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EVALUATION OF POTENTIAL HYPOGLYCEMIC ACTIVITY OF PRONIOSOMAL GEL CONTAINING GLIPIZIDE

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ABSTRACT: For the purpose of transdermal delivery of the hypoglycemic agent Glipizide, novel vesicular drug carrier system proniosomes are being developed, evaluated, and stability studies are being conducted. Proniosomes were investigated as a new drug delivery technique for enhancing Glipizide permeation through the skin. A glipizide proniosomal gel was made using a coacervation-phase separation technique, a non-ionic surfactant (span 60), cholesterol, and lecithin, along with various medication combinations. Physical appearance, pH, vesicle size, entrapment efficiency, drug content uniformity, surface morphology, zeta potential analysis, in-vitro drug release, kinetic model, skin irritant test, hypoglycemic action, and stability tests were all used to evaluate proniosome formulations. The AF4 formulation has a higher drug content and entrapment efficiency than all other formulations combined. *In-vitro* release after 24 hrs from AF4 formulation showing better control on release compare to other formulations. Proniosomal gel formulation AF4 was found to be non-irritant, superior stability, and a greater hypoglycemic effect than oral formulations. Because it reduces blood, glucose levels in a regulated manner for up to 24 hours. As a result, the Proniosomal drug delivery system was a proved to better option for controlled drug release via topical medication delivery.

Keywords: Glipizide, Proniosomes, Entrapment Efficiency, Controlled release, Hypoglycemic activity *etc*.

INTRODUCTION:

Despite years of research, the barrier function of the stratum corneum still poses a challenge in the development of new transdermal drug delivery systems, making it an intriguing task. Vesicles systems such as liposome / niosome were studied extensively as the vehicles to deliver the drug from transdermal route. Proniosome is an example of provesicular system. Proniosomes are physically more stable than niosomes. Niosomes provide extra ease in transport, delivery, storage facilities, and dosage despite having physical stability issues like accumulation, combination, and leakage.[1, 2]

Proniosomes offer a versatile approach for delivering drugs through the transdermal route via vesicular delivery. It would be possible if proniosomes, after being topically applied under occlusive circumstances, transformed into niosomes upon hydration with water from the skin. Proniosomes are mainly used in topical formulations.[3]

Proniosomes fall under the category of non-ionic surfactant vesicles that can be used to create liquid niosome dispersions by hydrating them. Proniosomes are used today to enhance the transport of therapeutic substances.[4]

In this study, Glipizide was formulated in the form of proniosomes for treating hyperglycemia. Glipizide transdermal delivery is a safer choice for solving problems linked to its oral delivery.

There are many advantages of transdermal drug delivery as compared to conventional dosage forms including avoid GI incompatibility, differential absorption of GI and bypass from first pass metabolism. They include also enhanced bioavailability, reduced drug taking frequency and enhanced patient compliance. A noninvasive transdermal delivery may maintain plasma concentration of drug. It would improve efficiency of hypoglycemic agent along with high patient compliance.[1, 5]

MATERIALS AND METHOD:

Materials:

Glipizide was received as a present from Bangalore's Biocon Limited. (India). Soya lecithin was obtained as a gift from Pharma Sonic Biochem Extractions Ltd., Indore (India). We bought Span 60, cholesterol, and ethanol from SD Fine Chem Limited in Mumbai. (India). No purification was performed before using any of the reagents. According to the Indian Pharmacopoeia, phosphate buffer solution with a pH of 7.4 was prepared.

PRE-FORMULATION STUDIES:

Determination of Melting point

Glipizide's melting point was obtained using a Digital melting point equipment. A small amount of Glipizide was collected, put in a thin-walled capillary tube, and suspended in an oil bath containing silicone oil. Capillary tube was about 10-12 cm long and 1 mm in diameter inside and closed at one end. After that, the device was turned on to start heating.The melting point was determined by the temperature range in which the sample melted.

Solubility analysis:

Analysis of solubility for Glipizide samples were carried out in many solvents. Water, methanol, methylene chloride, phosphate buffer pH 7.4 and acetone were used to dissolve 10 mg Glipizide in 10 ml of various solvents. The physical appearance was used as the basis to determine solubility.

Drug-Excipient interactions studies by FTIR:

FT-IR was used to investigate drug excipient compatibility studies. The IR spectrum of a physical mixture containing drug, cholesterol, soyalecithin, and span60 in a 1:1:1:1 ratio was recorded using liquid sampling technique, and the recorded spectrum was observed to be within the range of 400 to 4000 cm-1.

Drug excipient compatibility studies by DSC:

DSC (Differential Scanning Calorimetry) was employed to investigate the compatibility of drugs with excipients. The thermal properties of both the pure drug and a physical mixture consisting of drug, span 60, cholesterol, and soyalecithin in a ratio of 1:1:1:1 were determined using an automatic thermal analyzer system (Mettler DSC 823, Germany). At a scanning rate of 10 °C per minute, the complete sample was heated to a temperature range of 25 to 300 °C.

Method:

Preparation of proniosomal gel via Coacervation phase separation:

Quantities of surfactant (Span 60), lecithin, cholesterol, and drug (Glipizide) were initially precisely weighed. Then drug and other excipients were transferred in a wide mouthed glass vial which was then filled with alcohol (3ml). To avoid solvent leakage, the glass bottle’s open end was capped with a lid. Then this mixture were placed on water bath and heated for 5-10 minutes at 60°C-70°C until it was completely dissolved. Using a glass rod, all of the materials were well mixed after heating. The mixture was then combined with 3 ml of phosphate buffer solution (pH 7.4), and heated on a water bath until it became transparent. This clear solution was then cooled and transformed into proniosomal gel. In a dark environment, the gel was

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stored in the same glass container. The optimized proniosomal gel was incorporated into 1 % Carbopol based gel for animal studies. Table 1.[6-7]

Evaluation of Glipizide proniosomal gel [8-11]:

Physical appearance:

The resulting proniosomal gel compositions' physical properties, including colour, consistency, texture, and greaseiness, were evaluated visually.

Determination of pH:

Before and after the drug was incorporated, using a pH metre, the pH of each proniosomal gel formulation of Glipizide was evaluated. Firstly, two reference buffer solutions with pH values of 4.0 and 7.0 were used to calibrate the glass electrode. Following that, the pH for every formulation was measured three times, with the average findings being calculated.

Viscosity:

Brookfield Viscometer have used for the determination of viscosity of proniosomal gel.

Scanning electron microscopy (SEM):

A scanning electron microscope was utilized to examine the surface morphology of the proniosomes. 10 ml of phosphate buffer solution (pH 7.4). were mixed with 0.2 gm of proniosomal gel in a glass tube. Gold-palladium alloy of 120°A Knees (Model E5 100 Polaron UK) were used to coat the proniosomes on the sample sputter coating apparatus. Japan Scanning electron microscope (Jeol JSM-T330A) was used for the photography of their surface morphology.

Vesicle size analysis:

For vesicle size examination, proniosomal gel was hydrated with a tiny amount of PBS (pH 7.4) and shaken for five minutes in small test tube. Under a 10X and 40X optical microscope, the dispersion was observed. Average was taken after measuring about 300 proniosomes individually. An optical microscope with a calibrated ocular and stage micrometre connected was utilized to determine the average vesicle diameters.

Zeta potential analysis:

The colloidal characteristics of the produced formulations were determined using a zeta potential analysis. Zeta potential analyzer was used to determine niosomes dispersion which is derived by diluted proniosomes. The temperature was set at 25 °C. Measurements were made of the charge on the vesicles and their mean zeta potentials.

Drug content:

In 10 ml of methanol, a proniosome formulation containing 10 milligrammes of glipizide was dissolved. Utilizing a UV spectrophotometer to measure absorbance against a blank sample at a maximum wavelength of 276 nm, after a sufficient phosphate buffer solution pH 7.4 dilution, the drug content was calculated.

Entrapment Efficiency (EE %):

Proniosomal gel formulation weighing 100 mg in a test tube received 10 ml of phosphate buffer solution (pH 7.4). Sonicated bath were used to sonicate the aqueous suspension.

For 30 minutes at 5-6 °C, the niosome dispersion was spun at 18000 rpm to release the Glipizide-containing niosome from the entrapped medication. PBS ((pH 7.4) was used to wash the vesicular pellet-containing precipitate three times. The supernatant liquid was taken and mixed with PBS. The concentration of drug in the resultant solution was determined using a UV technique at 276 nm. The percentage of drug encapsulation was calculated using the following equation:

EE (%) = Total drug – Diffused drug/ Total drug × 100

***In-vitro* release studies:**

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Using egg membrane in a Dialysis tube, Niosomal suspension made using proniosomal gel was examined for its in-vitro release pattern. In dialysis tubing (Sigma Aldrich), A beaker with 75 ml of PBS (pH 7.4)was filled with one gramme of Glipizide proniosomes, which is equal to 20 mg of Glipizide .The 5 ml sample was taken at regular intervals and replaced with fresh buffer, and the test was performed for 24 hours. Throughout the experiment, the sink conditions were maintained. Utilizing a UV spectrophotometer set to 276 nm and a PBS blank (pH 7.4), the drug concentration in the withdrawn samples was assessed after being properly diluted.

***In Vivo* studies [11, 12]**

a. Skin irritation test

Studies on skin irritation were conducted using four young Wister albino rats. Each rat's back was shaved with a hair removal cream (about 6-cm2 area). After applying the developed formulations to the shaved area, the rats were secured. For a period of seven days, the animal was examined and evaluated for any signs of erythema or edoema. All of the treatments were continued for a total of seven days, after which the application sites were visually observed and scored using the visual scoring scale shown in Table 2.

b. Hypoglycemic activity:

i. Experimental model:

Adult Wister albino rats, weighing 150-200 gm were chosen for the experiment before the experiment began, the animals were divided into groups at random and maintained separately in polystyrene cages with a specific room temperature of 20–25 °C and 50% relative humidity during a 12-hour cycle of darkness and light. Throughout the experiment, the mice were fed a conventional rat diet and had access to water. The Bharathi College of Pharmacy's Institutional of Animal Ethical Committee (IAEC) examined and approved all of the listed methods. BCP/IAEC/PCEU/02/2015, Registration No.

ii. Induction of diabetes:

To get the fasting blood glucose levels, the acclimatized rats were fasted for 24 hours and their blood sugar levels were measured in each group. Each rat received 120 mg/kg body weight of alloxan monohydrate in normal saline through intraperitoneal route, and blood glucose levels were monitored using a digital glucometer (Accque check) after 24 hours. The study used rats with a 225–250% increase in fasting blood glucose levels.

iii. Preparation of Animal for studies:

Hair was removed from the rats' backsides (interscapular region) with a hair removing cream. On the shaved region of hyperglycemic rats, proniosomal gel was applied topically. Animals were separated into 4 groups (n=3) of diabetes rats before the experiment. The rats received the following care.

Group I- A single dose of 0.9% normal saline solution was administered to the normal control group.

Group II- Diabetic control was received a 0.9 % normal saline.

Group III- Hyperglycemic rats received oral dose.

Group IV- Hyperglycemic rats received proniosomal gel (AF4).

The blood was taken from the rat's tail by pricking it at regular intervals for 24 hours, and the blood glucose level was analysed instantly with a digital glucometer.

Stability study:

For six months, intermediate stability testing experiments were carried out. The optimized formulations were kept at 30 ± 2 ºC and 65 ± 5% RH. For the stability study, physical appearance, drug content, and percent drug release were set as evaluation parameters.

RESULTS AND DISCUSSION:

Preformulation Study:

Melting point determination:

The resulting drug sample's melting point was discovered to be 208 °C, which met IP criteria and denoted the drug's purity.

Solubility analysis

Glipizide was soluble in dimethyl formamide and methanol. Drug was essentially insoluble in water but just slightly soluble in acetone and methylene chloride. It is easily soluble in phosphate buffer solution (pH 7.4).

FTIR Study:

Pure Glipizide's FTIR spectra revealed clear distinctive peaks at 3248.23,2939.61,1689.70,1442.80,1157.33 cm^{-1}. There is no change for drug-excipient interaction, as evidenced by the presence of the FTIR distinctive peaks of the pure drug in the spectra of the physical mixture. This proves that the excipients used in the proniosome formulation are compatible with the drug. FTIR graphs for comparison are displayed in Figs. 1 and 2.

DSC Study:

The obtained thermogram was displayed in (Fig. 3, 4). The endothermic peak of the pure drug was present in the physical combination of the excipients and the drug. This demonstrates that the drug and excipients did not interact.

Evaluation of proniosomal gel:

Physical appearance, pH, Viscosity:

On application, developed formulations appeared translucent, yellowish, shiny, smooth and non-greasy translucent, yellowish shiny, smooth, and non-greasy. The pH of best formulation AF4 was found to be 6.52. Proniosomal gel compositions' viscosities were determined in ascending order AF1>AF2>AF3>AF4 respectively due to increasing the surfactant ratio. Proniosomal gel formulations were found to have good spreadability and viscosity, with the optimal formulation AF4 measuring 11,435 cps.

Optical microscopy and Surface morphology:

The photomicrographs of the hydrated AF4 proniosomal formulations taken using an optical microscope and displayed in Figure 5 show that spherical niosomes were created and no signs of aggregates were found. The surface morphology was studied by Scanning electron microscopy (SEM). The SEM photographs of optimized proniosome formulation AF4 as shown in Fig. 6. SEM photographs showed that the niosomes formed were spherical in shape.

Vesicle size analysis:

For AF1–AF4, the vesicle size were discovered to be in range 0.910 um and 1.93 um. According to the findings, increasing the surfactant concentration led to larger vesicles (span 60). The average vesicle sizes of formulation AF1-AF4 were found to be 0.910 μm, 1.32 μm, 1.65 μm and 1.93 μm, respectively Table 3. Particle size analysis also showed good result it is in the limit Fig. 7.

Zeta potential:

Zeta potential of the optimized formulation (AF4) Glipizide proniosomes was measure as shown in Fig 8 and found to be -34.3 mV, indicating that it has enough stability.

Drug content and Entrapment efficiency:

In several gel formulations with varying drug, cholesterol, soyalecithin, and surfactant ratios, the percentage of drug content and entrapment efficiency of Glipizide were determined spectrophotometrically. The results are shown in the following Table 3. The drug content in AF4 was greatest (95.26%). AF4 has the highest entrapment efficiency with 95.70%. The higher vesicle fluidity and larger vesicle size may both contribute to the higher entrapment

efficiency and the high drug entrapment. The findings show that an increase in the surfactant ratio boosts the efficiency of entrapment.

***In-vitro* release study:**

The release of Glipizide from proniosomal gel formulations were varied according to the concentration of surfactant. The gradual increase in span 60 content was the cause of the progressive decrease in the amount of medication that diffused through a dialysis membrane from formulations AF1 to AF4. According to research, the diffusion of drugs likewise reduces as surfactant concentration is raised. The amount of drug diffused from formulation AF4 was showed 46.55 % which was lower among the formulations AF1-AF3 which were showing 59.35 %, 55.95 %, 53.32 % Fig. 9. The gels' ability to hold the medicine for a long time, however, was clearly demonstrated by the results. All the formulations follows Higuchi model and the release mechanism was diffusion controlled. All formulations' 'n' values were discovered to be more than 0.5. It can be inferred that the release is close to a non-Fickian diffusion process. The gels' ability to hold the medicine for a long time, however, was clearly demonstrated by the results.

Skin-irritation test:

Table 4 shows the results of a skin irritation investigation using the proniosomal gel formulation AF4. It was observed that the formulations AF4 had an average primary irritation index of 0.16. It demonstrates that after 7 days of use, the proniosomal gel formulation showed no signs of erythema or irritation.

Hypoglycemic activity:

The results of decrease in blood glucose level of proniosomal gel in comparison with Glipizide oral, normal and diabetic control rats are shown in Table 5. The blood glucose level reduction in group III showed 99±1.52 at 10 hrs was high with oral administration and observed severe hypoglycemia in the initial hours after administration. Whereas, for the proniosomal gel the blood glucose level was reduced in a controlled manner and observed blood glucose level reduction in group IV was showed 155 ± 2.0 at 24 hrs for the optimized formulation AF4-G1, respectively. When compared, the optimized formulation AF4-G1 showed maximum reduction in blood glucose level 155 ± 2.0 at 24 hrs. Both normal control group and diabetic control were not showed any reduction in blood glucose level (no hypoglycemic effect).

Stability study:

The optimized formulation AF4 underwent intermediate stability testing at 30 ± 2 ºC and 65 ± 5 % RH while being monitored for drug content, pH, and a dissolution profile analysis. The findings, which are presented in Table 6, showed that all of the proniosomal gels were stable during the storage period.

Table 1: Formulation design for the preparation of proniosomal gel formulation:

Formulation code	Drug (mg)	Span(60) (mg)	Soya lecithin (mg)	Cholesterol (mg)
AF1	100	100	100	100
AF2	100	200	100	100
AF3	100	400	100	100
AF4	100	600	100	100

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Table 2: Standards for skin irritation study:

SKIN RESPONSES	SCORE
Erythema and scar formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet-redness) to slight scar formation	4
Edema formation	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well-defined by definite raising)	2
Moderate edema (raised approximately 1.0 mm)	3
Severe edema (raised more than 1.0 mm and extending	4
Total possible score for irritation	8

Table 3: Vesicle size, % Drug content and % Entrapment efficiency of proniosomes formulation AF1-AF4:

Formulation code	Average vesicle size in µm	% Drug content	% Entrapment efficiency
AF1	0.910	83.21	90.12
AF2	1.32	87.12	91.73
AF3	1.65	92.31	93.21
AF4	1.93	95.26	95.70

*Each value was the average of 300 Vesicles

Table 4: Reading after Skin irritation study of proniosomal gel formulation AF4- G1:

		AF4-G1 Formulation	
Skin responses	**Days**	**Score**	
		Rat 2	**Rat 2**
Erythema and Scar formation	1	0	0
	3	0	0
	7	0	0
Edema formation	1	1	0
	3	0	1
	7	0	0
Primary irritation index (PII)		0.16	0.16

Average Primary irritation index of formulation AF4-G1 = 0.16

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Table 5: Hypoglycemic activity of Glipizide proniosomal gel formulation AF4-G1:

Time in hrs.	Reduction in blood glucose level in mg/dl (mean ± SD, n=3)			
	Group-I	Group-II	Group-III	Group-IV
0	95±1.52	325±1	340±1.51	342±1.51
2	93±2.0	332±1.51	204±1.0	304±2.0
4	95±2.08	340±2.08	152±2.0	271±1.52
8	96±1	338±1.0	125±2.08	203±2.08
10	98±2.08	352±2.0	99±1.52	168±1.52
12	92±2	355±1.51	175±1.51	159±2.08
24	94±1.51	360±2.08	242±2.0	155±2.0

Table 6: Intermediate stability studies for optimized formulation of proniosomal gel AF4 at 30 ± 2ºC and 65 ± 5%:

Parameters	Duration in months			
	0	1	3	6
%Drug content	95.26	95.10	95.02	94.42
pH	6.52	6.57	6.59	6.72
% CDR	46.55	46.02	45.82	45.25

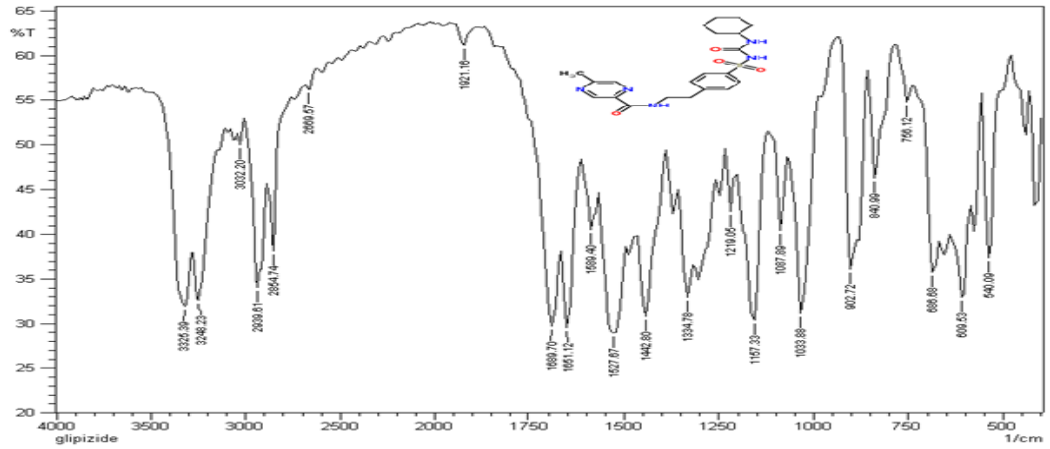

Fig. 1: FT-IR Spectroscopy of pure Glipizide

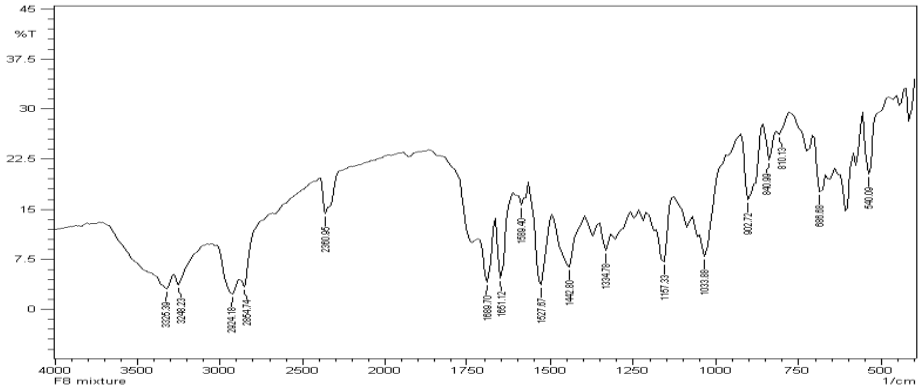

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Fig. 2: FT-IR Spectroscopy of Glipizide+Span60+Soyalecithin+Cholesterol

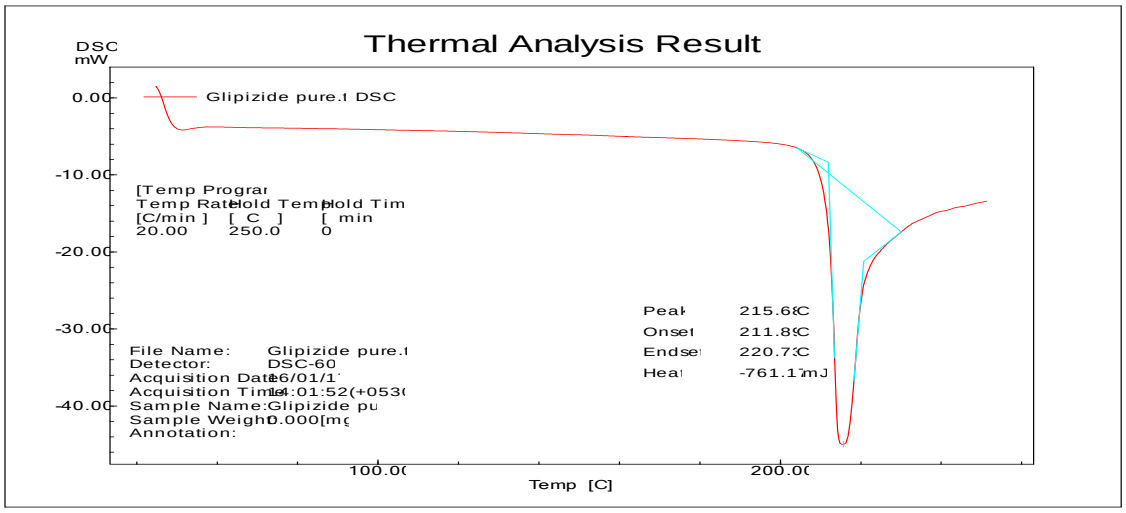

Fig. 3: DSC thermo graph of pure drug Glipizide

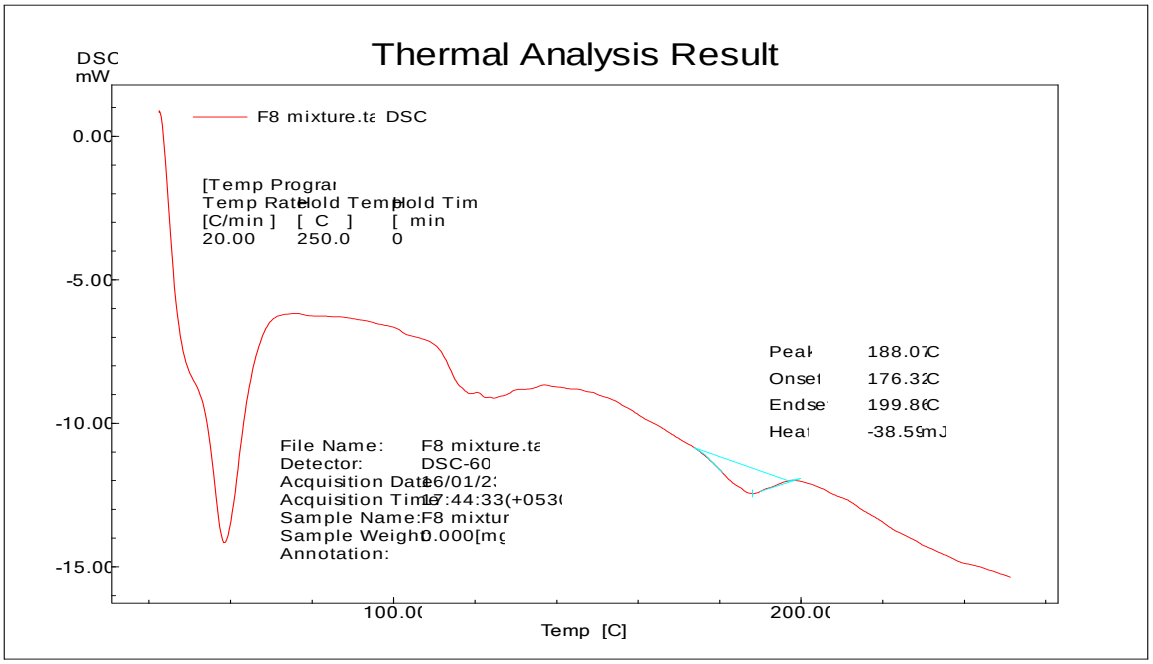

Fig. 4: DSC thermo graph of Glipizide+Span60+Soyalecithin+Cholesterol

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Fig. 5: Microphotographs of proniosomal gel formulation AF4

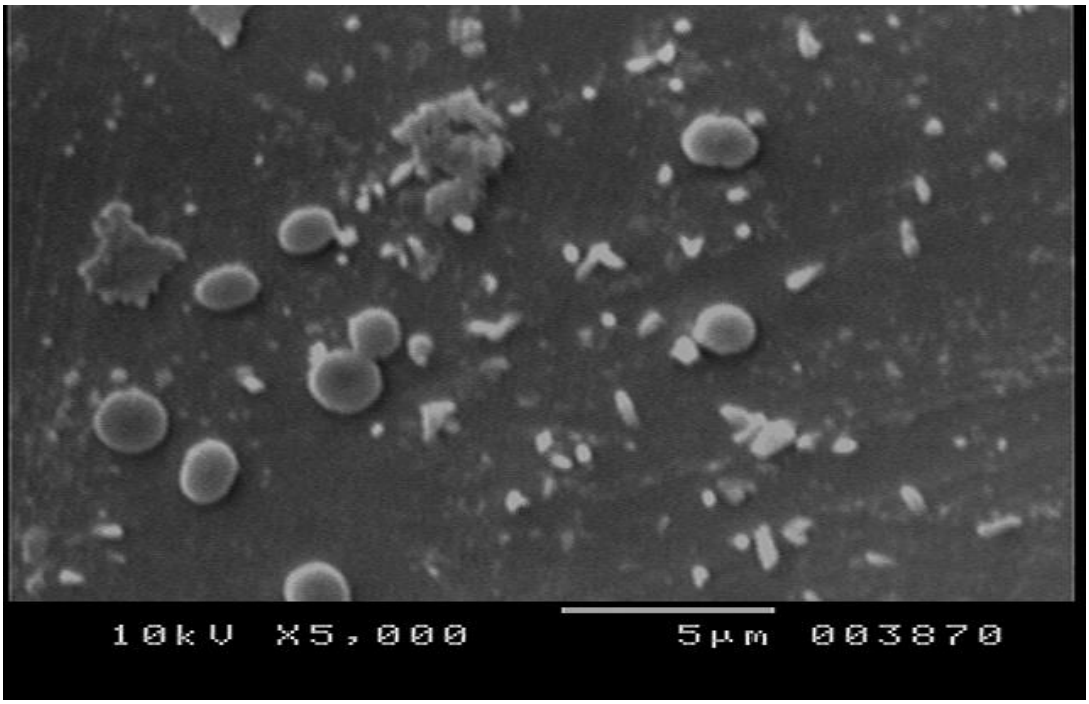

Fig. 6: Scanning electron micrograph of optimized proniosome formulation AF4

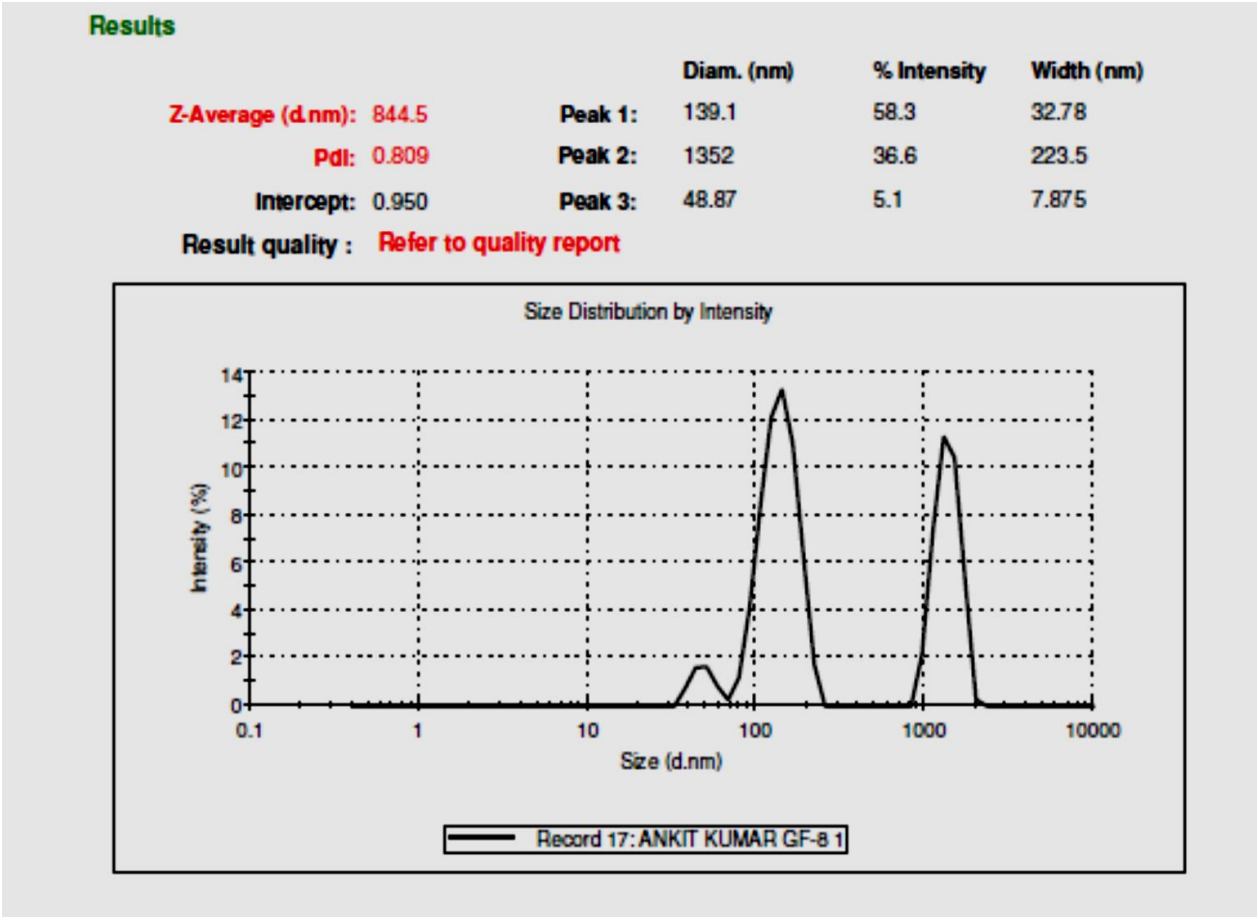

Fig. 7: Particle size data for proniosomal gel formulation AF4

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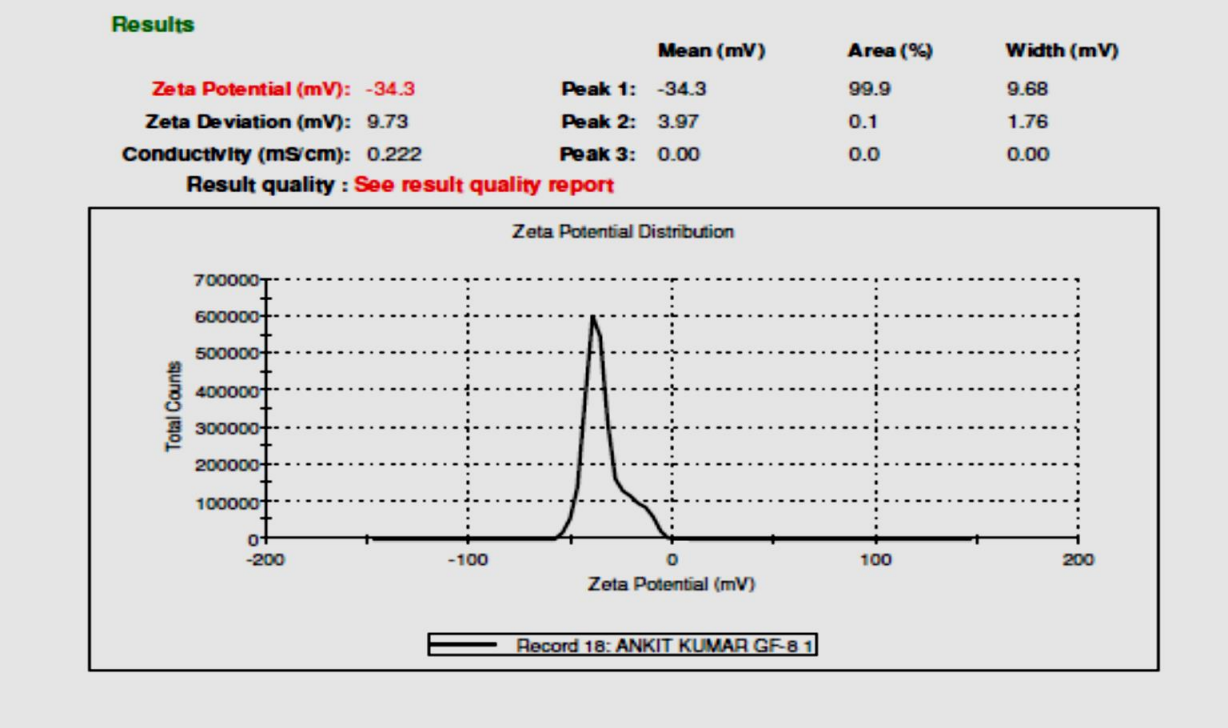

Fig. 8: Zeta potential of optimized proniosomal gel formulation AF4

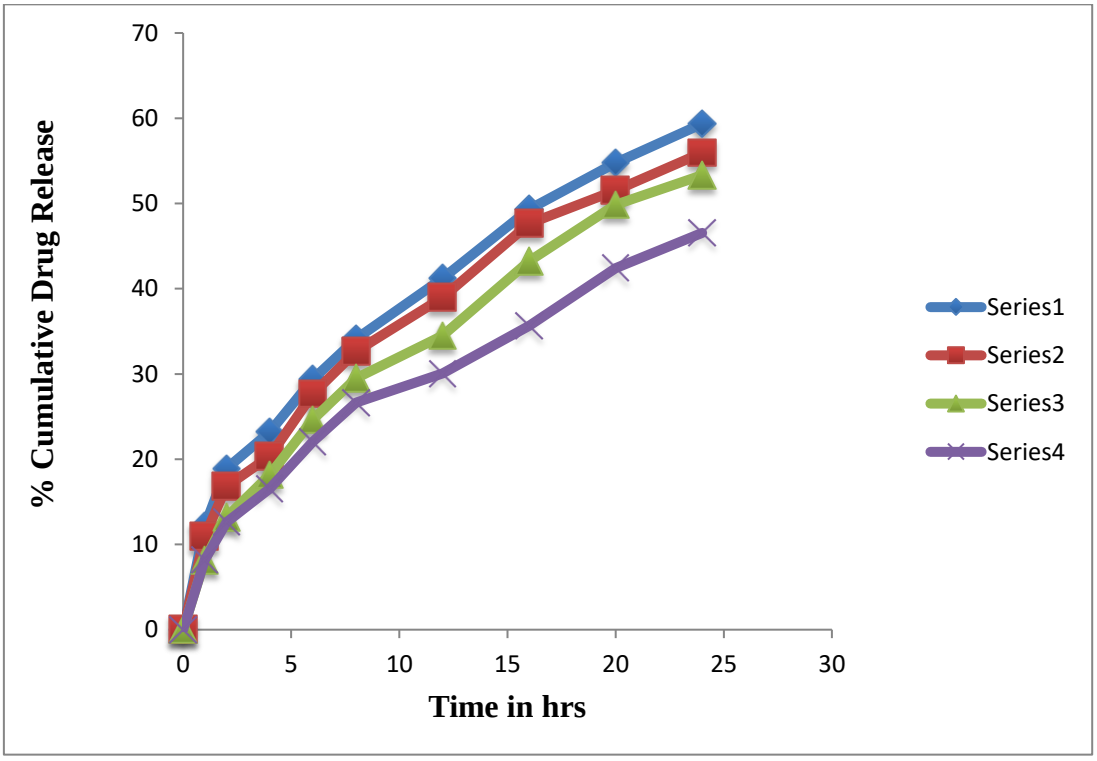

Fig. 9: % CDR of proniosomal gel formulation from AF1-AF4

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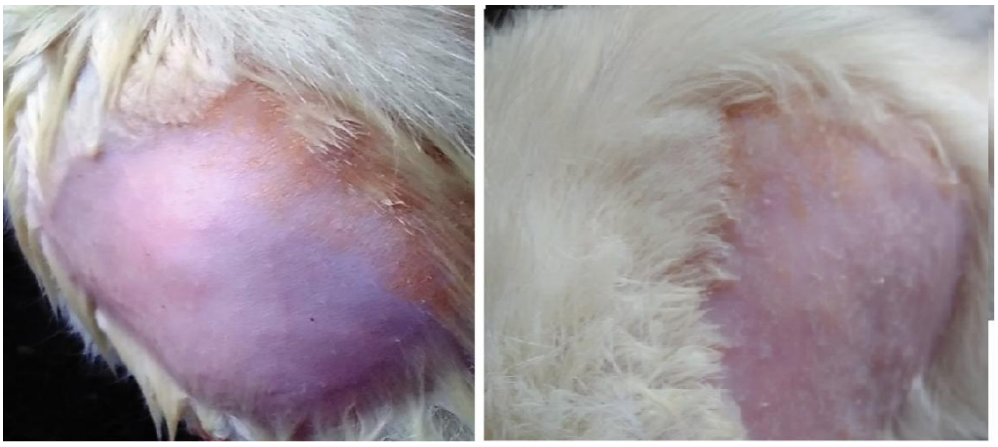

Fig. 10: Rat skin for observation of erythema and edema (After 7 days) of gel application

CONCLUSION:

Glipizide, a novel antidiabetic medication, was delivered via transdermal route in the form of proniosomal gel in the current investigation. The *in-vitro* permeation of Glipizide from proniosomes of various compositions of drug, cholesterol, soyalecithin and non-ionic surfactants have been studied and evaluated. Glipizide was successfully entrapped within the lipid bilayers of the vesicles by coacervation phase separation with high efficiency. The AF4 formulation showed larger vesicle size, more entrapment efficiency and drug content with better control on drug release compare to other formulation, on that basis only AF4 formulation chooses as an optimized formulation. The results of the experiments suggest that either the vesicles fuse with the stratum corneum's intercellular lipid and transfer the drug from the vesicles to the skin. It may be penetration enhancement due to the presence of surfactants and the use of alcohol, which is a penetration enhancer. Proniosomes exhibited good stability as compared to liposomes/niosomes. When compared to standard dose forms, proniosomal gel exhibited no skin irritation and supplied Glipizide in a controlled manner, as indicated by a considerable reduction in blood glucose levels in diabetic rats. Because of its ease of production and low quantity of excipients, proniosomal gel will be a good drug delivery method for Glipizide.

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