FORMULATION AND EVALUATION OF NANOSIZED GLIPIZIDE LOADED TRANSDERMAL FILM

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ABSTRACT

The present aim of the study was to develop a Proniosomal gel in Transdermal patches system for Glipizide for the Treatment of Diabetics mellitus that is capable of efficiently delivering entrapped drug over an extended period of time. Glipizide is a second generation of sulfonylurea, it can accurately lowered the blood glucose level in humans by stimulating the release of insulin from the pancreases and is typically prescribed to treat type ll diabetics (non insulin dependent diabetic mellitus).The half life of Glipizide is (3.4±0.7 hours) necessitate it be administered in 2 or 3 doses of 2.5 to 10mg per day. Thus the development of controlled-released dosage forms would clearly be advantageous.

Proniosomal gels are semisolid liquid crystal products of nonionic surfactants easily prepared by dissolving the surfactant in a minimal amount of an acceptable solvent and the least amount of aqueous phase. Proniosomal gel offers a great potential to reduce the side effects of drugs and increased therapeutic effectiveness The objective of the present study was to prepare proniosomal gel converted to transdermal patches in order to sustained release, increase the absorption rate, improve the drug efficiency, decrease the dose requirement, maintaining the concentration of the drug in the blood and decrease the renal excretion and maintaining the fluctuation of the dosage forms.

Keywords: Proniosomal gel, Transdermal, Glipizide, Diabetes

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Introduction

In the past few decades, extensive attention has been focused on the growth of new drug delivery system. The significant of NDDS, it should be deliver the drug at a rate directed by the needs of the body, over period of time. A number of NDDS have emerged encompassing various route of administration to achieve controlled and target drug delivery.

Recently different types of carrier systems and technologies have been briefly studied with the aim of controlling the drug release and improving the worth and selectivity of formulation. and to minimize drug degradation and loss, to prevent the harmful side effects and increased the bioavailability and the fraction of the drug accumulate in the required zone, various drug delivery and drug targeting systems are developed. The targeting is the capability to direct the drug. The two major mechanisms can be notable for desire sites for drug release are passive targeting-controlled release and active targeting-controlled release

Introduction of vesicular system

Vesicular system is one of the development novel drug delivery system. The development of vesicle as a carrier system have been become the vesicle choice in drug delivery and lipid vesicle were found to be a value in immunology, membrane biology, and diagnostic technique and most recent in genetic engineering. Vesicular system providing an efficient method for delivery to the site of infection, and reduce toxicity of drug and no adverse effect. It reduces the cost of therapy by improving bioavailability of drug especially for poorly soluble drug.

Advantages of vesicular system

- Prolong the existences of the drug in systemic and perhaps, reduces the toxicity if selective uptake can be achieved due to the delivery of drug directly to the site of infection.
- Improves the bioavailability especially in the case of poorly soluble drugs.
- Both hydrophilic and lipophilic drugs can be incorporated.
- Delays elimination of rapidly metabolizable drug and thus function as sustained release system.

Material and Method

Materials Used

The drug glipozide is a gift sample form Akums Haridwar and the other excipients like Cholesterol, Span 60, Glycerol, Chloroform, PEG is purchased from Loba Chem Pvt. Ltd. And Isopropyl alcohol, potassium dihydrogen phosphate is purchased from S.D fine chem. Ltd.

Drug interaction studies

FTIR

The FTIR study has been carried out check the purity of drug. The FT-IR spectrum of pure drug and span 60, cholesterol and physical mixture of drug were analyzed for compatibility study. The samples were taken separately for FT-IR analysis. A milligram or less of the finely ground sample is intimately mixed with about 100 mg of dried potassium bromide powder. Mixing can be carried out with a mortar and pestle; a small ball mill is more satisfactory, however. The mixture is then pressed in a special die at 10,000 to 15,000 pounds per square inch to yield a transparent disk. Best results are obtained if the disk is formed in a vacuum to eliminateoccluded air. The disk is then held in the instrument beam for spectroscopic examination.

Differential Scanning Calorimetry

DSC pattern of Glipizide, cholesterol and formulation complex were different which give clear evidence that there is formation of the complexes with cholesterol were recorded using Shimadu D thermal analyzer (Japan). Samples were conserved in aluminum pan; the lid was pierced and the DSC thermogram was recorded at heating rate of 20oC/min from 60 to 240oC using nitrogen atmosphere. (Hanwate RM *et al.*, 2011)

Preparation of standard graph

Standard curve of glipizide was prepared in phosphate buffer p^H 7.4

Procedure

Accurately weighed (10mg) of Glipizide was dissolved in 20ml of phosphate buffer 7.4 taken in 100ml calibrated volumetric flask and volume was made up to the mark using given buffer. From the stock solution, 0.5 ml of solution was withdrawn and diluted up to 10ml in volumetric flask this gives 5µg/ml. Similarly, 10 , 15 , 20 , 25 , 30 , 35 , 40 µ g/ ml were prepared by withdrawing 1,1.5,2,2.5,3,3.5,4,4.5ml respectively. Absorbance of each solution was measured at276nm. (Avinash singh et al.,2011)

Preparation of Proniosomal gel

Proniosomal gel was prepared by phase coacervation method. The weighed amount of surfactant (span 60), lipid (cholesterol), protein(egglecithin) and drug were taken in a clean dry wide mouth glass container. The isopropyl alcohol was used as a solvent, it was added to 2.5ml of above mixture and warm it. After warming all the ingredients were mixed well witha glass rod, the open end of the glass bottle was covered with the lid to prevent the loss of solvent. The temperature should be maintained at 60-70°C for (5 min) until the surfactant mixture dissolved completely. After dissolving the mixture, aqueous phase 1.6ml of 0.1% glycerol was added and warmed it till a clear solution was formed this was converted into proniosomal gel on cooling. The proniosomal gel was preserved in airtight container and stored in a dark place.(*Ankurguptha et al.,2007, Chandra.A et al., 2008, IntakhabAlam et al.,2010.*).

Table No: 1 Formulation of Different Proniosomal Gels

S No.	Formulation	Drug (mg)	Span 60 (mg)	Cholestrol (mg)	Lecithin (mg)
1.	F1	10	180	10	200
2.	F2	10	180	20	190
3.	F3	10	180	40	180
4.	F4	10	200	50	140
5.	F5	10	200	60	130
6.	F6	10	200	70	120
7.	F7	10	220	90	80
8.	F8	10	220	100	70
9.	F9	10	220	110	60
10.	F10	10	240	120	30

Preparation of rate controlling membrane

Rate controlling membrane was prepared by solvent evaporation method.

0.5 mg of ethyl cellulose polymer weighed and dissolved in 10ml of chloroform with Polyethylene glycol as plasticizers. Then the solution is poured on the horizontal surface of Petridis and left for evaporation of solvent in order to obtain a thin film. (Geeta Agrawal *et al*., 2009).

Preparation of drug reservoir and of Transdermal patch

The prepared proniosomal gels were fabricated by encapsuling within a shallow compartment of drug impermeable backing membrane (laminatedaluminum foil). A micro porous tape of larger areawas stuck onto the impermeable backing membrane to bring the transdermal patch in close contact with the skin. The device was closed by a release linear on the open side. (Chandra Amrish *et al*., 2009)

Evaluation

pH Determination

The pH of each proniosomal gel was determined using a pHmeter. The Electrode wasfirst calibrated with P^{H} 4.0 and P^{H} 7.0 solution, then reading was recorded on P^{H} meter. (HemanthN. Patil *et al., 2012*)

Viscosity Determination

The Viscosity of each Proniosomal gel was determined by using Brookfield viscometer with Spindle no: 64 at 20 rpm. (HemanthN.Patil *et al*., 2012)

Scanning electron microscopy

Particle size of Proniosomal gel is a very important characteristic. The surface morphology (round, smoothness, and formation of aggregates) and the size analysis was performed by Scanning electron microscopy. A small amount of Proniosomal gel samples were placed on a stud and platinum was coated on them by Auto sputter fine coater. JFC 1600, JEOL, Japan. Then the platinum coated samples were analyzed in a cold field emission scanning electron microscope, JEOL, JSM-6701F Japan and photographed.

Entrapment efficiency

The 0.2 mg of proniosomal gel was taken with 10ml of phosphate buffer. The above mixture was sonicated in a sonicator bath. After that solution placed in centrifuge for centrifugation at 20,000 rpm at 20oC for 30 minutes. The supernatant was collected and diluted with phosphate buffer. (Sandeep Gupta et al., 2009) The resulting solution was assayed by UV spectroscopy at 276nm. The percentage of encapsulation was calculated by following equation:

Drug Content

The drug content was determined by 0.2gm proniosomal gel sample was withdrawn from container and dissolved in 10ml ethanol. Then the absorbance was measured by UV spectrometer against blank at 276 nm and the drug content was calculated. (HemanthN.Patil *et al*., 2012)

In-vitro Drug Release Study

In-vitro drug release studies were performed on a Franz diffusion cell with an effective diffusion area of 3.12 cm2. The cellophone membrane was mounted between the donor compartment and receptor compartment. The proniosomal gel converted into Transdermal patch to be placed on one side of the cellophone membrane. The receptor compartment containing medium was phosphate buffer PH 7.4. The receptor compartment was surrounded by water jacket to maintain the temperature at 37±1oC. Heat was provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid was stirred by a Teflon coated magnetic bead fitted to a magnetic stirrer. At each sampling interval, samples were with drawn and replaced with an equal volume of phosphate buffer. The samples were filtered through a 0.2 µm filter membrane, absorbance of sample was measured UV-Visible spectrophotometer at 276nm against blank. The % of drug Release was plotted againsttime.(Kiranyadev et al., 2010).

Drug Release Kinetic Data Analysis

The release data obtained from various formulations were studied further for their fitness of data in different the kinetics models like zero, first, Higuchi, Peppas.

In order to understand the kinetics and mechanism of drug release, the result of in-vitro drug release study of proniosomal gel were fitted with various kinetic equation like zero order as cumulative % release vs time, Higuchi model as log cumulative % drug release vs square root of time.r2 and k values were calculated for the linear curve obtained by regression analysis from the plots.

Zero order kinetics Drug dissolution from pharmaceutics dosage forms thatdo not disaggratedandrelease the drug slowly, assuming the area does not change and no equilibrium conditions are obtained.

Stability analysis

The ability of vesicles to retain the drug was assessed by keeping the proniosomal gel at three different temperature conditions, the conditions are refrigeration Temperature (4-8oC), Room temperature (25±2ºC) and oven (45±2ºC). Throughout the study, proniosomal formulations were stored in aluminum foil-sealed glass vials. The samples were withdrawn at different time intervals over a period of two months and drug leakage from the formulations was analyzed for drug content. (*HemanthN.Patil et al., 2012, Shankar et al., 2010, Ankurguptha et al., 2007*)

RESULTS

Preformulation study

Preformulation testing is an investigation of Physical and Chemical Properties of a Drug Substance alone and when combined with excipients. It is first step in the lucid progress. The overall objective of Preformulation testing is to make information useful to the formulator in developing stable and bioavailability dosage forms clearly, the type of information needed will be depends on the dosage form to be developed. The use of preformulation parameters maximizes the changes in formulating an acceptable, safe, efficacious and stable product and at same time provides the foundation for optimization of the drug product quality.

Glipizide formulation Standard graph of Glipizide

Table 2 Standard graph of Glipozide

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE
1	5	0.113
2	10	0.235
3	15	0.376
4	20	0.496
5	25	0.628
6	30	0.745
7	35	0.871
8	40	0.996

Table No: 3 Different State of Proniosomal Gel Preparations

S.NO	F. NO	DRUG (mg)	SPAN60 (mg)	CHOLESTROL (mg)	LECITHIN (mg)	OBSERVATION

1	F1	10	180	10	200	Pale Yellowish Gel
2	F2	10	180	20	190	Yellowish Gel
3	F3	10	180	40	180	Yellowish Gel
4	F4	10	200	50	140	Yellowish cream
5	F5	10	200	60	130	Yellowish semi solid
6	F6	10	200	70	120	Yellowish semi solid
7	F7	10	220	90	80	Yellowish semi solid
8	F8	10	220	100	70	Yellowish semi solid
9	F9	10	220	110	60	Yellowish semi solid
10	F10	10	240	120	30	Yellowish semi solid

Evaluation

P^H Determination

The ten different proniosomal gel P^H was determined by the P^H meter.

Table No: 4 P^H of Proniosomal Gel

S.NO	Formulation Code	H
1.	F1	6.90±0.14
2.	F2	6.98±0.32
3.	F3	6.89±0.57
4.	F4	6.91±0.41
5.	F5	6.93±0.58
6.	F6	6.87±0.36
7.	F7	6.90±0.78
8.	F8	7.07±0.27
9.	F9	7.11±0.58
10	F10	7.18±0.63

n=3 ±S.D*

Skin compatibility is the primary requirement for a good topical formulation, it was

found that the pH of all the formulations were in the range of 6.87 to 7.18 that suits the skin pH, signifying skin compatibility. The results of pH determination are reported. The results were shown to the following table.No:10

Viscosity Determination

The ten different Proniosomal gel Viscosity was determined by the Brookfield viscometer. Viscosity extent of all the formulations revealed optimum consistency and the results were shown to the following table no:12.

Table 5 Determination of viscosity

S.No	Formulation Code	Viscosity
1.	F1	46127
2.	F2	45773
3.	F3	43672
4.	F4	42019
5.	F5	41371
6.	F6	38674
7.	F7	36096
8.	F8	35885
9.	F9	33098

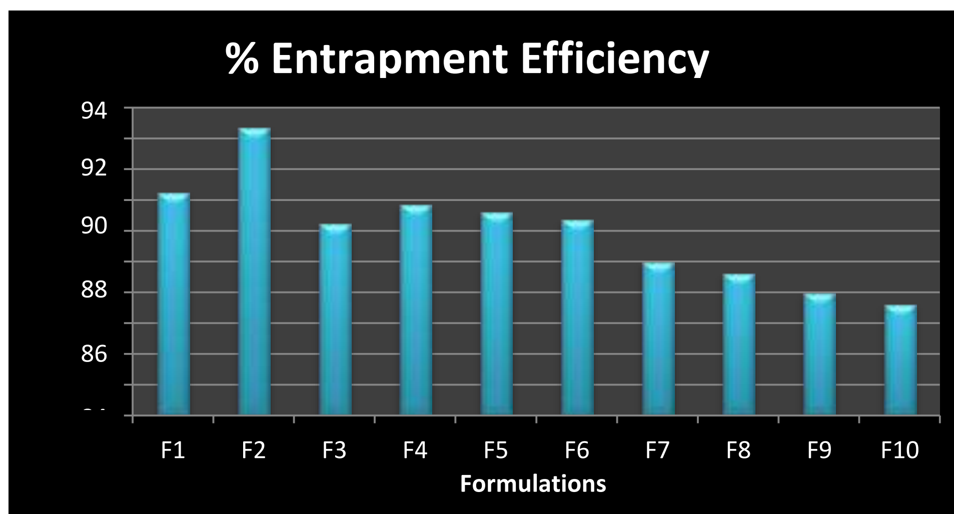
Encapsulation Efficiency

The percentage Encapsulation Efficiency of six different Proniosomal formulations was found. The Encapsulation Efficiency is one of the main parameters in a plan of the Proniosomal formulations. The Encapsulation Efficiency relies on the stability of the vesicle which is greatly dependent on the type and amount of surfactant forming the bilayers, the amount of both cholesterol and lecithin.

Effect on surfactant:

The nonionic surfactant is the central building block of Proniosomal vesicle. The stability and Encapsulation Efficiency were highly affected by the essential properties of surfactant such as chemical structure and phase transition temperature. HLB value either increase or decrease it was indicate changes of Encapsulation Efficiency. The chemical structure of span 60 which is length alkyl chains shown higher Encapsulation Efficiency. Span 60 having higher phase transition temperature were the largest partexpected in order to gel forming less leaky bi layers, so it produces higher Encapsulation Efficiency.

Effect on Cholesterol:



Graph No: 1 Entrapment Efficiency of Proniosomal Gel

Drug Content:

Uniformity in content of proniosomal gel (F1 to F10) were confirmed to assure Uniformity in dosage. The results were reported in following table.

Table No: 6 Drug Content of Proniosomal Gels

S.NO	Formulation Code	Drug Content
1.	F1	87.50± 0.144%
2.	F2	90.00± 0.25%
3.	F3	80.0±0.866 %
4.	F4	82.5± 0.520%
5.	F5	85.0±0.866%
6.	F6	75.0± 0.381%
7.	F7	70.0±0.577%
8.	F8	72.50± 0.381%
9.	F9	65.0±1.526%
10.	F10	62.5±1.041%

Scanning Electron Microscopy:
Shape and surface characteristic ofproniosomal gel examined by scanning electron microscopy analysis as shown fig No:

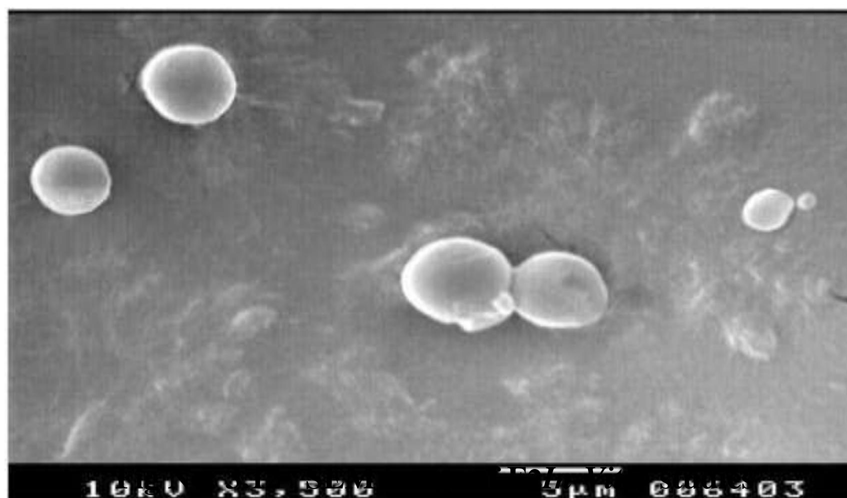
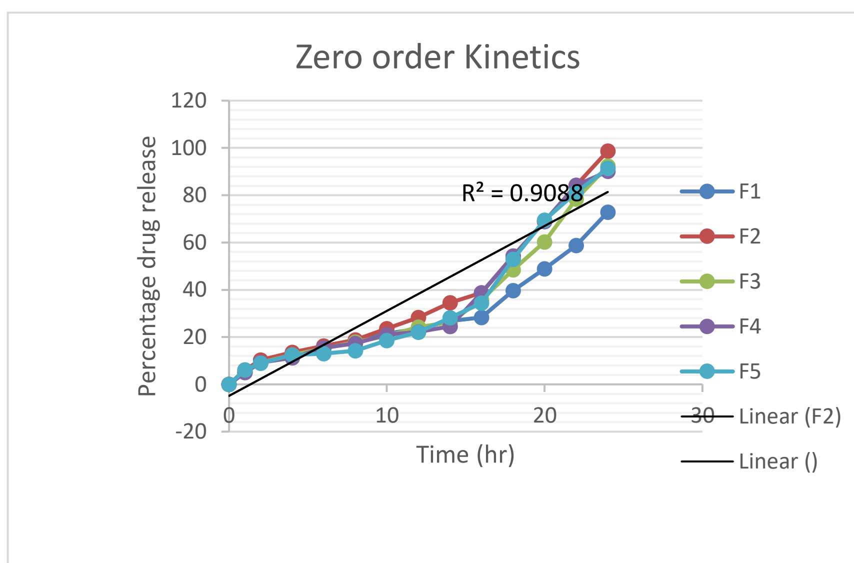
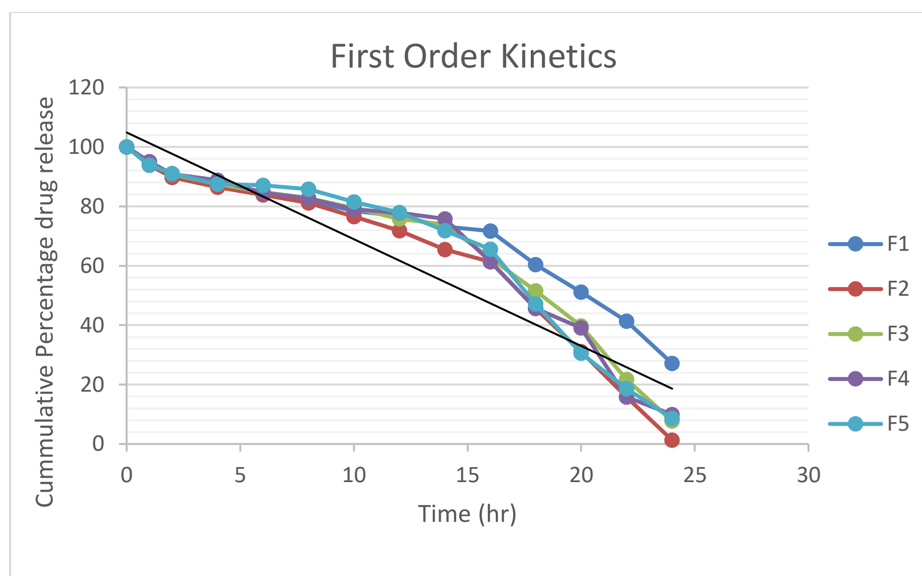


Figure 1 Scanning Electron Microscopy

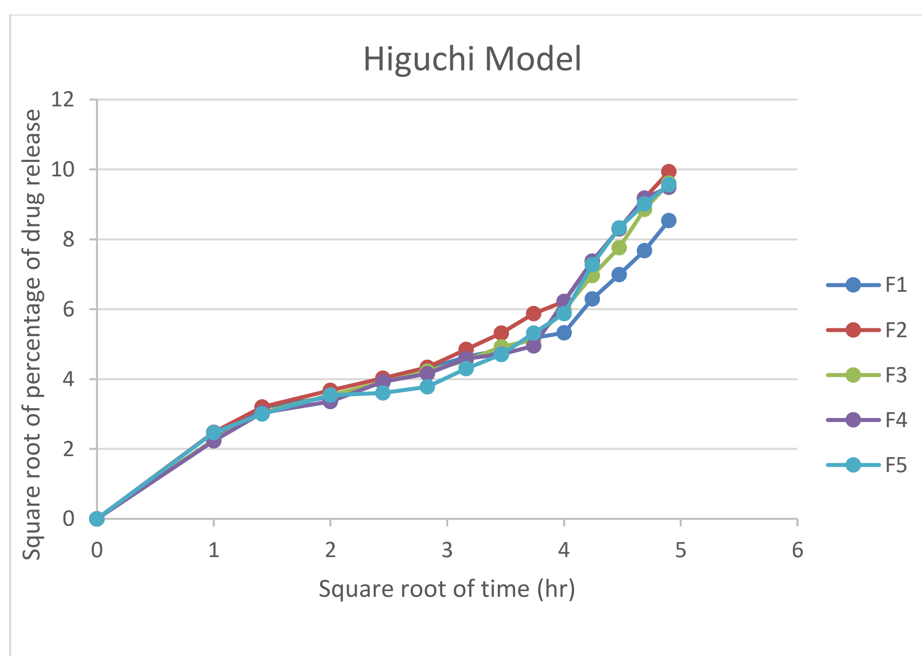
***In-Vitro* Drug Release of Prepared Transdermal patches**



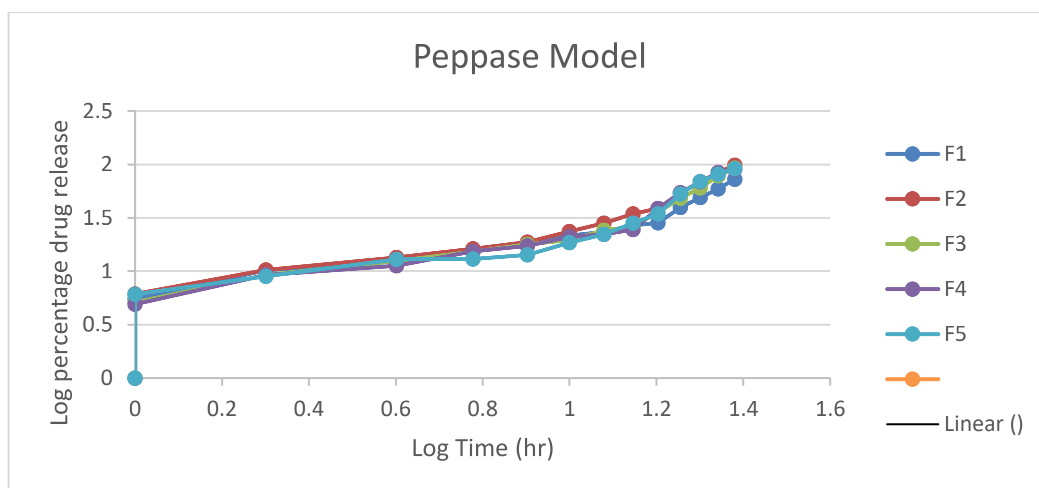
Graph 2 Zero order Drug release of formulation F1 to F5



Graph 3 First order release Kinetic of formulation F 1to F6



Graph 4 Higuchi Kinetic of formulation F1 to F6



Graph 5 Peppase Model F1 to F6

Stability Analysis

Stability analysis carried out to the optimized formulation. The amount of drug retained. The result shown the pronisomal gel formulation was quite stable at refrigeration and room temperature as not leakage of drug was found at these temperatures.

The percentage drug retained at evaluated temperature (45ºC) it should have decreased due to the melting of the surfactant. From the results of vesicular size and shape was similar then compared to SEM of optimized formulation (F2) before 2 months Fig No: 14. Therefore the proniosomal gels were stored in room or refrigeration temperature.

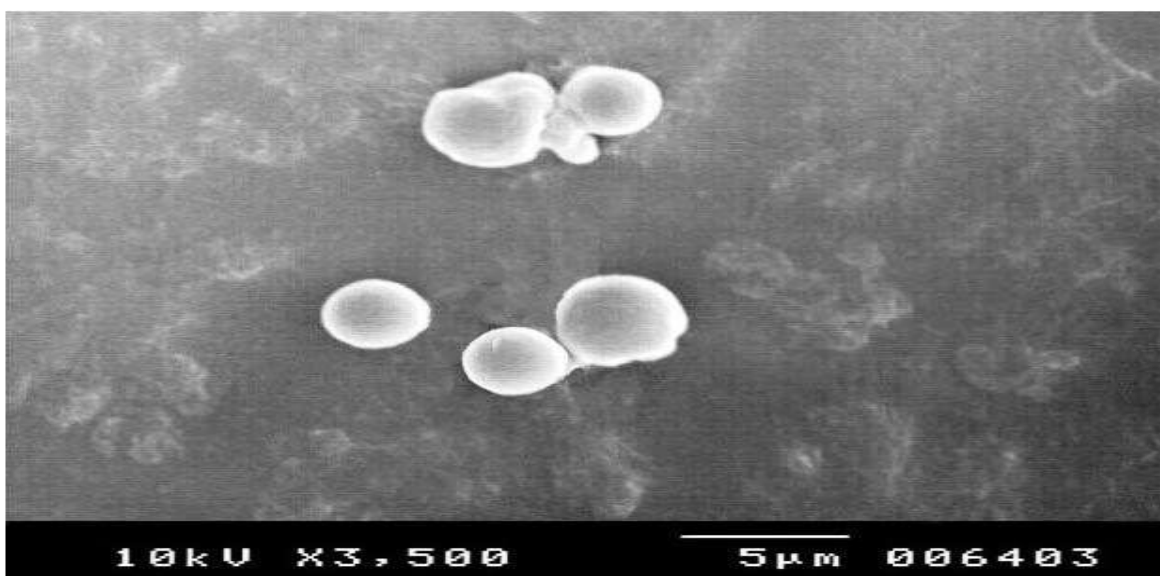


Figure 2 SEM Image of F2 after two months

SUMMARY AND CONCLUSION

In the present study, a variety of Proniosomal gels were prepared by phase coservation method with different ratio of surfactant, cholesterol and lecithin.

Drug polymer interactions were studied using FT-IR analysis. The result shows there was no change in the spectra of pure drug Glipizide alone and physical mixture. The DSC study of drug and cholesterol and infusion drug complex showed that there was no major difference in DSC thermo gram.

The morphology of prepared Proniosomal gel was observed under SEM. Itwasproduce good spectral smooth surface area is substantiation by the photographs. The observed vesicles with small diameter to permeate through the skin as small vesicle tend to fuse readily.

Proniosomal gel was produce high entrapment efficiency by using the alcohol, from the results of entrapment efficiency to depend upon the cholesterol level. The amount of cholesterol level increase to produce higher entrapment efficiency. Incorporation of lecithin to produce act as a permeation enhancer. According to the evaluation parameter like nature of the formulations, Viscosity, entrapment efficiency and drug content to the following formulations F6, to F10 cannot be applied to the Transdermal patches. So it can be avoid for the further steps.

Remaining formulation F1, F2, F3, F4, F5, and F6 can be taken for remaining studies. In this, *in-vitro* study showed the drug release was decreases by increase the amount of cholesterol content. The formulation F2 showed good of skin permeation (39.325 µg/cm^2) and cum percentage of drug releases (98.710%) at end of 24 hours. The *in-vitro* release applied various kinetic models. It was showed Zero order release which confirmed diffusion mechanism by the correlation value from proniosomal gel convert Transdermal patches. Correlations value of Higuchi's plot were in between 0.896 to 0.9.9 to which revealed that the mechanism of drug release and further more Korsmeyer-Peppas correlation values ranges from 0.847to
0.877 1also confirmed the diffusion mechanism.

Based on the entrapment efficiency, Release study, kinetic models and drug content formulation F2 was subjected for stability studies carried out various storage conditions. The percentage of drug content after a period of two months for 2-8°C, 25°C± 0.5^{o}C and 45°C were found to be 98%, 92% and 34% respectively. Observed that the result proniosomal gel Transdermal patches were stable under refrigeration temperature and room conditions with least leakage

- This project was design to investigate the chance of manufacturing to Proniosomal gel Transdermal patches. The result indicated the Proniosomal gels were very promising drug carriers.
- The present formulation study on Glipizide is an effort to prepare Proniosomal gel converted into the Transdermal patches and to evaluate the performance. The content of nonionic surfactant and cholesterol is evaluated in this study.
- The best formulation of Proniosomal gel was one which have high Efficiency is found to be surfactant and cholesterol content dependent. The release rate is also depending upon surfactant and cholesterol content. The FT-IR studies indicated no chemical interactions between drug,
- Other excepients and stability of drug during the method of preparations.
- The formulation F2 which shows higher entrapment efficiency was 92.75%. In-vitro release study of F2 shows release 98.710% and drug permeation 39.325µg/cm^2 at the end of 24 hrs which shows sufficient release of drug in phosphate buffer. The *in-vitro* release data applied to various kinetic models to

predict the drug release kinetics. Values were obtained from Higuchi's, Peppa's plot verifies result to Diffusion mechanism and zero order kinetics.

- By this facts study can be concluded the Proniosomal gel Transdermal patches showed controlled drug release properties. The combination of cholesterol and surfactant ratios was to produce sustained release of over a long period of 24 hours for the management of diabetics.
- This Proniosomal Transdermal patches as a device, penetrate to the skin barrier along to the skin moisture gradient. This Proniosomal gel is containing component that stabilize the lipid bi layer and thus important to comfortable vesicle.
- The Proniosomal gel could be an effective alternative vehicle for delivering the drug through Transdermal route to avoid side effects, first pass metabolism, GI irritations, patient compliance associated with oral route. Proniosomal Gel Transdermal patches were highly stable, more rate of Drug release and reducing the drug degradation then compared to other type of Transdermal patches.
- The method of preparation of Proniosomal gel Transdermal patches is very simple, do not involved long procedure and using limited number of pharmaceutical excepients.
- In the commercial market very less number of Transdermal patches are available. So may be our formulation proniosomal gel Transdermal type patches are potential and ideally suitable for.

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