enhancing property. In order to achieve this objective, the formulations were prepared with soya lecithin, isopropyl myristate and polyethylene glycol 600 as a co surfactant. The formulations were characterized for their organoleptic properties, homogeneity, conclusiveness, pH, viscosity.

The physiological observation shows that organogel formulations were washable, yellowish in color with no phase separation, smooth in feel and showed no clogging which indicate good texture of system. Freedom from grittiness reflects the degree of acceptability of verapamil hydrochloride formulation by the patients.

pH:

The pH of the organogels was measured at room temperature by using an electrode-based digital pH meter. The pH of all formulations ranged between 5.30±0.15- 6.30±0.15 indicating their probable use in the formulation of the transdermal or topical products.

Viscosity:

The viscosity values were measured for organogel formulations using Brookfield viscometer DV-E with spindle no. 7 at 50rpm. The viscosity ranged from 96500-188000cp.

Spreadability:

The spreadable nature of organogel was checked. Spreadability of all the batches shows in the range 12.79-25.11%, results for the spreading ability of organogel.

Drug Content:

The content of organogel formulations was found in the range of 97.58±2.10 - 100.34±0.22 indicating uniform distribution of drug through the base and no interaction of drug with component of base.

Invitro Permeation Studies:

Invitro permeation studies were carried out for all 9 formulations using dialysis membrane as barrier in phosphate buffer pH 7.4. The maximum and minimum drug release obtained for optimized are 86.25 and 92.15, respectively. The verapamil hydrochloride release was found to be decreased with an increase in soyabean oil content, an inverse correlation exist between the release rate and the gel viscosity value. But a significant decrease in verapamil hydrochloride release was obtained as the soyabean oil concentration was further increase. Further increase in concentration of organogelator decrease cumulative percentage drug release which might be due to extensive entanglement of long cylindrical micelles with each other, forming network like structure with increase in viscosity.

Kinetics of Drug Release data:

In this study, different formulations released variable amount of verapamil hydrochloride through membrane into the *invitro* fluid. To study the drug diffusion kinetics and mechanism the results were fitted to zero, first order, Higuchi and the release data were also analyzed as per Korsemeyer-Peppa's plot.

The *invitro* permeation data were fit to different equations and kinetic models to explain permeation profile (Table No. 5, Fig No. 1). The coefficient of correlation of each of the kinetics was calculated and compared. The *invitro* permeation profiles of all the different formulations of VH organogel did not fit to zero order behaviour truly and they could be beat expressed by Higuchi's equation for the release of drug from organogel system that depends on rate controlling parameters in the drug release. The data was further treated as per Korsemeyer-Peppas equation. It was observed that the release exponent n was 0.5, this suggested that an anomalous or non fickian diffusion. Batch VOT 3 has R^2 value (0.9823) and n value (0.6572). The slope (n) values obtained by this equations indicated that the drug released by Fickian diffusion predominated with all formulations.

EXPERIMENTAL DESIGN[19-21]

The evaluation of data for optimization process was carried out by Design Expert Software™ 11.1.2.0. The 3^2 factorial design was used to optimize the formulation variables and the data generated was used to fit in a quadratic polynomial equations for dependent variable as shown in the equation 1.

$$y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \varepsilon \quad .... \ 1$$

In this equation, y is a dependent variable; β_1, β_2, β_3, β_4, and β_5 are constant regression coefficient of the factor (linear terms), their interaction and quadratic terms, respectively; β_0 is the arithmetic mean response of the 9 runs and ε is random error.

For estimation of quantitative effects of the different combination of factors and the factor levels on the percentage drug release, the response models were calculated with Design Expert software by applying coded values of factor levels. The model described could be represented as:

Coded level: **Percentage Drug Release (Y_1)** = 5965 - 3.03A + 2.71B - 3.20AB - 0.7950A^2 + 3.45B^2 2

Fitting of Data to the Model

A 3^2 statistical experimental design as the RSM requires 9 experiments. Formulation 9 showed a significantly better percentage drug release among the experimental runs. All the responses observed for 9 formulations prepared were simultaneously fit to first order, second order, and quadratic models using Design Expert 11.1.2.0. It was observed that the best fit model was quadratic model and Sum of squares is Type III -partial. A positive value represents an effect that favours the optimization, while a negative value indicates an inverse relationship between the factor and response. It is evident that all the three independent variables, viz. the Pluronic F-127 (X_1), and Lecithin (X_2) have positive effects on the response, viz. percentage drug release.

The quantitative effects of the different combination of factors and factor levels on the percentage drug release was calculated using response surface models. The significant p value (p<0.05), R^2, adjusted R^2, and coefficient of variation values of this model indicated that the assumed regression model was significant and valid for each considered response. The values of the coefficients in the model are related to the effect of these variables on the response. Form this model quadratic was best, indicating that combination of above system had the greatest potential influence on the telmisartan organogel.

3D response surface plots give a representation of the variations in each response when the two factors are simultaneously changed from lower to higher level. It gives a three dimensional curvature of the change in response at different factor levels. It also gives the variation in design points from the predicted response value. The 3-D response surface (Fig. No. 2) and counter plot (Fig. No. 2) were drawn to estimate the effects of the independent variables on response and to select the optimal formulation.

Data Analysis

The percentage drug release (dependent variable) obtained at various levels of the three independent variables (X_1, and X_2) was subjected to multiple regression to yield a polynomial equation. The value of correlation coefficient (r^2) of the equation was found to be 0.9683, indicating good fit. VIF value

found to be 1, indicating model is significant. According to table 6, the result calculated using equation 2 was statistically significant with $p<0.005$, indicating that the developed model exhibited good agreement between the response Y_1 and the significant variables. The value of lack of fit for the equation more than 0.05 indicating that the proposed statistical model fit well. The ANOVA result for Y_1 provides F value 18.33 as compared to the critical values from the cut off point for F distribution (=0.05 (Table 145). These F value suggested that the derived quadratic models has significant influence on the response R^2 and adjusted R^2 value for Y_1 were 0.9155, 0.6831, respectively demonstrate the accuracy of the test and the fitness of the results with prepared model. The percentage drug release measured for the different formulations showed wide variation (i.e. vales ranged from 88.75 to 92.15%). The results clearly indicate that the percentage drug release is strongly affected by the variables selected for the study. The main effects of X_1, and X_2 represents the average result of changing one variable at a time from its low level to its high level. The interaction terms (X_1X_2, X_1X_3, X_2X_3, X_1^2, X_2^2, X_3^2) shows how the percentage drug release changes when two variables are simultaneously changed. The negative coefficient for all three independent variables an unfavourable effect on the percentage drug release, while positive coefficients for the interactions between two variables indicate a favourable effect on percentage drug release.

Search for the Optimum Formulation:
The search for the optimized formulation composition was carried out using the desirability function approach with Design Expert software, criterion being one having the maximum desirability value. The optimization process was performed by setting the responses within selected ranges. Target ranges for the % drug release on TM organogel (Y). The suggested formulation was considered as optimized batch (VOT3). The composition of VOT3 and the responses predicted by software are listed in table no. 7. Batch VOT3was found to exhibit the value of observed parameters close to the values predicted by software.

Stability Studies:
The optimized formulations was subjected to stability studies at three different temperatures (2-8ºC, RT and 40ºC). It was found that more than 98% of drug was present in all the formulations after 90days at RT whereas at 2-8ºC, there was about 2% and at 40ºC there was also 2% decline in the drug content observed in the tested formulations. Other characteristics like transparency, feel and pH were also observed as given in the table no. 8 and no significant change was found in these characteristics, which showed that during stability studies, the prepared formulation was found to be stable without any significant changes at RT.

Table No. 1: Formulation and design of 3^2 full factorial experiment design layout for Verapamil hydrochloride organogel

Batch	Variable level coded formulation	
	X_1	X_2
VOT 1	-1	-1
VOT 2	-1	0
VOT 3	-1	+1
VOT 4	0	-1
VOT 5	0	0
VOT 6	0	+1
VOT 7	+1	-1
VOT 8	+1	0
VOT 9	+1	+1

Table No 2: Values of variables in 3^2 full factorial design for Verapamil hydrochloride Organogel

Coded values	Actual values (X_1 = Pluronic F-127)	Actual values (X_2= Soya Lecithin)
-1	10	2.5
0	15	5
+1	20	10

Table No. 3: Actual formulation design layout for Verapamil hydrochloride Organogel

Content	TOT1	TOT 2	TOT 3	TOT 4	TOT 5	TOT 6	TOT 7	TOT 8	TOT 9
Verapamil hydrochloride (%)	1	1	1	1	1	1	1	1	1
Lecithin Soya (%)	2.5	2.5	2.5	5	5	5	10	10	10
Sorbic Acid (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Polyethylene Glycol 600 (%)	10	10	10	10	10	10	10	10	10
Isopropyl Myristate upto (%)	100	100	100	100	100	100	100	100	100
Pluronic F-127 (%)	10	15	20	10	15	20	10	15	20
Potassium Sorbate (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Purified water upto (%)	100	100	100	100	100	100	100	100	100

Table no. 4: Characterization of Verapamil hydrochloride Organogels Formulation

Batch	Appearance	pH	Drug Content	Phase Separation	Spreadability	Viscosity (cp)	% Drug diffused
VOT 1	Good	6.48±0.15	95.132	No	8958	18.21	90.02
VOT 2	Good	6.96±0.15	97.416	No	9253	18.11	90.04
VOT 3	Good	7.10±0.15	98.768	No	8751	19.50	92.15
VOT 4	Good	6.87±0.15	94.960	No	9026	17.92	90.11
VOT 5	Good	6.95±0.15	94.960	No	9172	17.70	90.71
VOT 6	Good	7.10±0.15	90.192	No	7741	18.06	91.02
VOT 7	Good	6.77±0.15	99.392	No	7652	18.11	89.42
VOT 8	Good	6.52±0.15	99.564	No	7800	18.66	86.25
VOT 9	Good	7.21±0.15	94.192	No	7720	17.97	88.75

Table No 5: Kinetics of drug release of formulation of Verapamil hydrochloride organogel

Batch	Zero order R^2	First order R^2	Higuchi Model R^2	Korsemeyer-Peppas Model R^2	n
VOT 1	0.9764	0.6821	0.7948	0.9762	0.6643
VOT 2	0.9737	0.7518	0.7878	0.9734	0.5341
VOT 3	0.9822	0.6938	0.8073	0.9823	0.6572
VOT 4	0.9672	0.7736	0.9245	0.9677	0.5758
VOT 5	0.9781	0.7894	0.9164	0.9867	0.5821
VOT 6	0.9925	0.7997	0.8977	0.9995	0.5692
VOT 7	0.9222	0.7992	0.8323	0.9898	0.5858
VOT 8	0.9874	0.6819	0.9770	0.9924	0.5862
VOT 9	0.9636	0.7735	0.9342	0.9854	0.5910

Table No. 6: A Summary of ANOVA for response Y_1 for fitting to quadratic model for verapamil hydrochloride Organogel

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	164.98	5	33	18.33	0.0186	significant
A-Soyalecithin	54.9	1	54.9	30.49	0.0117	
B-Cholesterol	44.12	1	44.12	24.5	0.0158	
AB	40.96	1	40.96	22.75	0.0175	
A^2	1.26	1	1.26	0.7021	0.4636	
B^2	23.74	1	23.74	13.18	0.036	
Residual	5.4	3	1.8			
Cor Total	170.38	8				
Std. Dev.	1.34		R^2	0.9683		
Mean	61.41		Adjusted R^2	0.9155		
C.V. %	2.18		Predicted R^2	06831		

Table no. 7: Simultaneous optimal solution by RSM for Verapamil hydrochloride Organogel

Response	Pred. Mean	Pred. Median	Observed	Std. Deviation	SE Mean	95% CL Low	95% CL High	95%TL Low	95% High
Drug Release	96.87	96.87	97.92	2.06	1.53	91.97	101.77	77.73	116.01

Table no. 8: Stability study data of optimized formulation of Verapamil hydrochloride Organogel

| Stability conditions	Months	Evaluation Parameters			
		Phase separation	pH	Spreadability	Drug Content (%)
2-8ºC	0	No Change	6.20±0.03	31.5±0.01	98.68±0.014
	1	No Change	6.32±0.04	30.8±0.04	99.11±0.020
	2	No Change	6.11±0.02	30.5±0.02	98.77±0.017
	3	No Change	6.58 ±0.02	30.1±0.04	99.16±0.023
Room Temperature	0	No Change	6.70±0.03	31.2±0.01	97.68±0.032
	1	No Change	6.59±0.04	30.7±0.04	98.25±0.019
	2	No Change	6.24±0.02	30.3±0.02	97.45±0.013
	3	No Change	6.38±0.02	30.1±0.04	97.56±0.025
40±2ºC/75% RH±5%	0	No Change	6.35±0.03	31.5±0.01	99.12±0.014
	1	No Change	6.44±0.04	31.0±0.04	98.03±0.020
	2	No Change	6.55±0.02	30.8±0.02	97.41±0.023
	3	No Change	6.31 ±0.02	30.4±0.04	97.75±0.013
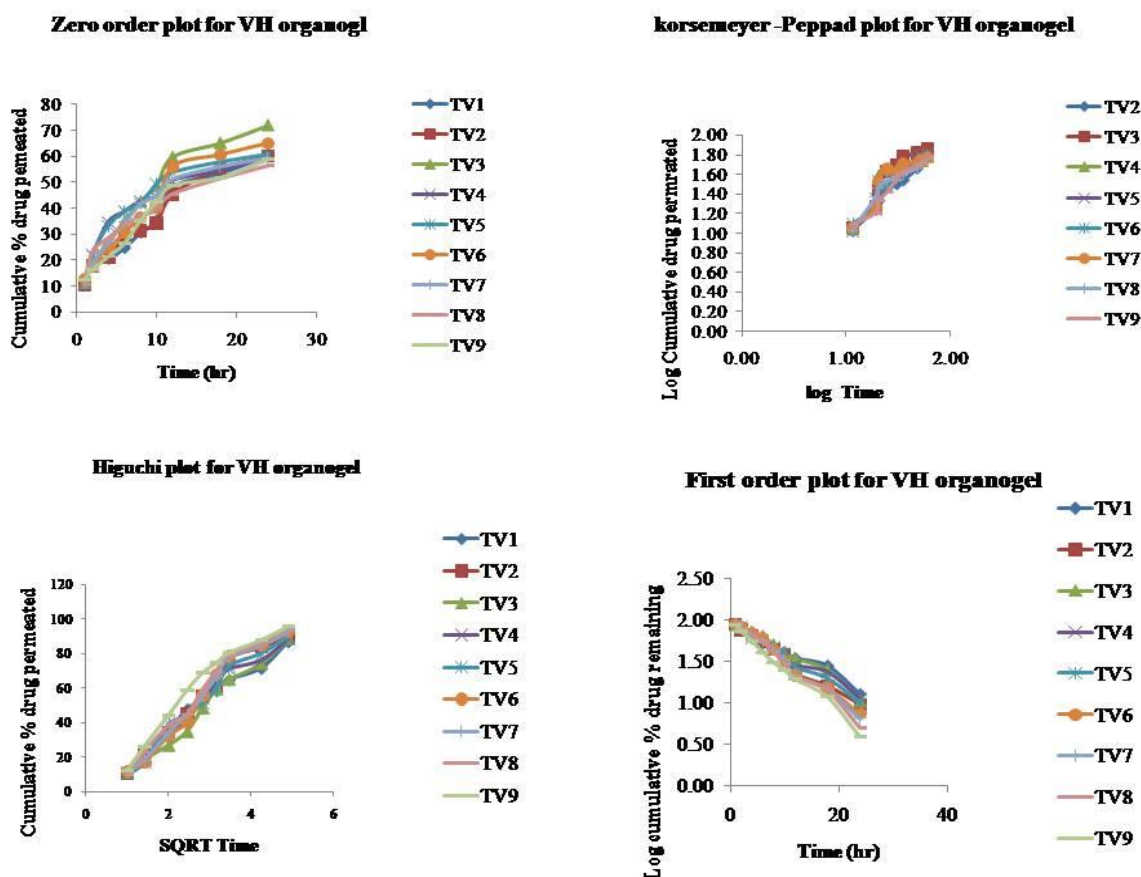
Fig. No. 1: Kinetics of drug release for formulations of verapamil hydrochloride organogel
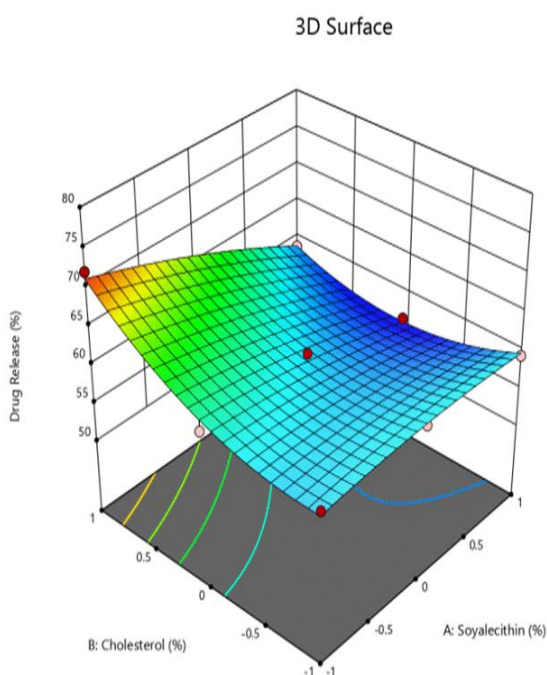
Fig. No. 2: Response Surface plot and Counter Plot for verapamil hydrochloride organogel
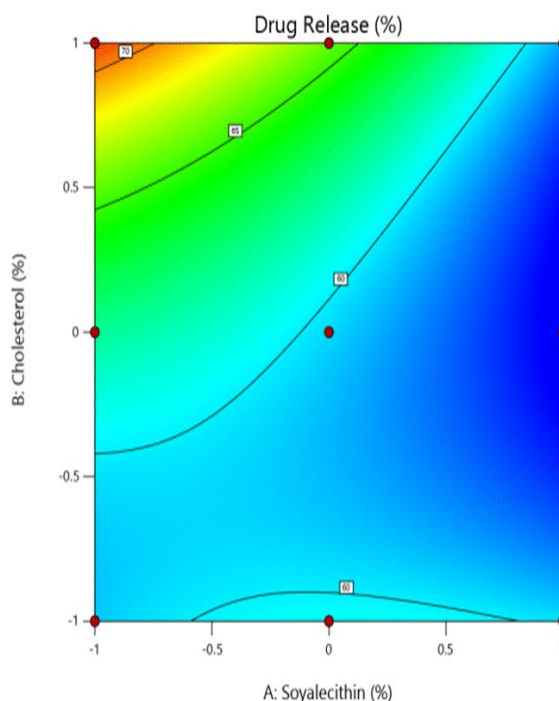
CONCLUSION:

Pluronic organogel was thought to penetrate into skin, interact and disorganize the lipid to penetrate the lipid layers of stratum corneum. However, improved topical drug delivery has been attributed to the biphasic drug solubility, the desired content and modifications of skin barrier function by the organogel components. The finding of the present study suggest that the prepared verapamil hydrochloride organogel containing Pluronic Lecithin were observed to be safe, stable drug delivery system and hold promise for improved bioavailability and better management of hypertension on long term basis. The optimized formulation of organogel

should be carried out on human volunteers to confirm improved pharmacokinetic parameters.

Conflict of Interest: Nil

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