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FORMULATION AND EVALUATION OF PRONIOSOMAL TRANSDERMAL GEL OF DITHRANOL

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ABSTRACT

The current study was undertaken to prepare and evaluate proniosomal transdermal gel of dithranol. Dithranol (DTH) is a drug which used in the treatment of psoriasis. Proniosomal transdermal gel has prolonged delivery and more importance because the proniosomes are more stable than existing liposomes and niosomes. simultaneously, gel based formulations are better dermal absorption than other preparation such as already existing creams and ointment preparation. Therefore, transdermal gel of dithranol was prepared using different surfactant and incorporated gel base polymers such as Carbopol 934. The study encompasses compatibility studies using DSC spectra, drug content, viscosity, spreadability, and rheological consideration. Optimization of formulation was subjected to 3^2 full factorial designs by Design Expert 9.0.1 Version software. Additional, the optimized formulation was evaluated by Rheological parameter and *ex vivo* diffusion study. Formulation batch DPNS6F8 was containing Carbopol 934, Span 60 and cholesterol (act as permeation enhancer) showed 89.80 % PDE and drug Flux 9.89 ($\mu/cm^2/h$). Stability studies conducted under accelerated condition were shown acceptable results. It was concluded that surfactant span 60 produced better results than other grade of Span with combination of cholesterol. Proniosomes incorporated in Carbopol gel containing dithranol showed good consistency, spreadability, homogeneity as well as stability. Proniosomal transdermal gel had wider prospect for treatment of Psoriasis.

KEY WORDS: DTH: Dithranol, Proniosomes transdermal gel, Niosomes, Psoriasis.

INTRODUCTION

Transdermal gel preparations are projected for external skin application or to some mucosal surfaces for local action or skin penetration of medicament or for their soothing or protective action [1]. Transdermal application of gels at pathological sites offer great advantage in a faster release of drug directly to the site of action, independent of water solubility of drug as compare to creams and ointments [2,3]. Present time the various treatments available but topical therapies is the most widely used approach, avoiding the possible toxicity issues associated with systemic therapy or phototherapy of psoriasis [4] . Psoriasis is mainly affected of the skin tissue so that it has been rationally suggested to target the afflicted site locally without harming other tissues or organ of body. The aim of this study is to investigate the viability of using proniosomes as a transdermal drug delivery system by dithranol for treatment of psoriasis. The epidermal layer of skin, the Stratum cornified layer, forms a strong barrier to most exogenous substances including drugs. The barrier layer differentiates keratin rich epidermal cells (corneocytes) are embedded in an intercellular lipid-rich matrix[5, 6]. Psoriasis is also a skin disorder characterized by hyperproliferation and abnormal differentiation of the stratified epidermis of skin [7]. In between year 2003 to 2011, National Psoriasis Foundation reported through survey of US patient of psoriasis and decided psoriatic patient have not taken proper treatment for controlling the disease [8].

A diversity of topically preparation of antipsoriatic drug is available in the market. But dithranol, regarded as old and a ‘‘Gold Standard’’ drug for the topical treatment of the disease owing to its promising antipsoriatic activity [9]. In spite of its effectiveness in topical therapy, the drug is not relatively widely accepted by patients owing to its strong tendency to cause skin irritation, erythema, peeling and staining. The drug also creates problems in formulation development due to its lipophilic nature and photo sensitivity of drug. Several efforts have been made in the past to improve upon the patient acceptance of this sensitive drug molecule, including the usage of liposomes [10]. A scientific approach, proniosomes derived niosomes are promising drug carriers as they possess greater stability and lack of many disadvantages associated with liposomes, such as high cost and the variable purity problems of phospholipids [11]. Proniosomes are novel preparation as provesicular carriers composed of non ionic surfactant Span and Tween and phospholipids in the form of gel preparation. Liposomes and niosomes owing to their low physical stability such as aggregation, fusion and leaking and to provide additional convenience in transportation, distribution, storage and dosing etc [12]. In order to minimize the problems associated with

vesicular preparation, provesicular system was prepared. Proniosomes are formulation composed by nonionic surfactants and can be converted into niosomes immediately before use, by hydration on skin surface [13]. Encapsulation of dithranol with the non ionic surfactant and phospholipids can accordingly considerably enhance its permeation across skin and retention in the skin tissues with improves the drug stability.

MATERIALS AND METHODS

Dithranol IP (DTH; M/s Agon Pharma Pvt. LTD. India), As a Gift Sample, Span (Ranbaxy Fine Chemical Limited, New Delhi.) and Cholesterol (Loba Chemie Pvt., Mumbai-400002, India), Carbopol 934, HPMC (Hydroxypropyl methyl cellulose) (Himedia Laboratories Pvt. Ltd. Mumbai, India) were provided by the SRGI Jhansi (UP). All other ingredients used in various studies were of analytical grade and were employed as such as procured. Double distilled water was used during the experiment. DEROBIN® 1.15% Vardhaman Remedies Pvt. Ltd. was purchase from local drug store.

1. Preformultaion Studies

Preformulation may be illustrated as a stage of the research and development process where characterized the physical, chemical and mechanical properties of drug substances, to facilitate develop stable, safe and effective dosage forms. During this preparation, possible interaction with various inert ingredients intended for use in final dosage form was also considered in the present study [14]. The compatibility Studies by DSC thermograms of pure drug and its physical mixture with polymers (span, cholesterol and lecithin) were carried out to investigate any possible interaction between the drug and the polymer. The heat is from 30.00°C to 350.00°C at 10.00°C/min rate using Differential Scanning Calorimeter (Jade DSC).

2. Analytical Method Development

Determination of the λ max of DTH was determined prior to developing the standard curves. In this study 10 µg/mL solutions of DTH were prepared in dichloromethane scanned for maximum 200 to 400 nm wavelength range. After that prepared Calibration curve was developed of DTH in dichloromethane and phosphate buffer pH 7.4.

3. Preparation of Dithranol Loaded Proniosomes (DLP)

Proniosomes were prepared by Coacervation phase Separation method [15, 16]. Accurately weighed surfactant, cholesterol and drug with Lecithin, Alcohol (0.5 ml) were in a dirt free

dry and wide mouth small glass tube. Subsequent to mixing all the ingredients, the open end of the glass tube was enclosed with a lid to escape loss of solvent, and then heat on a water bath at 60–70 ^{0}C for about 5-6 minute. When the surfactants were dissolved entirely after that added aqueous phase (phosphate buffer 7.4) and warmed on a water bath until an apparent solution was produced. For conversion to proniosomal gel this mixture was permitted to cool at room temperature. Add the antioxidants as sufficient amount in all the formulations such as sodium metabisulphite (0.5% w/w) and BHT (2.0% w/w) for prevention of oxidation of dithranol [10]. Preparation of equivalent gel of PNS containing 1.0% w/w dithranol by carried out using by polymeric gels Cabopol (carbomer 934) and HPMC (Hydroxypropyl methyl cellulose) at a ratio of 2:1, this ratio of gel containing high viscosity gel and most excellent drug diffusion [17].

4. Experimental Design With Statistical Analysis

A **3^2** randomized full factorial design was performed by taken as independent and dependent variables. The independent variables are amount of span (A) and cholesterol (B) and dependent variables are entrapment efficiency Y1, and drug permeation Y2. The factors were calculated by low, medium and high, at 3 levels indicating **(−1, 0, +1**) respectively (Table1). Different formulation optimized with the help of software such as Design Expert 9.0.1 (Stat-Ease Inc.USA) was used for statistical optimization of proniosomes gel. The software performs response surface methodology (RSM) which includes the multiple regression analysis (MRA), ANOVA and statistical optimization [18, 19].

Table1. Relationship of Independent Variables and Actual Levels

Factor	Value in mg		CODE
	SPAN 60	Cholesterol	
Low	50	20	-1
Medium	100	40	0
High	150	60	+1

5. Characterization of Optimized Drug Loaded Proniosomal Transdermal Gel (PTG)

a) Particle Size Analysis

The particle size analysis of the formulations was performed using an optical microscope with stage micrometer. The Proniosomes of DTH particles was shown in figure1.

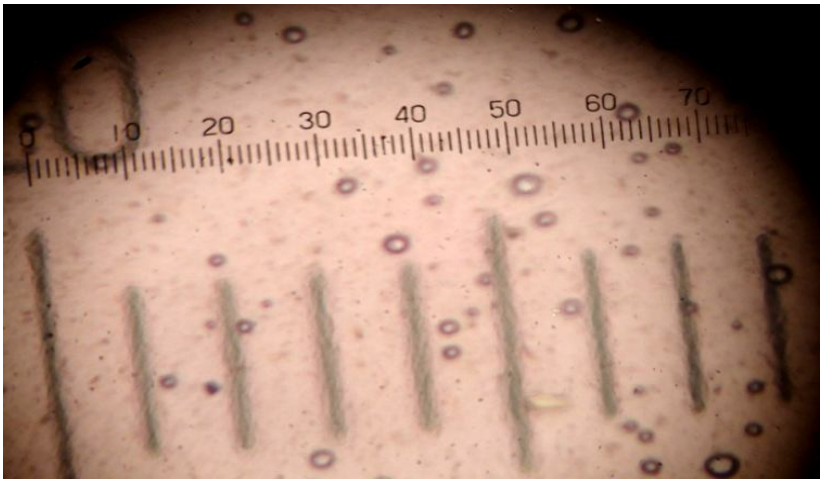


Fig.1 Optical Photo Micrograph of Proniosomes

b) Entrapment Efficiency

Entrapment efficiency determination of DTH in proniosomes were performed by separation of free drug through centrifugal mechanism, proniosomal gel were weighed 100 mg in a glass tube and 10 ml of the phosphate buffer pH 7.4 (aqueous phase). This aqueous suspension was sonicated by sonicator. This sample were added in chloroform and warmed to dissolve drug completely after that treated with dimethyl formamide (DMF) which dissolved only dithranol not other encapsulated drug and filter the solution. Free drug were spectrophotometrically determined by un-entrapped liquid of supernatant which was obtained after ultra-centri-fugation assayed at 257 nm [20]. The encapsulation efficiency (EE) was calculated by the following equation

$$\% \, EE = \frac{Mass\ of\ entrapped\ drug\ in\ PNs}{Total\ mass\ of\ drug\ added} \times 100$$

c) Drug content

A precise quantity (100 mg) drug loaded PTG was taken and dissolved in 250 ml of mixture of PBS pH 7.4 and dichloromethane in volumetric flask. Drug loaded solution was shaken on mechanical shaker to facilitate complete dissolving of drug, for 2 hour. Dissolved drug was separated by filtration by membrane filter. Filtrate was analysed on UV spectrophotometer at 257 nm by mixture of PBS and dichloromethane as blank [21]

$$\% \, Drug\ Content = \frac{Mass\ of\ Drug\ in\ PTG}{Total\ mass\ of\ PTG} \times 100$$

d) Zeta Potential

Horiba nano particle analyzer was used for Zeta potential on particle surface. There are three paths by which a solid particle (colloid) dispersed in a liquid media can get hold of a surface charge ions present in the solution adsorbed on the surface, through particle's surface functional groups ionization, dielectric constant difference in between the particle and the medium[22].

e) Spreadability

Spreadability is expressed to indicate the degree of area to which PTG quickly spreads on application. Spreadability was calculated by wooden block and glass slide apparatus. About 5 gm weights were put on the pan and notice time for upper slide (movable) to separate totally from the permanent slide. The following formula was used for calculating spreadability.

S = M.L / T

Where,

S = Spreadability, M = Weight tied to upper slide, L = Length of glass slide, T = Time taken to separate the slide completely from each other

f) Homogeneity

Gel preparations were checked for their appearance and existence of any aggregate in product. This were done by visual examination following the prepared gels have been position in the container.

g) Ex -Vivo Permeation Studies

Permeation of proniosomal transdermal gel (PTG) of DTH was determined through using Franz diffusion cell. The Wistar rat (7–9 weeks old) skin was used, whole skin equilibrated in phosphate buffer solution (pH 7.4) for 1 hour before the experiment. The rat skin was mounted on the receptor compartment with the dermis facing the receptor compartment and the stratum corneum side facing into the donor compartment. The donor compartment was charged with the preparation [23]. A 10 ml aliquot of dichloromethane and pH 7.4 phosphate buffers as 40:60 % v/v was used as receptor medium, at 37± 0.5 ^{0}C temperature as replicate of human blood and to maintain a sink condition. The diffusion area of cell membrane was 2.54 cm^2. The receptor compartment was constantly stirred at 100 rpm by a magnetic bead. 1 ml samples were taken from the receptor fluid at different time intervals up to 24 hrs and replaced immediately by fresh buffer solution. The samples were analyzed by

spectrophotometically at 257 nm. The drug permeation mechanism and flux value calculated by direct slope value of graph, plotted between amounts of drug permeated per unit area against time.

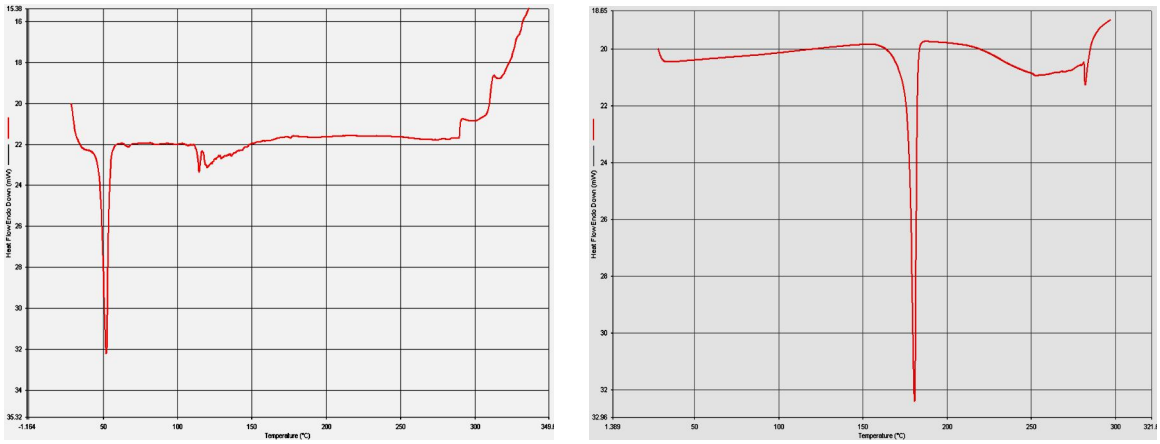
h) Stability Study

Coherent design and evaluation of proniosomes as transdermal preparation of drugs, stability of the active component must be a major standard in determining their approval or refusal. Stability of the drug can be defined as the ability of a particular formulation, in a specific storage, to remain within its physical, chemical, therapeutic and toxicological requirement. The stability test requirements for drug Stability studies as per ICH guidelines. Sealed glass ampoules (three each) were stored for this task at 5± 2^{o}C in refrigerator, 25± 2^{o}C, and 40± 2^{o}C for a period of at least 8 weeks in dark place [24].

RESULTS AND DISCUSSION

1. Preformultaion Studies

The DSC thermograph of DTH exhibits endothermic peak at 170 °C corresponding to its melting point. Drug with excipient exhibits peak at 50°C. This peak occurs due to phase transition temperature peak of Surfactant exhibits peak at 50 °C. So, results indicate that interaction occurs between drug and Excipients.



(a) **(b)**

Fig.2. a) DSC Spectra of Dithranol Excipients mixture b) Pure Dithranol drug

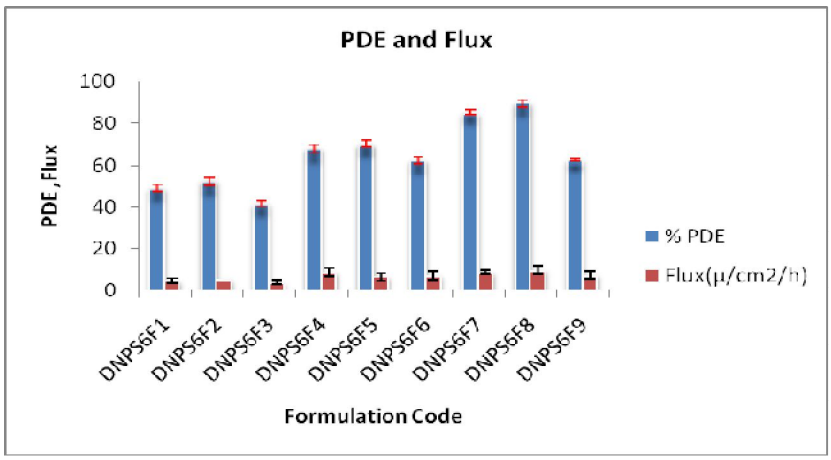
2. Analytical Method Development

UV Spectroscopy analytical method for DTH was developed. For that different dilution of drug was prepared in dichloromethane. λ_{max} of solutions were found out by UV spectrophotometer which were 257 nm of solution of DTH. The R^2 values were for

dichloromethane solution and with mixture of phosphate buffer and dichloromethane was found 0.998, 0.994 respectively. After detection of partition coefficient this was confirm that DTH is lipophilic in nature.

3. Preparation of Dithranol Loaded Proniosomes (DLP)

The Proniosomal of dithranol was prepared using Coacervation phase separation method. Total nine formulations were prepared with different ratio of non ionic surfactant Span and Cholesterol table other ingredients remain constant Subsequently, prepared nine formulations were designed with 3^2 factorial designs by Design Expert 9.0.1 version software.



**Each value represents the mean value ± SD (n=3)*

Fig.3 PDE and Flux Measurements of Formulation Batches of DNPS6F1 To DNPS6F9

4. Experimental Design and Statistical Analysis

The objective on preface studies non ionic surfactant Span 60 and Cholesterol were chosen for preparation of PNS of dithranol. A **3^2** full factorial design was selected as it helps study the effect on response parameters by changing both variables concurrently with a least number of experimental runs. The PDE and Flux for the 9 batches (DNPS6F1 to DNPS6F9) showed an extensive variation and 41.7 to 89 % and 4.12 to 9.89; respectively (Figure 3). This data obviously indicated strong dependence of response variables such as PDE and Flux on the preferred independent variables shown in table 2.

Multiple Regression Analysis

To facilitate quantify on the response parameters by the effect of formulation variables, this was compulsory to fitting a mathematical model so that predicting values of response parameters perform statistical analysis and generates different polynomial equations for

different models, with interacting terms and regression coefficients, useful in evaluating the responses.

$Y = k + b_1A + b_2B + b_{12}AB + b_{11}A^2 + b_{22}B^2$

Where Y is the response evaluated, k is the intercept; b_1 to b_{22} is the five coefficients of independent variables.

Table2. Formulation response in 3^2 Factorial Design for DTH Proniosomal Gel

Proniosomes code DNPS6	Variable			
	INDEPENDENT		DEPENDENT*	
	Surfactant	Cholesterol	% EE	Flux(µ/cm^2/h)
F1	50	20	48.7±1.86	4.82±1.23
F2	50	40	52.2±1.92	5.25±0.065
F3	50	60	41.7±1.44	4.12±1.06
F4	100	20	67.7±2.01	8.86±2.01
F5	100	40	69.6±1.98	6.65±1.85
F6	100	60	62.4±1.65	7.25±2.30
F7	150	20	84.4±2.11	8.89±1.085
F8	150	40	89.8±1.35	9.89±1.89
F9	150	60	62.8±0.30	7.56±2.10

Each value represents the mean value ± SD (n=3)

Table3. ANOVA analysis on PDE (Percentage drug entrapment)

ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob > F**	
Model	1922.96	5	384.59	14.93	0.0249	**significant**
A-SURFACTANT	1485.23	1	1485.23	57.64	0.0047	
B-CHOLESTROL	191.54	1	191.54	7.43	0.0722	
AB	53.29	1	53.29	2.07	0.2460	
A^2	21.78	1	21.78	0.85	0.4257	
B^2	171.12	1	171.12	6.64	0.0820	
Residual	77.30	3	25.77			
Cor Total	2000.26	8				

In this Model F-value of 14.93 implies the model is significant. There is only a 2.49% chance that an F-value this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. We can say A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant.

Table4. Value of r^2 for PDE

Std. Dev.	5.08	R-Squared	0.9614
Mean	64.37	Adj R-Squared	0.8969
C.V. %	7.89	Pred R-Squared	0.5813
PRESS	837.45	Adeq Precision	10.318

The "Pred R-Squared" of 0.5813 is not as close to the "Adj R-Squared" of 0.8969 as one might normally expect; i.e. the difference is more than 0.2. This may indicate a large block effect or a possible problem with this model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doing confirmation runs."Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 10.318 indicates an adequate signal. This model can be used to navigate the design space.

Table5. Value of Coded Factors for Pde

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	72.73	1	3.78	60.69	84.77	
A-SURFACTANT	15.73	1	2.07	9.14	22.33	1.00
B-CHOLESTROL	-5.65	1	2.07	-12.25	0.95	1.00
AB	-3.65	1	2.54	-11.73	4.43	1.00
A^2	-3.30	1	3.59	-14.72	8.12	1.00
B^2	-9.25	1	3.59	-20.67	2.17	1.00

Final Equation in Terms of Coded Factors

PDE = +72.73+ 15.73*A-5.65*B-3.65*AB -3.30*A^2-9.25*B^2

Final Equation in Terms of Actual Factors

PDE = +12.2333+ 0.72467*SURFACTANT-1.93250*CHOLESTEROL-3.65000E 003*SURFACTANT* CHOLESTEROL -1.32000E-003* SURFACTANT^2-0.023125* CHOLESTEROL^2

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor.

Table6. ANOVA analysis on FLUX

ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob > F**	
Model	28.53	5	5.71	4.97	0.1087	not significant

A-SURFACTANT	24.60	1	24.60	21.41	0.0190	
B-CHOLESTROL	2.21	1	2.21	1.92	0.2597	
AB	0.099	1	0.099	0.086	0.7880	
A^2	1.38	1	1.38	1.20	0.3527	
B^2	0.24	1	0.24	0.21	0.6785	
Residual	3.45	3	1.15			
Cor Total	31.98	8				

The Model F-value of 4.97 implies the model is not significant relative to the noise. There is a 10.87 % chance that an F-value this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant.

Table7. Value of r^2 for FLUX

Std. Dev.	**1.07**	**R-Squared**	**0.8922**
Mean	7.03	Adj R-Squared	0.7126
C.V. %	15.24	Pred R-Squared	0.1418
PRESS	27.45	Adeq Precision	6.013

The "Pred R-Squared" of 0.1418 is not as close to the "Adj R-Squared" of 0.7126 as one might normally expect; i.e. the difference is more than 0.2. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doing confirmation runs. "Adeq Precision" measures the signal to noise ratio.

Table8. Value of Coded Factors For FLUX

Factor	**Coefficient Estimate**	**df**	**Standard Error**	**95% CI Low**	**95% CI High**	**VIF**
Intercept	7.82	1	0.80	5.27	10.36	
A-SURFACTANT	2.03	1	0.44	0.63	3.42	1.00
B-CHOLESTROL	-0.61	1	0.44	-2.00	0.79	1.00
AB	-0.16	1	0.54	-1.86	1.55	1.00
A^2	-0.83	1	0.76	-3.24	1.58	1.00
B^2	-0.35	1	0.76	-2.76	2.07	1.00

Final Equation in Terms of Coded Factors

FLUX = +7.82+ 2.03*A-0.61*B-0.16*AB -0.83*A^2-0.35*B^2

Final Equation in Terms of Actual Factors

PDE = -0.36222+ 0.11333*SURFACTANT+0.054750*CHOLESTEROL-1.575000E 004*

SURFACTANT* CHOLESTEROL -3.32667E-004* SURFACTANT^2-8.66667E-004* CHOLESTEROL^2

Since the r^2 values of are relatively high for both the responses, i.e., 0.9614 for PDE and 0.8922 for FLUX, the polynomial equations form a best fit to the experimental data and are highly statistically valid table 4 and 7. Response surface plots for each response constraint were constructed by three-dimensional structure to determine the effects of both variables concurrently along with the performance of the system.

Fig. 4 and Fig. 5 shows response surface plot for PDE and Flux, respectively. In Fig.4, it can be observed that effect of variation in ratio of surfactant and cholesterol level had opposite effect on PDE i.e. Entrapment efficiency. Surfactant was shown positive effect and cholesterol shown negative effect. Reason that when raise in the concentration of surfactant could increase the number of niosomes hydrophobic domain therefore increases in entrapment efficiency but some limitation, Simultaneously, negative effect of higher level of cholesterol on PDE that due to the reason that a cholesterol particle will compete with drug for the same space within the bilayer and eliminate the drug from the bilayer and also to this will interrupt the vesicular membrane structure [25,26]. In Fig. 5, It can be observed that increase the concentration of cholesterol level had decreased on Flux and opposite effect was shown with surfactant.

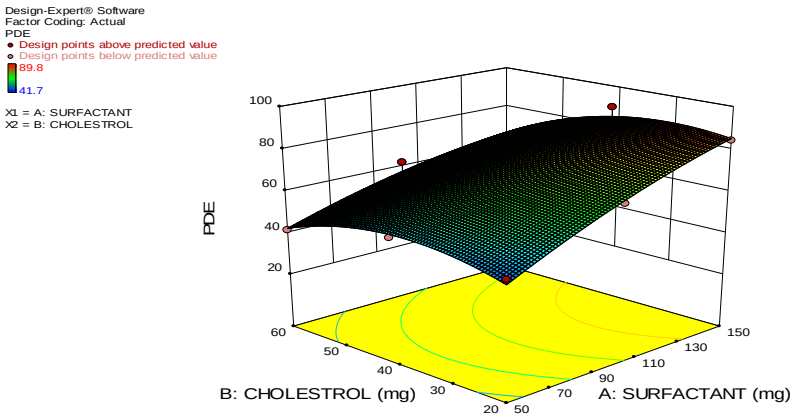


Fig.4 Three-Dimensional Response Surface Plots For PDE

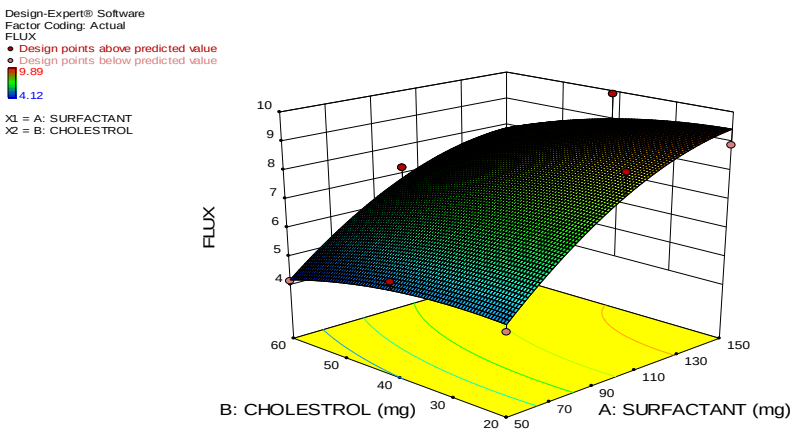


Fig.5 Three-Dimensional Response Surface Plots For Flux

5. Characterization of Optimized Drug Loaded Proniosomal Transdermal Gel (Ptg)

Particle Size

The particle size of proniosomal transdermal gel formulations ranges from 1759 to 4032 nm.

Drug Content

Drug content describes the consistent distribution of drug in the preparation. Percentage drug content was measured for all DTH proniosomal transdermal gel and found out range of percentage 60-98.99 %.

Zeta Potential Determination

Zeta potential of optimized formulations is shown potential stability of PTG dispersion. Result of data was shown that zeta potential tends to be more negative and repels to each other, with more stability. Result found that -44.5 mV and formulation also shown good stability as shown in fig 6

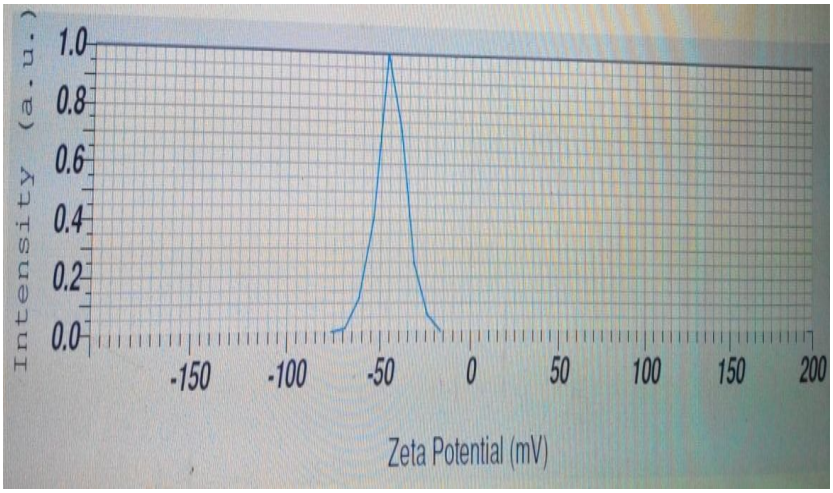


Fig.6 Peak of Zeta Potential Determination

Spreadability

Better quality for PTG this should is fulfilling the ideal capacity is that it must hold the good spreadability. Spreadability value of all optimized PTG formulations ranged from 12.4 to15.3 g.cm/sec. Spreadability values were shown that the PTG is spread without difficulty.

Homogeneity

Optimized all preparations were shown that high-quality homogeneity without noticed of bulges and clear and transparent vision.

Ex-Vivo Drug Permeation Study

Permeation flux increased through skin with increase in non ionic surfactant and cholesterol concentration because disturb the structural composition of stratum corneum and promote the thermodynamic properties of the drug as well as skin vesicles partitioning. The proniosomal gel of optimized formulations (DNPS6F7, F8, and F9) and a marketed Derobin ointment 1.15 % were demonstrate for their drug permeation via rat skin and the results are reported in Figure. Rising the cholesterol level create in a best intact lipid bilayer same as a barrier layer for drug release and decreased its leakage by enhance the fluidity of the lipid bilayer and dropping its permeability, which result to reduce drug elution from the PTG.

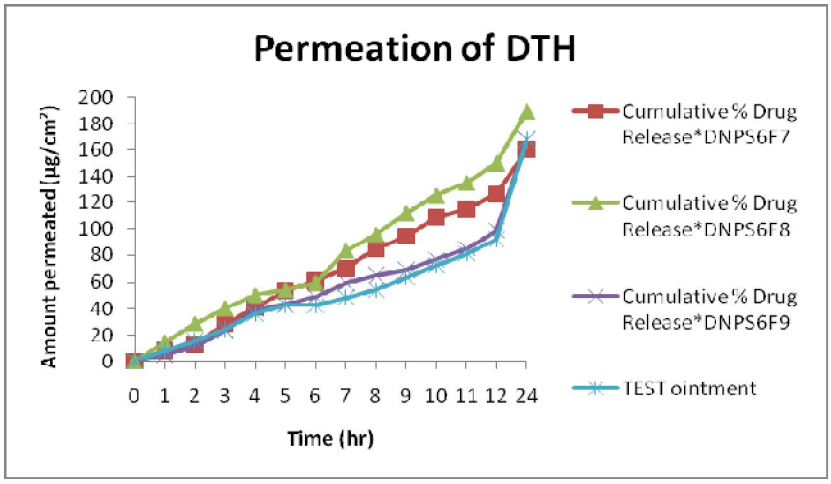


Fig.7 *Ex-Vivo* Drug Permeation study of DNPS6F7, F8, and F9 and Test ointment

6. Stability Study

The physical appearance showed that it does not show any changes in compare of the freshly prepared formulation. The percentage drug retained (PDR) was evaluated on 15th, 30th, 45th 60th day shown in the table that there are no significant changes in the drug entrapment during the storage for 60 days in all conditions. In this study, the per cent drug retained was

found in range 98.59 to 88.43 of DTH content after storage of 60 days at low to higher temperature respectively, (Figure 8). However, the drug content remained relatively above 85%, the lower limit of acceptance as per British Pharmacopoeia guideline. However, the formulation is more stable at low temperature compared to room or exceed temperature.

Table 9. Stability Study of Optimized Formulation DNPS6F8

Percentage drug retained (PDR)			
DAYS	**5°C ± 2°C**	**25°C ± 2°C**	**40°C ± 2°C**
15	98.59	98.79	98.46
30	98.54	98.22	98.02
45	98.08	97.12	89.12
60	97.86	95.12	88.43

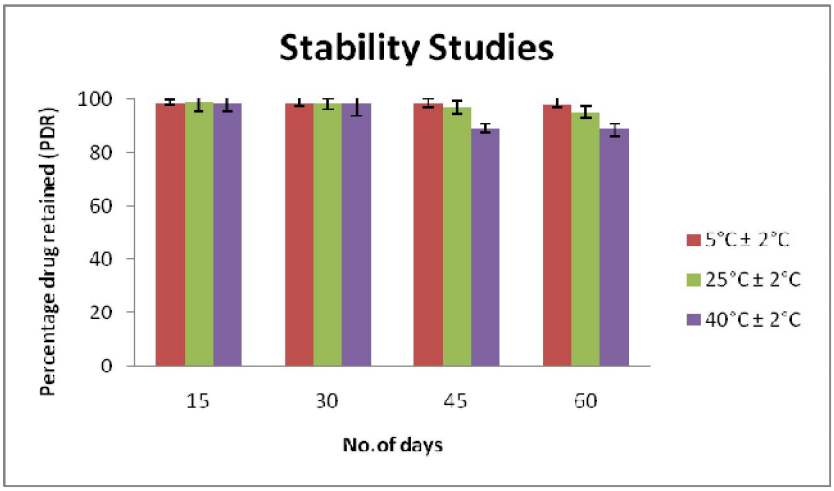


Fig.8 Stability Study of Optimized Formulation DNPS6F8 [*Each Value Represents the Mean Value ± SD (n=3)]

CONCLUSIONS

The current researches unambiguously confirm the enormous potential of proniosomes in accomplishment of high skin permeation flux of DTH and with potential optimized formulation devoid of any skin irritation. DTH is the old and gold drug in the treatment of psoriasis. PTG of DTH was prepared with aim to deliver the drug via transdermal route and evaluated for their efficiency to form a transdermal gel. Different parameters studied were carried out for PTG formulations. Nonionic surfactant span 60 with cholesterol and use for gel composition Carbopol 934 was found to be suitable for better consistency, viscosity, spreadability, homogeneity, and Ex-vivo drug diffusion. The relevance of 3^2 factorial designs establishes to be a useful tool for optimization of DTH-PTG. The results of the ex-vivo

penetration studies confirmed that about a deep penetration of DTH with localization in skin as compared to existing marketed preparation.

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