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DESIGN AND EVALUATION OF DIACEREIN PRONIOSOMAL GEL FOR ENHANCED TOPICAL DELIVERY

Swathi Krishna C.* and Sujith S. Nair

Department of Pharmaceutics, Crescent College of Pharmaceutical Sciences, Payangadi P O Kannur-670358, Kerala, India.

***Corresponding Author: Swathi Krishna C.**

Department of Pharmaceutics, Crescent College of Pharmaceutical Sciences, Payangadi P O Kannur-670358, Kerala, India.

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ABSTRACT

Proniosome are microscopic lamellar structure, they combine a non-ionic surfactant and cholesterol followed by hydration in aqueous media. Diacerein is NSAID with short half-life 4hr and undergo first pass metabolism such that only 35-56% of administered dose reaches systemically. The primary objective of the research is to create a proniosomal gel that enhances transdermal delivery and improves drug availability, by using a Central composite design to statistically optimize the formulation. The goal is to investigate how the addition of non-ionic surfactant and cholesterol can increase drug entrapment and release. The proniosomal gel containing Diacerein was made through a coacervation phase separation method using Span 60, cholesterol, and other ingredients. By using the central composite design, the impact of the components on the physicochemical properties of the proniosomes was examined, and the best formulation was identified. The findings showed that the optimal combination of surfactant and cholesterol resulted in high-quality proniosomes with sustained drug release. The optimal cholesterol and span 60 content level were determined to be 1860.761mg and 309.693mg, with a maximum desirability value 0.969. The entrapment efficiency, % drug release and vesicle size of the optimized formulation was found to be 95.3998%, 96.8901% and 5.5752 respectively. This study has demonstrated that the problem of poor Diacerein absorption can be resolved through the use of the proniosomal gel formulation. Furthermore, the concentration of both cholesterol and the non-ionic surfactant was found to be highly significant in terms of enhancing drug entrapment efficiency and drug release.

KEYWORDS: *Diacerein, proniosomal gel, span 60, cholesterol.*

INTRODUCTION

In recent times no single delivery system fulfils all the criteria, but attempt have been made through novel approaches. Many novel approaches emerged covering various routes of administration, to achieve their controlled or target drug delivery. The prime aim of novel drug delivery is maintenance of the constant and effective drug level in the body and minimizing the side effects and it also localizes the drug action by targeting the drug delivery by using drug carriers.[1] Transdermal therapeutic systems are recently developed device, which are non-invasive to skin as compared to other routes. Although the skin, particularly the stratum corneum presents a barrier for the various type of transdermal therapeutic system are utilized for long term continuous infusion of therapeutic agents including anti-hypertensive, anti-fungal, analgesic, steroids and contraceptive drugs.[2] Transdermal route bypasses the GI tract hence avoiding the gastric irritation, reduces number of dose, improved patient compliance, enhanced bioavailability and can maintain the constant and effective drug level in the body with simultaneous minimization of side effect. Various transdermal delivery system includes liposomes, erythrosomes, liposomes, niosomes and proniosomes.[3]

Proniosomes are dry formulation of surfactant-coated carrier, which can be measured out as needed and re-hydrated by brief agitation in hot water. These proniosmes minimize problems of noisomes physical such as aggregation, fusion and leaking and provided additional convenience in transportation, distribution, storage and dosing. Stability of dry proniosome is expected to be more stable than a pre-manufactured niosomal formulation. They are microscopic lamellar structure. They combine a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class of cholesterol followed by hydration in aqueous media. On the basis of method of preparation proniosomes are unilamellar or multilamellar.[1]

Osteoarthritis is a most common type of arthritis. It is connected with a crumbling of cartilage in the joints and can occur in nearly any joints in the body. It usually

occurs in the joints that carry weight on the hips, knees, and spine. NSAIDs are a class of drugs utilized to treat inflammation and pain but their utility become greater the risk of upper gastrointestinal adverse effects and does not later the underlying pathogenesis of articular disease thus have very little role in modifying disease course and boost quality of life. Diacerein is a drug used for the treatment of Osteoarthritis at a dosage of 50-100 mg twice a day; it retards the synthesis and activity of interleukin 1-β (inflammatory mediators in Osteoarthritis). Diacerein classified as BCS class II drug with a low solubility and high permeability, poor dissolution rate and low oral bioavailability were reported. Oral administration of Diacerein result in diarrhea.[4]

The main aim of the study is to develop and statistically optimize the proniosomal gel for enhanced transdermal delivery and improve the bioavailability using Central composite design and investigate the influence of both non-ionic surfactant and cholesterol to maximize the entrapment efficiency and drug release. Diacerein loaded proniosomal gel was prepared by co-acervation phase separation method using span 60, cholesterol and other excipients.[5]

MATERIAL AND METHODS

Materials

Chemical used

Diacerein (Yarrow chem products, Mumbai), span 60 (Sisco Research laboratories Maharashtra), Lecithin (Sisco Research laboratories Maharashtra), Cholesterol (Sisco Research laboratories Maharashtra), Carbopol (Loba Chemie).

Instruments used

Double beam UV Spectrometer, Electronic weighing balance (Price scale industries, Ahmedabad), Bruker alpha-Attenuated Total Reflectance FTIR.

Methods

Preformulation study

Preformulation study is the first step in the rational development of dosage form of a drug substance. It can be defined as an investigation of physical and chemical properties of drug alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable, effective and safe dosage form which can be mass produced. Obviously, the type of information needed depend on the dosage form to be developed.[6]

Determination of standard calibration curve of diacerein

10mg of Diacerein weighed and transferred in a 100ml standard flask. Then dissolved it with 10ml of phosphate buffer pH 7.4 and 10ml DMSO and made up the volume to 100ml with phosphate buffer 7.4 (stock solution). 10ml solution taken from the above stock solution 1 in a 100ml standard flask and made up to the volume to 100ml with phosphate buffer 7.4 (stock solution II). 2,4,6,8,10ml solution transferred from stock solution II to a series of 10ml volumetric flasks. The volume was made up with phosphate buffer pH 7.4. The absorbance of these solutions measured at 258nm against blank.[4]

Physicochemical properties of drug

Drug was tested for Color, Odor and Taste and Compared with official monograph.

Solubility of drug

Solubility test was conducted to determine its solubility in the diffusion medium and other solvents. Solubility of Diacerein was observed in different solvent such as distilled water, phosphate buffer pH 7.4, ethanol, methanol, and chloroform.

Drug- excipients compatibility

FTIR spectroscopy method was used to carry out drug-excipients compatibility study. FTIR spectra of pure drug, span 60, cholesterol, lecithin and their physical mixture were taken by KBr pellet technique between 400- 4000cm^{-1}. Once spectra were recorded, the peaks of pure drug, polymer and physical mixtures of polymers and drug were compared for incompatibility.[4]

Determination of melting point of pure drug

Melting point of compound help in the identification of sample and to establish its purity. It can be checked by placing the sample in a capillary tube and heated using melting point apparatus.[8]

Method of preparation diacerein loaded proniosomal gel

Proniosomes were prepared by the coacervation method. The drug with surfactant, lecithin and cholesterol were put in a wide mouth container (the composition is listed in table 1). To this absolute alcohol was added and container was covered with a lid to prevent loss of solvent from it. The above mixture was warmed on a water bath at 60-70°c until the surfactant mixture dissolve completely. Then to this phosphate buffer of pH 7.4 added, and the mixture was further added in a water bath for 2min. The above mixture was allowed to cool down at room temperature until the dispersion was converted to proniosomal gel.[5]

Table 1: Formulation design of Diacerein loaded proniosomal gel.

Formulation Code	Drug (mg)	Span60 (mg)	Cholesterol (mg)	Lecithin (mg)	Ethanol (ml)	Phosphate Buffer (ml)
F1	50	900	150	900	5	5
F2	50	1800	300	900	5	5

F3	50	900	450	900	5	5
F4	50	2700	450	900	5	5
F5	50	2700	150	900	5	5
F6	50	1800	300	900	5	5
F7	50	1800	300	900	5	5
F8	50	2700	300	900	5	5
F9	50	1800	150	900	5	5
F10	50	1800	300	900	5	5
F11	50	900	300	900	5	5
F12	50	1800	450	900	5	5
F13	50	1800	300	900	5	5

Entrapment efficiency

The Diacerein loaded proniosomal gel was hydrated with phosphate buffer and was sonicated in a sonicator. The formed Diacerein loaded niosomes were separated from unentrapped drug by centrifugation at 5000 rpm at 27°c for 45 min. The supernatant was taken and diluted with phosphate buffer. The Diacerein concentration in the resulting solution was assayed spectrophotometrically at 258nm. The percentage of drug encapsulated was calculated by the following equation.[5]

$$\% EE = [(C_t - C_f) / C_t] \times 100$$

Where C_t is the concentration of total Diacerein, and $C_{f\ is}$ the concentration of free Diacerein.

Vesicle size analysis

A small quantity of proniosomal gel was taken and suspended in 10 ml of PBS (pH 7.4). The dispersion of proniosome was manually shaken for few seconds so that lumps of proniosome are disintegrated in to individual proniosomes. A drop of dispersion was placed on to the slide and examined under the microscope at 100x magnification, circular vesicles bodies were observed with uniform small size.[8]

***In-vitro* diffusion studies**

In vitro release studies of proniosomal gel were performed using locally manufactured Franz-diffusion cell. The capacity of receptor compartment was 10ml. The dialysis cellophane membrane was mounted between donor and receptor compartment. The receptor medium was phosphate saline buffer pH 7.4. The receptor compartment was surrounded by a water jacket to maintain the temperature at 37.5±2°c. Heat was provided using a thermostatic hot plate with magnetic stirrer. The sample were withdrawn and were replaced by equal volume of fresh receptor. Sample withdrawn were analyzed spectrophotometrically at 258nm for the study of the drug release over a period of 12hr.[9]

Optimization by design expert stat ease software

Statistical design of experiment, a computer aided optimization technique, was used to identify critical factors, their interactions and ideal process conditions that accomplish the targeted response. The best formulation was determined using Design Expert State Software. Central composite design was used for the optimization. In this study span 60, cholesterol was selected as the two factors and percentage entrapment efficiency, vesicle size and in vitro drug release were considered as the responses. Hence, thirteen experimental trials were done. Countour plots were drawn and optimum formulation were selected by optimization criteria.[10]

Table 2: Factor combination by CCD for the formulation of diacerein proniosomal gel.

Formulation code	Point type	Coded factor level	
		X_1	X_2
F1	Factorial	-1	-1
F2	Central point	0	0
F3	Factorial	-1	+1
F4	Factorial	+1	+1
F5	Factorial	+1	-1
F6	Central point	0	0
F7	Central point	0	0
F8	Axial	+1	0
F9	Axial	0	-1
F10	Central point	0	0
F11	Axial	-1	0
F12	Axial	0	+1
F13	Central point	0	o

X_1- Span 60, X_2- Cholesterol

Scanning electron microscopy (SEM)
The surface morphology and size distribution of proniosome were determined by SEM. A double-sided tap was affixed on the aluminum stub, and the proniosomal powder was evenly spread over it. The aluminum stub was further kept in a vacuum chamber of SEM.[11]

Drug Release kinetics
In order to understand the exact mechanism of drug release from the dosage form, the data of *in-vitro* dissolution study of optimized formulation was fitted in various kinetics equations (zero order, first order, Higuchi model and Korsmeyer Peppa's model).[4]

***In-vitro* anti arthritic activity**
The activity was evaluated using albumin denaturation test. The reaction mixture was prepared which consist of 1ml proniosomal gel and 1ml of 1% bovine albumin solution. The prepared solution was incubated at 27±1°c for 15min. The reaction mixture was kept at 70°c in a water bath for 10min to induce denaturation. The solution was cooled and turbidity was measured spectrophotometrically. Percentage inhibition of denaturation was calculated using control. For this, marketed product was considered as standard and the solution containing no drug was considered as control.[12]
% inhibition of protein denaturation = 100× $[A_1 - A_2]$ / A_1
A1 = Absorbance of control
A2 = Absorbance of test

Stability studies
Stability study were carried out at temperature and humidity conditions as per ICH guidelines and the test were carried out in a stability chamber. The ability of vesicle to retain drug was assessed by keeping the proniosomal gel at three different temperature conditions, i.e., Refrigeration temperature 4-8°c, Room temperature 25±2°c at 60%±5% RH and oven temperature 40±2°c at 75% ±5% RH. Throughout the study the, proniosomal formulation were stored in aluminium foil-sealed glass vials. The sample were withdrawn at different time intervals over a period of 3 months and evaluated for entrapment efficiency, vesicle size and drug release.[13]

RESULT AND DISCUSSION

Calibration curve of diacerein

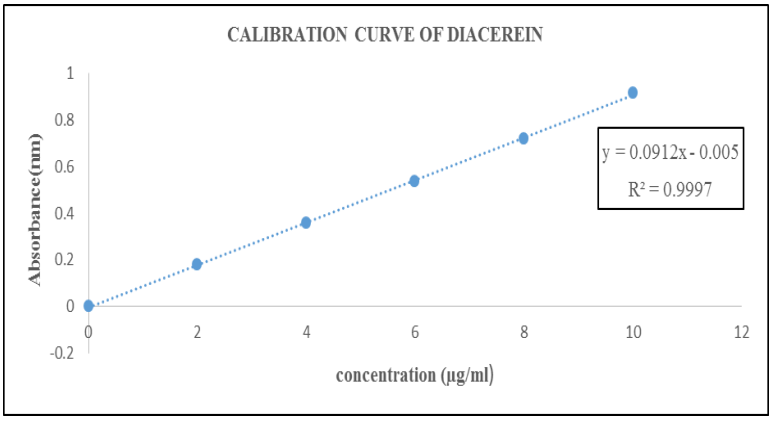

Fig. 1: Standard calibration curve of diacerein.

The drug was scanned in UV region (200-600nm) by preparing 1µg / ml solution using phosphate buffer pH 7.4 to find out wavelength of maximum absorption (ʎ max). The ʎ max was found to be 258nm. So, the standard calibration curve of Diacerein was developed at this wavelength. Standard calibration curve of Diacerein was determined in phosphate buffer pH 7.4 by plotting absorbance against concentration at 258nm. The calculation of entrapment efficiency, drug release and stability studies are based on this calibration curve.

Physicochemical properties of drug
Organoleptic properties of Diacerein was studied and it was concluded that, Diacerein is a fine yellow smooth powder odourless and bitter in taste.

Solubility studies were carried out in different solvent and it was found that Diacerein is sparingly soluble in phosphate buffer pH 7.4, slightly soluble in ethanol and insoluble in water, methanol and chloroform. The result complies with the pharmacopoeia specification.

Identification of compatibility by FTIR studies
FTIR studies were conducted in pure Diacerein, span 60, cholesterol, lecithin and physical mixture of drug with lecithin, span60, and cholesterol. The FTIR spectra shown below. Drug identification is done by performing FTIR studies. During FTIR studies, the peaks of Diacerein was obtained at 3069cm^{-1}(C-H stretching aromatic), 2837cm^{-1}(C-H stretching aliphatic),1764cm^{-1}(C=O stretching),1673cm^{-1}(COOH stretching), 1593cm^{-1}(C=C stretching) etc. There are no significant changes in the peak of the pure drug in the FTIR spectrum of physical mixture of pure drug with the polymers i.e., the span 60, cholesterol and lecithin. It indicates that there is no chemical interaction between the drug and the polymers. This shows that Diacerein was compatible with excipient.

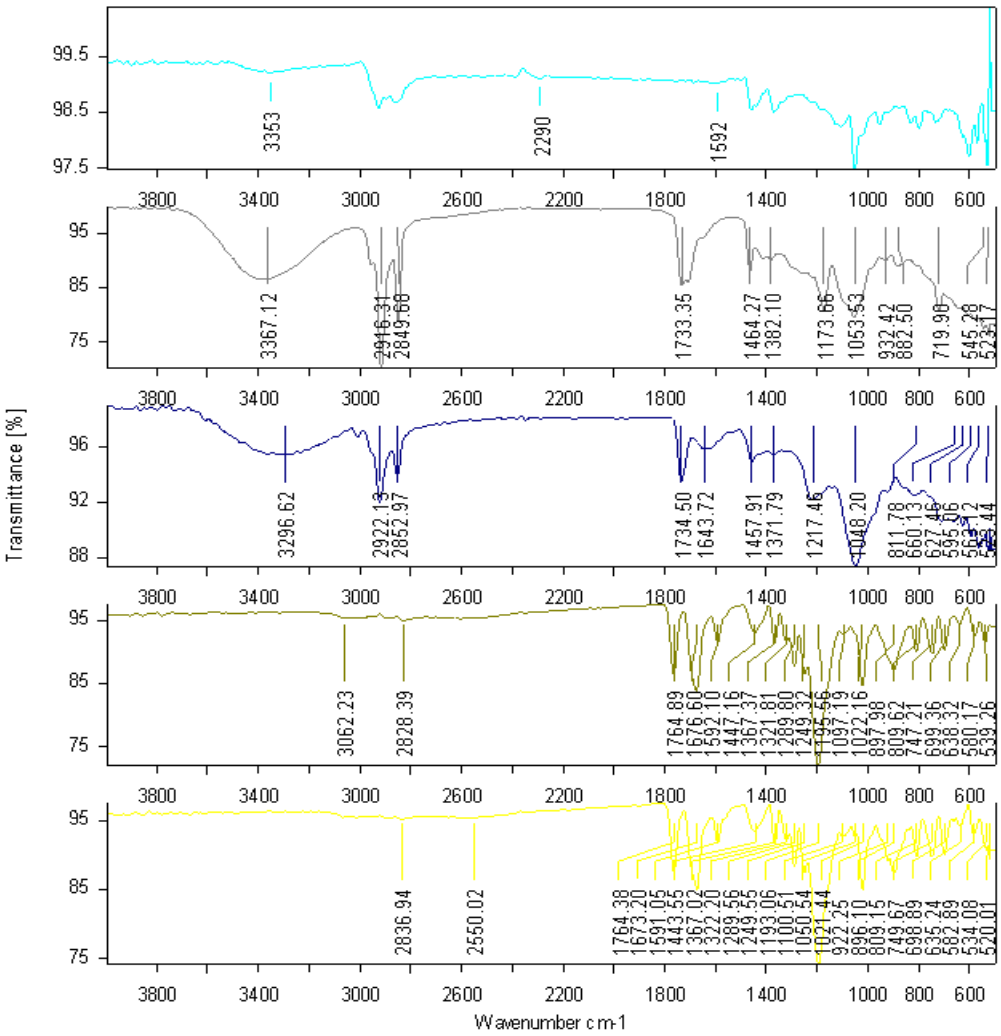

Fig. 2: Stacking report of FTIR.

Melting point determination

Melting point of Diacerein was found to be 220°c (n=3)

Percentage encapsulation efficiency

Table 3: Percentage encapsulation efficiency of formulation F1 - F13.

Sl. No.	Proniosomal Code	Encapsulation Efficiency (%)
1	F1	60.6023 ± 0.1284
2	F2	95.4053 ± 0.5481
3	F3	52.2267 ± 0.2842
4	F4	65.7708 ± 0.1584
5	F5	82.3463 ± 0.4821
6	F6	95.4053 ± 0.5481
7	F7	95.4053 ± 0.5481
8	F8	86.8763 ± 0.3158
9	F9	91.7233 ± 0.2184
10	F10	95.4053 ± 0.5481
11	F11	63.8263 ± 0.2879
12	F12	77.5213 ± 0.4698
13	F13	95.4053 ± 0.5481

All value expressed as mean of ± SD, n = 3

To investigate the influence of various concentration of span 60 and cholesterol on the Diacerein entrapment efficiency was determined. The result listed in table shows that the entrapment efficiency of these formulation varies from 52.2267±0.2842% - 95.4053±0.5481%. Here span 60 is taken as the non-ionic surfactant because it has a long unsaturated alkyl chain and highest phase transition temperature which provides the highest entrapment for drug. Vesicular entrapment efficiency is an important parameter that convey the stability of vesicles and this depends upon the amount of surfactant and cholesterol used. When the concentration of span60 varied from 900mg to 2700mg, the maximum and minimum entrapment efficiency were found. Variation in the concentration of surfactant from 900mg to 1800mg showed significant increase in entrapment efficiency, whereas further increase in concentration from 1800 mg to 2700 mg decreased the entrapment efficiency.

The cholesterol plays an important role in the entrapment of drug in the vesicles. The variation in the cholesterol significantly affect the entrapment efficiency. The observed entrapment efficiency was increased significantly when cholesterol amount was increased from 150mg to 300mg, but further increasing the cholesterol decreased the entrapment efficiency.

Vesicle size analysis

Table 4: Mean vesicle size of formulation F1 -F13.

Formulation code	Mean vesicle size(µm)
F1	5.8 ± 0.187
F2	5.2 ± 0.124
F3	8.3 ± 0.387
F4	6.7 ± 0.211
F5	9.8 ± 0.570
F6	5.2 ± 0.124
F7	5.2 ± 0.124
F8	7.4 ± 0.157
F9	10.2 ± 0.420
F10	5.2 ± 0.124
F11	7.9 ± 0.359
F12	6.1 ± 0.652
F13	5.2 ± 0.124

All value expressed as mean of ± SD, n = 3

The result of optical microscope under 100X was depicted in table showing that vesicles formed are spherical without any aggregation. Vesicle size ranges from 5.2 ± 0.124 to 10.2 ± 0.420µm. Both cholesterol and span 60 has significant effect on vesicle size. Increase in the surfactant concentration led to an increase in vesicle size and was attributed to the increase in the overall degree of hydrophilicity. The opposite held through with increasing the cholesterol amount that was associated with a decrease in the hydrophilicity of bilayers, thus limiting the water intake to the vesicle core and resulted in a subsequent decrease in mean vesicle size.

***In vitro* diffusion studies**

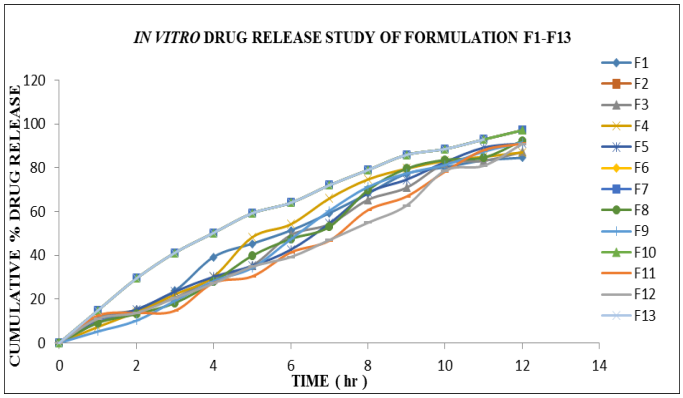

Fig. 3: *In vitro* drug release.

In vitro drug release studies were conducted for all the 13 formulations as shown in the fig.4. All of the formulation found to have a linear release and the formulation were found to provide approximately 90%

release with in a period of 12hrs. Sustained drug release pattern was observed with Diacerein proniosomal gel prepared using span 60. Among all the formulations, F2 showed greater in vitro drug release (97.1±0.04) than all other formulations for more than 12hrs. The release profile of Diacerein from the different prepared proniosomal gel formula were found to be biphasic release. A rapid drug release was observed in the initial phase, where about 35-60% of the entrapped drug was released within the first few hours. While in the second phase, a slow release of Diacerein was observed from the different proniosomal formulations.

Optimization by design expert software

Optimization was done by Design Expert Stat Ease Software version 13.0.7.0. Two factors were selected for optimizing the formulation. The factor selected were span 60 and cholesterol. Central composite design was used for optimization. To determine the best formulation, 3 responses that is vesicle size, entrapment efficiency and drug release were considered. 13 formulation were suggested by the software. The average values were submitted to multiple regression analysis using Design Expert Software. Polynomial models were generated or all response variables. The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the coefficient variation (CV), the multiple correlation coefficient (adjusted R^2) and predicted residual sum of square (Table 5).

Table 5: Numerical test result of model adequacy checking for influence of independent variables on response variable.

Response	Model	Sequential P Value	Adjusted R^2	Predicted R^2	Adequate Precision	% CV
Entrapment efficiency (%)	Quadratic	<0.0001	0.9936	0.9625	52.0226	0.9625
Vesicle size	Quadratic	<0.0581	0.4779	-1.5783	5.7325	19.12
% drug release	Quadratic	<O.0001	0.9839	0.9239	32.3449	0.6287

The fit of the model was evaluated using R^2-values. As observed from the table 5 the predicted R^2 value was in good agreement with the adjusted R^2 value (The difference is less than 0.2), indicating the reliability of the models. Based on the fit summary Quadratic model was selected as best fit for entrapment efficiency, vesicle size and % drug release as suggested by the software. Adequate precision (Which measures signal to noise ratio) was greater than 4 for all responses showing that the proposed models can be used to navigate the design space.

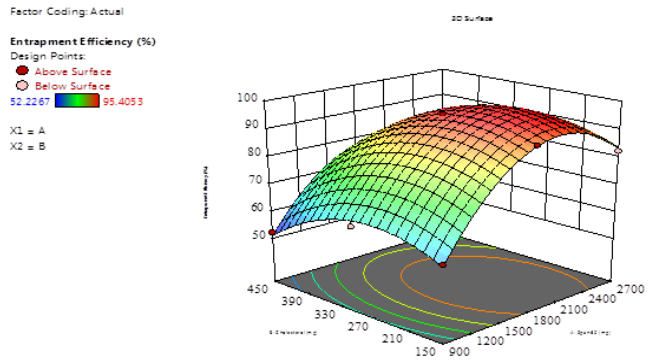

Fig. 4: Response surface plots for the effect of amount of cholesterol and span 60 on % entrapment efficiency.

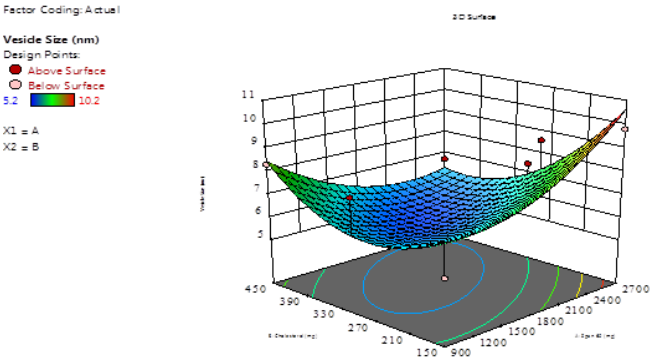

Fig. 5: Response surface plot for the effect of amount of Cholesterol and Span 60 on particle size.

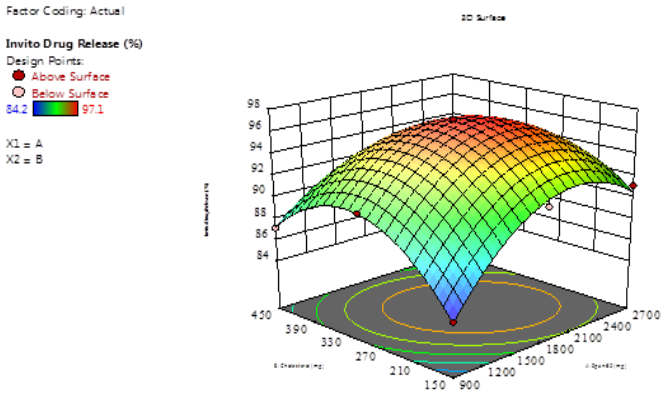

Fig. 6: Response surface plot for the effect of amount of cholesterol and span 60 % drug release.

The desirability function approach is one the most widely used method for optimization of multiple responses. Overall desirability function is a measure of how well the combined goals for all responses are satisfied. Desirability function ranges from 0 to 1, with value closer to 1 indicating a higher satisfaction of response goal. The numerical optimization tool provides 3 set of optimal solution (table 6) among which 1860mg of span 60 and 309.63mg of cholesterol was selected (by the software) as optimized concentration with desirability of 0.969. The area of optimized formulation was also ratified using overlay plot as shown in fig 8 in which the yellow region represent the area satisfying the imposed criteria.

Table 6: Desirability table.

Sl. No	Span 60	Cholesterol	Entrapment Efficiency	Vesicle Size	*In vitro* Drug Release	Desirability	
1	1860.761	309.693	95.405	5.583	96.903	0.969	**Selected**
2	1831.562	312.832	93.121	6.368	90.621	0.892	
3	1865.371	305.720	90.934	4.689	92.248	0.835	

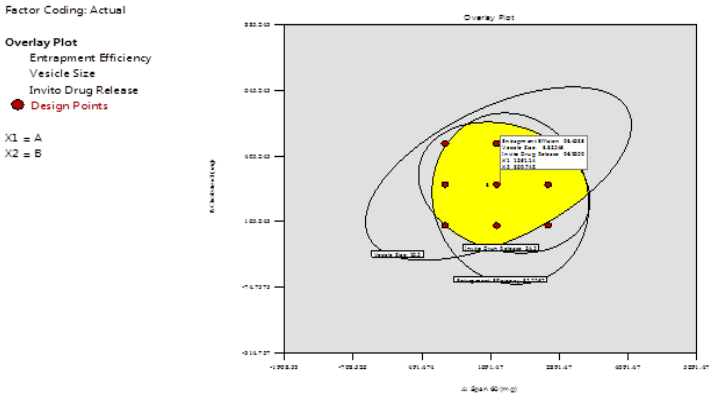

Fig. 7: Overlay plot of optimized formulation of diacerein proniosomal gel.

The experiment was carried out in triplicate at the selected optimum concentrations (1860.761mg of span 60 and 309.693mg of cholesterol) and the resulting proniosomal gel were evaluated for entrapment efficiency, vesicle size and drug release. The result are shown in table 7.

Table 7: Predicted and observed responses for optimized formulation.

Solution 1 of 1 Response	Predicted	Observed	% Error
Entrapment Efficiency	95.4053	95.3998	-0.00576
Vesicle Size	5.5825	5.5752	-0.1309
In vitro Drug Release	96.9029	96.8901	-0.0132

Scanning electron microscopy examination

The fig clarifies the SEM image of the niosomal formula. It has nearly spherical shape with a smooth surface showing that encapsulated drug vesicles are in nano-size range with no sign of aggregation, signifying the physical stability of the produced proniosom.

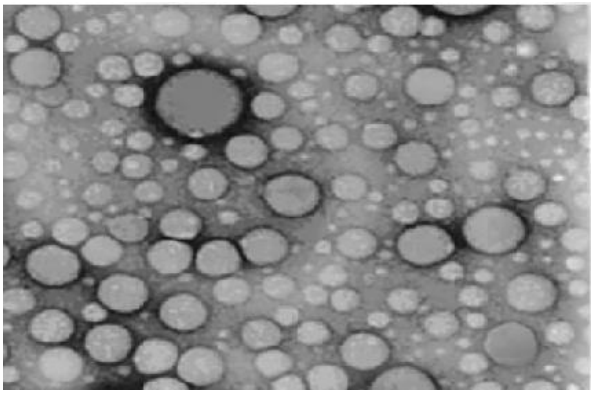

Fig. 8: Scanning electron image of optimized formulation.

Drug release kinetics

In optimized formulation, correlation coefficient of zero order kinetics was found to be 0.903, first order release kinetics was 0.9809 and Higuchi plot was found to be 0.9709. Hence the formulation follows first order kinetics. To confirm the exact mechanism of drug release from the proniosomal gel, data was fitted according to Korsmeyer Peppa's plot. The value of slop of plot n gives indication of release mechanism when n=1, release is independent of time that is zero order. If n=0.5, then release is fickian diffusion. If n=0.5-1, diffusion is non-fickian and n>1then it is super case transport. The 'n' exponent value of best batch was 0.7337. Hence it shows non-fickian transport mechanism.

Table 8: Drug release kinetics of optimized formulation.

Zero order	First order	Higuchi	Korsmeyer-Peppas	
R^2	R^2	R^2	R^2	n
0.903	0.9809	0.9704	0.9861	0.7337

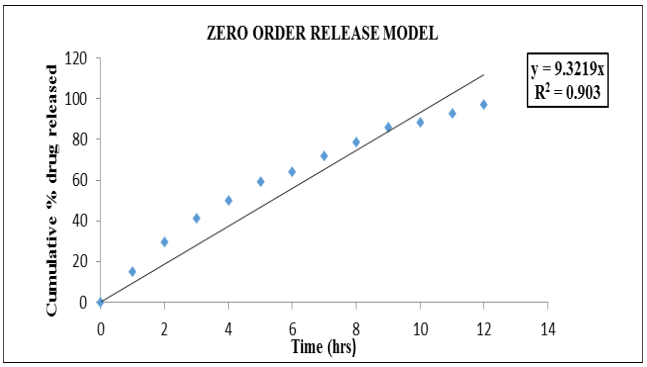

Fig. 9: zero order release plot.

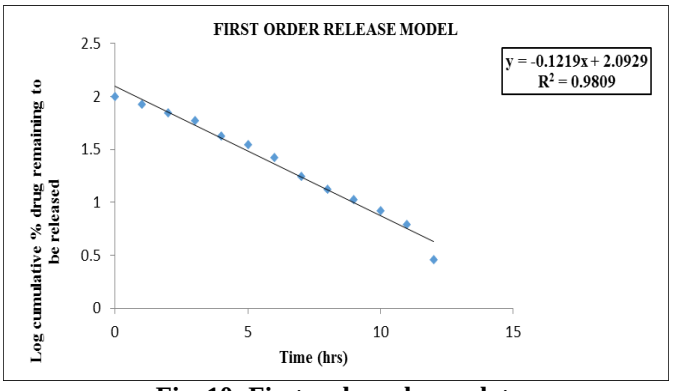

Fig. 10: First order release plot.

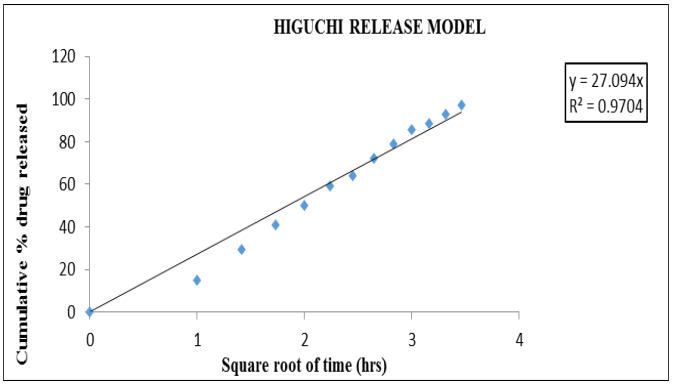

Fig. 11: Higuchi release plot.

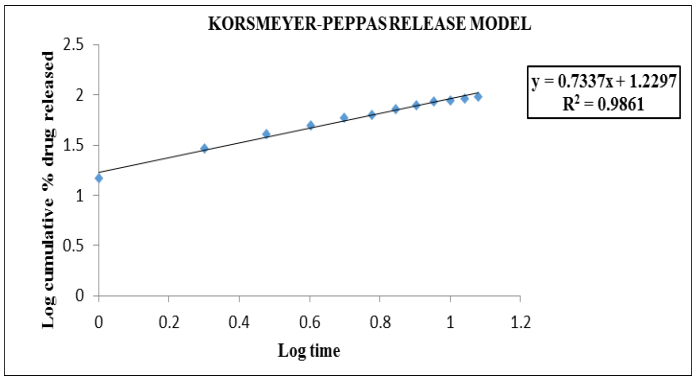

Fig. 12: Korsmeyer peppas plot.

***In vitro* anti-arthritic activity**

The optimized Diacerein loaded proniosomal gel were found to be effective as anti-arthritic agent and showed significant activity as compared to standard drug. The percentage inhibition of protein denaturation of optimized formulation found to be 75.45%.

Table 9: *In-vitro* anti-arthritic study.

Sample	Absorbance	Mean Absorbance±SD	Inhibiton (%)
Optimized Formulation	0.0210	0.0202±0.114	75.45%
	0.0198		
	0.0199		
Standard	0.0351	0.0338±0241	58.93%
	0.0329		
	0.0334		
Control	0.086	0.0823±0.103	
	0.079		
	0.082		

All value expressed as mean of ± SD, n = 3

Stability studies

The optimized formulation was used for stability studies as per the ICH guidelines for 3 months. It shows that prepared proniosomal gel pass stability studies with not much significant changes in the vesicle size, entrapment efficiency and *in vitro* drug release (Table 10).

Table 10: Stability data of optimized formulation.

Storage Condition	Sampling Interval	Vesicle Size (m)	*Invitro* Drug Release (%)	Entrapment Efficiency (%)
40ºC ± 2ºC at 75% ± 5%RH	Initial study	5.20±0.124	97.104±0.21	97.1±0.04
	30 days	5.19±0.120	96.989±0.15	96.70±0.012
	90 days	5.17±0.118	95.788±0.21	96.0±0.025
25ºC ± 2ºC at 60% ± 5% RH	Initial study	5.20±0.124	97.104±0.21	97.1±0.04
	30 days	5.20±0.121	96.924±0.19	96.8±0.04
	90 days	5.14±0.121	96.158±0.14	95.9±0.361
5ºC ± 3ºC	Initial study	5.20±0.124	97.104±0.21	97.1±0.04

	30 days	5.13±0.124	96.856±0.23	96.8±0.0214
	90 days	5.10±0.123	95.971±0.26	96.2±0.354

CONCLUSION

Diacerein-loaded proniosomal gel formulations were prepared using Central Composite Design (CCD), all of which exhibited sustained drug release. The optimized formulation, chosen to maximize entrapment efficiency, percent drug release, and maintain proper vesicle size, contained 1860.761mg of Span 60 and 309.693mg of cholesterol, with a desirability score of 0.969. This study has shown that the proniosomal gel is a suitable carrier for the transdermal delivery of Diacerein with enhanced efficacy. The optimization studies clearly indicated that the size of the vesicles, entrapment efficiency, and drug release are mainly dependent on the concentrations of both surfactant and cholesterol.

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