FORMULATION AND EVALUATION OF PRONIOSOMAL TRANSDERMAL PATCHES OF GLIPIZIDE

A Dissertation submitted to

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Submitted by

Reg. No: 26104201

Under the guidance of

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CERTIFICATE

This is to certify that the work embodied in this thesis entitled **"FORMULATION AND EVALUATION PRONIOSOMAL TRANSDERMAL PATCHES OF GLIPIZIDE"** submitted to The Tamilnadu Dr. M.G.R. Medical University Chennai, was carried out by**Miss.Kalpanadevi.M (Reg.No.26104201)** in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 in the practical fulfillment of the degree of "Master of Pharmacy" in Pharmaceutics under my direct supervision and guidance.

This work is original and has not been submitted in part or full for any other degree or diploma of any university.

Place: Erode **Mr.Raja.K,M.Pharm,(Ph.D.,).**

Date: Research Guide

DECLARATION

The work presented in this thesis entitled "**FORMULATION AND EVALUATION PRONIOSOMAL TRANSDERMAL PATCHES OF GLIPIZIDE"**was carried out by me in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode, under the direct supervision and guidance of **Mr.RAJA.KM.Pharm.,(Ph.D).,**Professor, Department of Pharmaceutics,Nandha College of Pharmacy, Erode -52.

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CONTENTS

ABBREVATIONS

µg	Microgram
mg	Milligram
µm	Micrometer
hrs	Hours
mmol	MilliMol
^{o}C	Degree celcious
dL	Deciliter
%	Percentage
Fig	Figure
Tab	Table
EE	Encapsulation Efficiency
TDDS	Transdermal drug delivery system
NDDS	Noval drug delivery system
SEM	Scanning electron microscopy
DSC	Differential Scanning Calorimetry
FN	Formulation No
FT-IR	Fourier Transform Infrared Red Spectroscopy
v_s	versus

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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 system s 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 two major mechanisms can be notable for desire sites for drug release (1) passive, (2) active targeting controlled release.

Drug delivery carrier:

Colloidal drug carrier systems as micellar solutions, vesicle and liquid crystal dispersion, as well as nanoparticle dispersion consist of small particles of 10-400 nm in diameter is effective drug delivery system. When developing these are formulations to generate systems with optimized drug loading and release properties, long shelf life and low toxicity. The incorporated drug participates in the microstructure of the system and may persuade it due to molecular interactions, especially if the drug posses amphiphillic and or mesogenic properties. Drug delivery system using colloidal particulate carriers such as liposomes, niosomes and proniosomes have distinct advantages over conventional dosage forms. These liposomes, niosomes, proniosomes are used to improve the therapeutic index of both existing and new drug molecules by encapsulating an active medicament inside vesicular structure in one such system.(*Dwarakandha reddy.P,et.al.,2010*)

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. They can incorporate both liphophilic and hydrophilic drugs. The different types vesicular system such as liposomes, proniosomes, noisome, transferosome and pharmacosomes.

Vesicular system- carrier for drug delivery

The vesicular systems are highly ordered assemblies of one or several concentric lipid bilayers formed, when certain amphiphilic building blocks. Drug carrier can be engineered to slowly degrade, react to stimuli and be site-specific. To control degradation of drug and loss, prevention of harmful side effects and increases the bioavailability of the drug at the disease site. Encapsulation of a drug in vesicular structures can be predict to prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity if selective update can be achieved.(*kavitha,et,al.,2010*).

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 liphophilic drugs can be incorporated.
- Delays elimination of rapidly metabolizable drug and thus function as sustained release system.

Liposomes

The liposomes have join as most practically useful carriers for in vivo drug delivery as majority of formulations has concentrated on the of phospholipids vesicles or liposomes as potential drug carrier system. Liposomes or lipid base vesicles are microscopic vesicles that are formed as result self assembly of phospholipids in an aqueous media resulting

closed the belayed structures. This system is a closed bilayered structures is a spontaneous process and usually needs some input energy in the form of physical agitation, sonication, heat etc. The lipid bilayered membrane enclosed aqueous core, both water and lipid soluble drugs can be successfully entrapped into the liposomes. The lipid soluble drug or liphophilic drug get entrapped into bilayered membrane whereas water soluble or liphophilic drugs gets entrapped in to central of aqueous core of the vesicles. Liposomes are potential carrier for controlled drug release of tumors therapeutic agents of antibiotic, for gene and antisense through nucleic acid, sequence delivery, immunization though antigen and anti-Parkinson's.(*Ravi kumar,et,al.,2011*)

Advantages

- Liposomes supply both a lipophilic environment and aqueous milieu interne" in one system and are therefore suitable for delivery of hydrophobic, amphipathic and hydrophilic drugs and agents.
- Liposomes could encapsulate not only small molecules but also macromolecules like superoxide dissimulates hemoglobin, erythropoietin, interleukin-2 and interferon-g.
- Liposomes reduced toxicity and increased stability of entrapped drug via encapsulation.
- Liposomes help to reduced exposure of sensitive tissues to toxic drugs.

Disadvantages

- Less stability (chemical and physical instability)
- High production cost
- Leakage and fusion of encapsulated drug
- Sometimes phospholipid undergoes oxidation and hydration

Niosomes

Niosomes are non-ionic surfactant vesicles that entrap a solute in a manner analogous to liposomes. They are osmotically active, and a stability of the entrapped drugs. Handling and storage of surfactants required no special condition. Niosomes having infrastructure consisting of hydrophilic and hydrophobic moieties together, and as a result, can accommodate drug molecules with a range of solubility's.(*Akhilesh.D el,al.,2011*) Niosomes as drug carrier have shown advantages such as being cheap and chemically stable, they are associated with problem related to physical stability such as fusion, aggregation, sedimentation and leakage on storage. The size of niosomes is microscopic and lies in nanometric scale. The

particle size ranges from 10nm-100nm.(*Sudhamani.T.et,al.,2010, Ravi kumar,et,al.,2011, Narayan DuttShukla,et,al.,2011*)

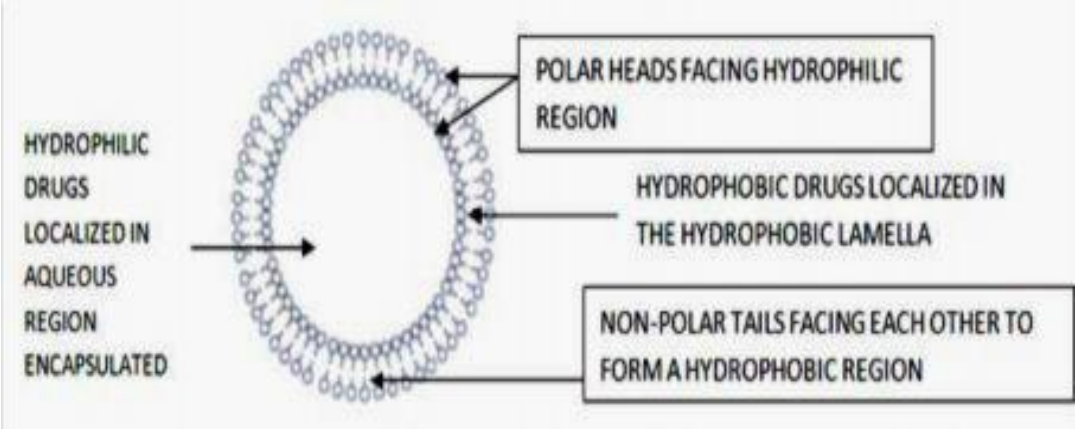


Figure: 1 Structure of Niosomes

Disadvantage of Niosomes

- Physical instability
- Aggregation
- Fusion
- Leaking of entrapped drug
- Hydrolysis of encapsulated drugs which limiting the self life of the dispersion

PRONIOSOMES

Proniosomes is dry formulation using suitable carrier coated with non-ionic surfactant and can be converted into niosomes immediately before use by hydration. The proniosomes are minimize the problem of niosomes physical stability such as aggregation, fusion and leaking and provide additional convenience in transportation, distribution, storage and dosing.(*RishuKakar,et,al.,2010*)

Types of proniosomes

Dry granular proniosomes

According to the type of carrier and method of preparation of dry granular proniosomes are

I. Sorbitol based proniosomes
II. Maltodextrin based proniosomes

Sorbitol based proniosomes is a dry formulation that involves sorbitol as a carrier, which further coated with non ionic surfactant and is used as a niosomes within minutes by addition of hot water following the agitation. These are normally made by spraying surfactant mixture prepared by organic solvent on to the sorbitol powder and then evaporating the solvent. The residual sorbitol decrease the entrapment efficiency to less than one half of that observed without sorbitol. The difficulties lie in testing of sorbitol particles because sorbitol is soluble in chloroform and organic solvents. It is prepared by sloe slurry method.(*Walve J.R,et,al.,2011*)

Maltodetrin based proniosomes prepared by fast slurry method. Time required to produce proniosome by slurry method is independent of the ratio of surfactant solution to carry out. Proniosomes of high surface to carriers ratio can be prepared. The preparation has potential of application in delivering of hydrophobic and amphiphilic drugs.

Liquid crystalline proniosomes

When the surfactant molecule are kept in contact with water, there are three ways low which liphophilic chains of surfactants can be transformed into a disordered, liquid state called lyotropic liquid crystalline state. This method avoids the use of pharmaceutically unacceptable solvents and it is easy to scale up. This system may directly be formulated into transdermal patch, up to hydration with water from skin it may be converted into niosomes. As the formulation is in direct contact with skin, it itself act as permeation enhancer.(*Walve J.R,et,al.,2011*)

Mechanism of Action

On the transdermal/ topical application of vesicle have rendered conflicting results. The four types of mechanism used in vesicle-skin interactions observed in human skin which induced various effects on dermal or transdermal delivery system.

Proniosomal gel vesicles are composed both nonionic surfactant and phospholipids both can act as penetration enhancer and useful increase penetration power of many drugs. The proniosomal formulations can increase amount of drug permeated through the stratum corneum. The hypothetical mechanism of skin permeation related to a possible reorganization of the proniosomal membrane at the level of stratum corneum. The improved drug passage through the outer skin layer seems to be medicated by the high flexibility of the bilayer structure.

There is a direct contact of proniosomal gel with skin. Proniosomal gels are composed to the non ionic surfactant, these are mainly interact with skin. The hydrogen bonding will strengthen and stabilize the lipid bilayer and as a result will pass on the barrier property of stratum corneum.

- Adsorption and fusion of proniosomal gel on the surface of skin leading to a high thermodynamic activity gradient of drug at the interface, which is the driving forces for permeation of lipophillic drug.
- The penetration enhancers effect of vesicles to reduce stratum corneum barrier property.
- Interactions are the skin formulation interface involve adsorption and fusion of vesicle of proniosomes on the stratum corneum structure, resulting in a new structure formation.
- Vesicle skin interactions are found in the deeper layers of stratum corneum involve bilayer alter structure.(*Ashwini singh rawat et al*.,2011,*Nidhipanday et al*.,2011, *Geetha agarrwal et al*., 2010,*KiranYadav et,al.,2010*)

In addition of the several other mechanism which could explain the ability of vesicle to modulate drug transfer across skin, including:

- Nature of drug
- The vesicles act as penetration enhancers to reduce the barrier properties of the skin
- Size and composition of vesicles
- Biophysical factors

Materials used in proniosomal gel

Proniosomal gel is generally consisting of non-ionic surfactant, lecithin, alcohol, aqueous phase and miscellaneous.

Surfactant

The selection of surfactant should be done on the basis of HLB value. As hydrophilic lipophilic Balance is a good indicator of the vesicle forming ability of any surfactant, HLB number in between 4 and 8 was found to be compatible with vesicle formation. The HLB values are responsible for degree of entrapment efficiency. Transition temperature of surfactant

also affects the entrapment of drug in vesicles. Span with highest phase transition temperature provide the highest entrapment efficiency for the drug.(*Walve J.R,et,al.,2011,Kiranyadev,et,al.,2010*)

Phosphatidyl choline

Phosphatidyl choline is a major component of lecithin. Depending upon the source it is named into egg lecithin and soya lecithin. Lecithin used in a Proniosomal gel as permeation enhancers. Adding of lecithin in Proniosomes is produce the percentage of entrapment should be increased and to produce vesicle in smaller size due to increase the hydrophobicity which result in reduction of vesicle size. There is probably formation of more compact and well organized bi-layers which prevents the leakage of drug.

Cholesterol

Cholesterol is important for the vesicle formation. It is response for an entrapment of drug in vesicles. There are reports that entrapment efficiency increase with increase the cholesterol content and by usage of span 60 which higher transition temperature. It was also observed that very high cholesterol content had a lowering effect on drug entrapment to the vesicle. This could be due to the fact that cholesterol beyond a certain level starts disrupting the regular bi-layered structure leading to loss of drug entrapment.

Solvent

Alcohol used in Proniosomal preparation has a great effect on vesicle size and drug permeation rate. Vesicle formed from different alcohols are of different size and they follow order Ethanol> Propanol>Butanol> isopropyl alcohol. Highest size of vesicle in case of ethanol is due to its greater solubility in water and smallest in size of isopropyl alcohol, may be due to branched chain present in it.

Aqueous phase

Phosphate buffer p^H 7.4, 0.1% glycerol, hot water is used as aqueous phase in preparation of Proniosomal gel.(*Kiranyadev,et,al.,2010,Walve J.R,et,al.,2011*)

Preparation of Proniosomes

The Proniosomes are prepared by different methods such as

- Slurry method.
- Coacervation phase separation method
- Slow spray-coating method

Slurry method

Maltodextrin powder 10 gm as carrier is added to a 250 ml round bottom flask and the entire volume of surfactant solution was added directly to the flask to form slurry. If the surfactant solution volume is less, then additional amount of organic solvent can be added to get slurry. The flask is attached to the rotary evaporator and vacuum is applied until the powder appeared to be dry and free flowing. The flask was removed from the evaporator and kept under vacuum overnight. Proniosomes powder was stored in sealed containers at 4^0C. The time required to produce Proniosomes is independent of the ratio of surfactant solution to carrier material and appear to be scalable. (*Thejaswi.C,et,al.,2011,Raja K,et,al.,2011*)

Advantages

- Maltodextrin is a polysaccharide easily soluble in water and it is used as carrier material in formulation, it is easily coat the maltodextrin particles by simply adding surfactant in organic solvent to dry maltodextrin.
- Due to uniform coating on carrier it protects the active ingredients and surfactant from hydrolysis and oxidation etc.
- The higher surface area results in a thinner surfactant coating, which makes the rehydration process more efficient.

Coacervation phase separation method

In this method, the weighed amounts of surfactant, lipid and drug are taken in a clean and dry wide mouthed glass vial of 5 ml capacity and alcohol is added to it. After warming, all the ingredients are mixed well with a glass rod, the open end of the glass bottle is covered with lid to prevent the loss of solvent from it and warmed over water bath at 60-70^0c for about 5 min until the surfactant mixture is dissolved completely.
(*IbrahimA.Alsara,et,al.,2005,IntakhabAlam,et,al.,2010Chandra.A,el,al.,2008,*) Then the aqueous phase is added and warmed on a water bath till a clear solution formed which is then converted into Proniosomal gel on cooling.(*Hanan.M.Ei-laithy,et,al.,2011,NandKishore,et,al.,2010*)

Advantages

- Method is simple and without time consumable so it does required any specialized equipment.
- Specially adopted for gel preparation.
- Small quantities or small dose formulation can be prepared on lab scale.

- It is used to reduce the side effects of drug and increased therapeutic effectiveness.

Slow spray-coating method

In this method, the Proniosomes are prepared by spraying surfactant in organic solvent onto sorbitol powder and then evaporating the solvent. The sorbitol carrier is soluble in the organic solvent, it is necessary to repeat the process until the desired surfactant loading has been achieved. This method was reported to be tedious since the sorbitol carrier for formulating Proniosomes is soluble in the solvent used to deposit the surfactant. Sorbitol is also found to interfere with the encapsulation of certain drugs.(*SankarV,et,al.,2010*)

Advantages

- Simple method and suitable for hydrophobic drug without concerns of instability or susceptibility of active pharmaceutical ingredient to hydrolysis.

Advantages of Proniosome over the Liposome and Niosome

The disadvantages of liposome and noisome are overcome by Proniosome.

- Liposome and Niosome have a problem of degradation by hydrolysis or oxidation.
- Liposome and Niosome are required special storage and handling.
- Sedimentation, aggregation or fusion on storage is usually seen in liposomes and Niosome.
- Purity of natural phospholipids is also varied in Liposome.
- Difficult in transportation, distribution, storage.
- Difficult in uniform of dose and scale up.

The design of the transdermal drug delivery system should be primarily aimed at achieved more predictable and increased bioavailability of drugs. Targeting the drug to the desire site of action would not only improve therapeutic efficacy but also enable a reduction of amount of the drug which must be administrated to achieve a therapeutic response, thus minimized unwanted toxic effects.(*Sudhamani.T.et,al.,2010*)

INTRODUCTION OF TRANSDERMAL DRUG DELIVERY SYSTEM:

The transdermal drug delivery is one most important of the novel drug delivery system. The transdermal drug delivery is one of the most effective methods of applications. Transdermal patches are flexible pharmaceutical preparations of varying sizes, containing one or more active substances. They are intended to be applied to the unbroken skin in order to deliver the active substance(s) to the systemic circulation after passing through the skin barrier. In this

drug delivery system, across the skin to have an effect on the adjacent to the site of application or to have an effective distribution of the systemic circulation.

TDDS has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin as well as for systemic delivery of drug.

TDDS has provide many advantages over conventional method are frequency excessive toxic and sometimes ineffective. The conventional drugs are in the form of tablets, capsules, injectables and ointment of in the body as pulses that usually produce large fluctuations of drug concentration in the blood stream and tissues.

Transdermal delivery system has provide an improved approach to the administration of drug by maintaining therapeutic constant concentration of the drug in the blood for desired period of time, high bioavailability and the fact that is non-invasive.

Transdermal delivery enables avoidance of gastrointestinal absorption and hepatic first pass metabolism. It produces not only the controlled constant administration of drug, but also continues input of drugs with short biological half life and eliminates the pulses into systemic circulation which often cause undesirable side effects.

ADVANTAGES OF TDDS

The advantages of transdermal drug delivery system follow as **(***Eseldinkeleb,et.al. 2011,Tyagi.R.K,et,al., 2011)*

- To avoid first pass metabolism, salivary metabolism and Intestinal metabolism.
- It is very useful for self medications to patients.
- In case of any emergency or reactions produced means removing the patch at any point of time during therapy can instantly stop drug input.
- Drugs showing gastrointestinal irritation and absorption can be suitably administered through the skin.
- It is convenient to non invasive route.
- Avoid the risk and Incovenience of IV therapy.
- Byepass Veriation in absorbance permits continues drug administraton.
- Reduce the chances of over dose or under dosing through prolonged , Preprogrammed delivery of drug at the required therapeutic rate.
- It provides reduce the dose frequency, so there is better patient compliance.

- Therapeutic failures associated with irregularities in the dosing with conventional therapies can be avoided.
- The adverse effects are minimized due to a steady and optimum blood concentration time profile.
- The release rate more prolong than compared to oral sustained drug delivery systems.
- The daily doses require is lower than that with conventional therapies.
- The drug release is such that there is a predictable and extended duration of activity.
- It can be used for chronic conditions where drug therapy is desired for a long period of time. e.g. Hypertension, Angina and Diabetics etc.
- Transdermal therapy is not feasible for ionic drugs.
- It cannot deliver drug in pulsate fashion.

FACTORS AFFECTING TDDS

1. Physicochemical properties of permeation

1.1 Partition coefficient

For molecules with intermediate partition coefficient and for highly lipophilic molecules, the intercellular route will be almost the pathway used to traverse the stratum corneum. These molecules are ability of partition out of the stratum corneum into the aqueous viable epidermal tissues. For more hydrophilic molecules, the transcelluar probably predominates. A water partition coefficient of 1 or garter is generally required for optimal transdermal permeability. It may be altered by chemical modification without affecting the pharmacological activity of the drug.

1.2 Molecular size

In this factor in determining the flux of a material through human skin is the size of the molecule. Molecular size is inversely relationship existed between transdermal flux and molecular weight of the molecules. In transdermal delivery the drug used within narrow range of molecular weight.(100-500).

1.3 Solubility/Melting point

The most organic materials with high melting points have relatively low aqueous solubility at normal temperature and pressure. The liphophilic molecules tend to permeate though the skin faster than more hydrophilic molecules. Liphophilicity is a desired property of

transdermal candidates, it is also necessary for the molecule to exhibit some aqueous solubility since topical medicaments are generally applied from an aqueous formulation.

1.4 Ionization

A unionized form drug can more permeate though the lipid barrier than compare to ionized drugs.

1.5 Other factors

Interactions between drug substance and their tissue can vary from hydrogen bonding to weak Vander Waals forces, and the effect of drug binding on flux across the tissue will vary depending on the permeate. Depending on the type of formulation selected, other may be important in a transdermal delivery system. (*Vinod K,et,al.,2010*)

2. Physiological factors

2.1 Skin barrier property in the neonate and young infant

The skin of new born is known to relative susceptible to irritants, other variables related to stratum corneum function such as p^H and stratum corneoum hydration may enhance the irritant potential to newborn skin. Skin surface pH values in new born are significantly higher in all body sites than those in adult skin. There are also changes in the metabolic capacity are not observed until 2 months or even 6-12 months of age which may additionally account for the sensitivity of baby skin to irritants. The skin surface of the newborn is slightly hydrophobic and relatively dry and rough when compare to older infants.

2.2Skin barrier properties in aged skin

The aged has no of physiological changes than compare to other skins. The corneocytes area shown to increase in surface area which may have implications for stratum corneum function due to resulting decrease the volume of inter neomeoctye space per unit volume of stratum corneum. The moisture content of human skin is decrease with age. There is flattening of the dermo epidermal junction. The area available for diffusion into the dermis is diminished.

2.3 Race

Radical differences between black and white skins have been shown in some anatomical and physiology functions of the skin. In black skin, increased intracellular cohesion, higher lipid content and higher electrical skin resistance levels compared to whites have been

demonstrated. Black skin suggesting the stratum corneum modulates the different radical response to irritant.

2.4 Body

The relative permeability of different skin sites is not simply a function of stratum corneum thickness as a different premeants exhibit varied rank orders through different skin sites. It is apparent that genital tissue usually provides the most permeable site for transdermal drug delivery. The skin of the head and neck is also relatively permeable compared to other sites of the body such as the arm and legs.

3. Physiological factors

Numerous disorders result in an eruption of the skin surface. In this case, the barrier properties of the stratum corneum are compromised, allowing the passage of drug into and through the skin. The skin disease associated with reduced barrier skin function with trans epidermal water loss up to twenty times higher in active disease. The reduced barrier function, which correlated with signs of scaling, enables increased percutaneous absorption of topically applied compounds. The plagues are largely devoid of intercellular lipid, reducing the convoluted lipid pathway to the dermo epidermal junction, thus enhancing permeation.(*Vinod K,et,al.,2010*)

TYPES OF TRANSDERMAL PATCHES:

The different type of transdermal systems were developed and fabricated. The types TDDS such as

- Matrix type
- Reservoir type
- Membrane matrix type
- Micro reservoir type
- Drug in adhesive type

Matrix type

Drug reservoir is prepared by dissolving the drug and polymer in a common solvent. The insoluble drug should be homogenously dispersed in hydrophilic or lipophillic polymer. The required quantity of plasticizer and permeation enhancer is then added and mixed properly. The medicated polymer formed is then molded into rings with defined surface area and controlled thickness over the mercury on horizontal surface followed by solvent evaporation at

an elevated temperature. The film formed is then separated from the rings, which is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. Most of the matrix patches are prepared by solvent evaporation method.*(GeetaArrarwalet.al., 2009)* Commonly used of matrix are cross linked polyethylene glycol, eudregit, ethyl cellulose, polyvinyl pyrrolidone and hydroxyl propyl methyl cellulose.

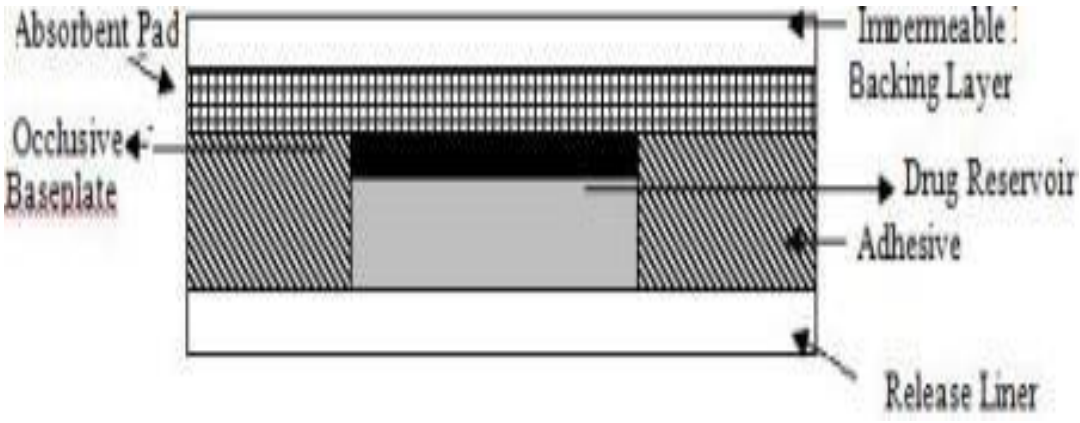


Figure:2 Design of matrix type transdermal patches

Reservoir type transdermal patches

Drug reservoir prepared by homogeneously dispersing drug particle in a rate controlling polymer matrix fabricated from either a lipophillic or a hydrophobic polymer. The drug dispersion in the polymer matrix is accomplished by either (1) blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer, followed by cross linking of the polymer chains, or (2) mixing drug solids with a rubbery polymer at elevated temperature. The resultant drug-polymer dispersion is then molded or extruded to form drug delivery device of various shape and sizes designed for specific applications. It can also fabricated by dissolving the drug and polymer in a common solvent, followed by solvent evaporation at an elevated temperature.

The drug reservoir is made up of homogenous dispersion of drug particle suspended in an unleachable viscous liquid medium to form a paste like suspension or gel or a clear solution of drug in an evaporating solvent. The drug reservoir is made by sandwiched

between rate controlling membrane and backing laminate layer.(*Debjitbhowmiket,al.,2010*) Rate controlling membrane materials are such as EVA, ethyl cellulose, silicon rubber, and polyurethanes.

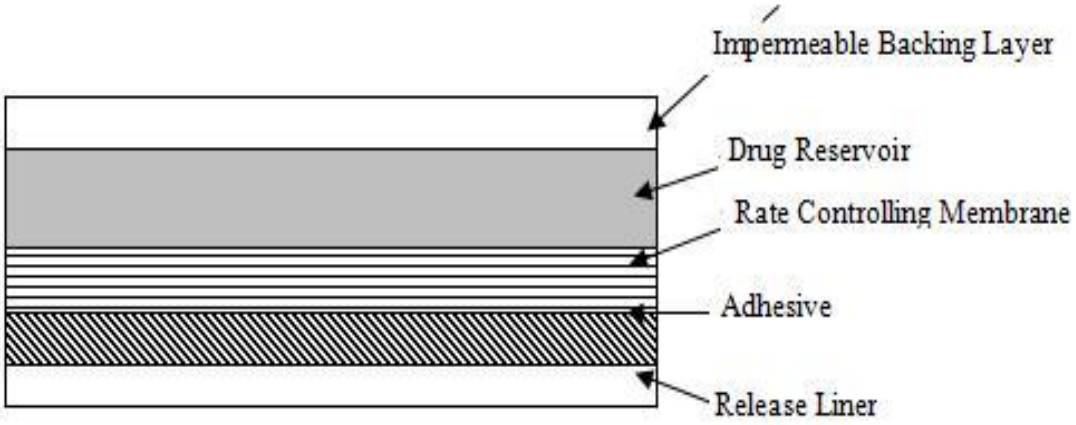


Figure: 3 Design of reservoir type transdermal patches

The rate controlling membrane may be prepared by solvent evaporating method. The solvent evaporation by polymer is dissolved in solvent with or without plasticizer. The solution poured on the horizontal surface and left for evaporation of solvent in order to obtain a thin film. The main advantage of reservoir type patches is that this patch design can provide at zero order release pattern to achieve a constant serum drug level.

Membrane matrix hybrid type patches

This is the modification of reservoir type transdermal patch. The liquid formulation of the drug reservoir is replaced with a solid polymer matrix which is sandwiched between rate controlling membrane and backing laminate.*(GeetaArrarwalet.al., 2009)*

Micro reservoir type transdermal patches

The drug reservoir is formed by suspending the drug in an aqueous solution of water miscible drug solubilizer e.g. polyethylene glycol. The drug suspension is homogenously dispersed by a high shear mechanical force in liphophilic polymer, forming thousand of un leachable microscopic drug reservoirs.(*Ashok kumar.J, et, al., 2010*) the dispersion is quickly stabilized by immediately cross linking the polymer chains in situ which produces a medicated polymer disc of specific area and fixed thickness.

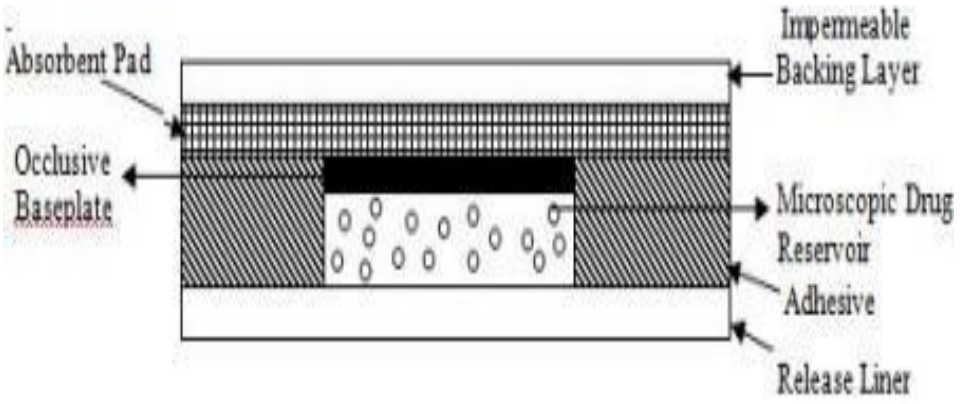


Figure: 4 Design of micro reservoir transdermal patches

Drug in adhesive type transdermal patches

The drug and others selected excipients, if any, are directly incorporated into the organic solvent based pressure sensitive adhesive solution, mixed cast as a film and dried to evaporate the solvents, leaving a dried adhesive matrix film containing the drug and exicipents. This drug in adhesive matrix is sandwiched between release liner and backing layer. Drug-in-adhesive patch may be single layer or multi layer. The multi layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane. (*GeetaArrarwalet.al., 2009,Eseldinkeleb,et.al., 2011*)

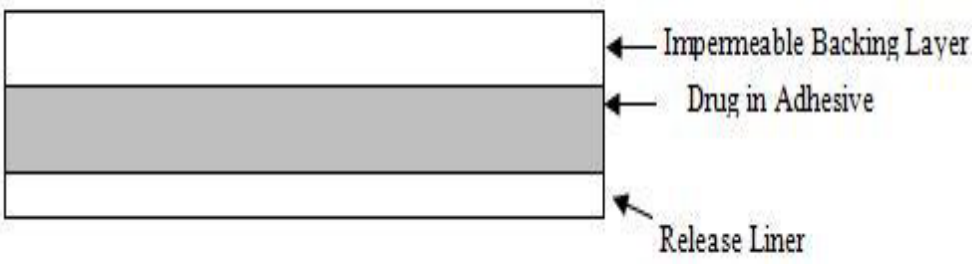


Figure: 5 Design of adhesive type transdermal patches

Conditions which Transdermal patches are used

- When the patient has intolerable side effects and who is unable to take oral medication and is requesting an alternative method of drug delivery.
- Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self medicate with their analgesia.
- It can be used in combination with other enhancement stregiges to produce synergistic effects.(*Vinod K,et,al.,2010*)

Mechanism of drug delivery in transdermal drug delivery system

Transdermal absorption occurs through a slow process of diffusion driven by the gradient between the high concentration in the delivery system and the zero concentration prevailing in the skin. The delivery system must kept continuous contact with the skin for a considerable time. It is a formulation or device that maintains the blood concentration of the drug within the therapeutic window. The drug levels neither fall below the minimum effective concentration not exceeding the minimum toxic drug.

A transdermal drug delivery system is a device that is made of one or more types of polymers embedded with drugs to deliver the embedded drug through the skin over a period of time. In this delivery system with the patch and its different layers are involved.

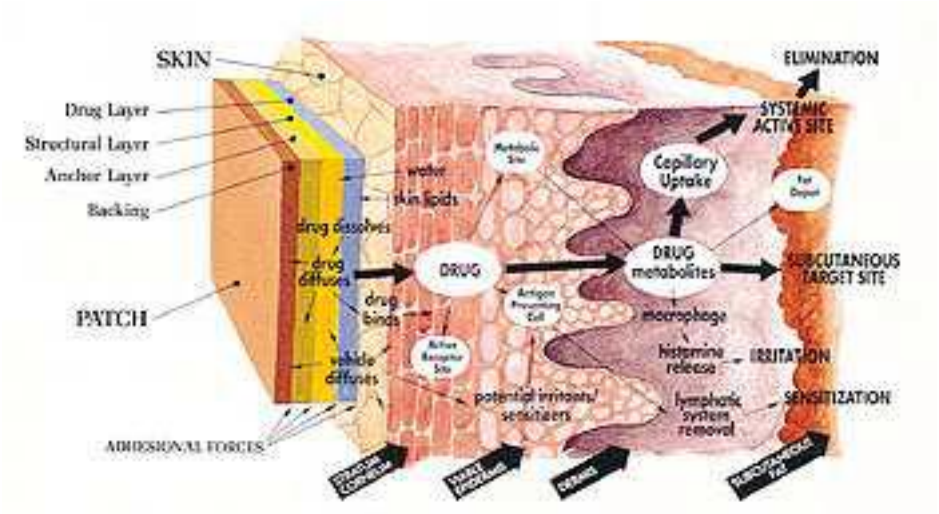


Figure: 6 Structure of skin permeation

The drug penetrate the skin obey's the fick's first law where steady-state flux (J) is related to the diffusion coefficient(D) of the drug in stratum corneum over a diffusional path length or membrane thickness(h), the partial coefficient(P) between the stratum cornuem and the vehicle and the applied drug concentration(C_0) which is assumed to be constant.

$$Dm/dt - J - DC_0P/I$$

ANATOMY AND PHYSIOLOGY OF SKIN

The skin is the major organ of the body making upto 16% of body weight, with a surface area 1.8cm^2.

The most vital functions are to form a physical barrier to the environment, allowing and restrictive the inward and outward passage of water. It is protective obstruction that prevents internal tissues from exposure to trauma, ultraviolet radiation, temperature extremes, toxins and bacteria.

The anatomy of skin divided into three layers such as epidermis, dermis and fat layers. (*Eseldinkelebet,al., 2011*)

Epidermis

The epidermis is the comparatively thin, tough, outer layer of the skin. The epidermis is made up of most of the cells of keratinocytes. The originate from cells in the deepest layer of the epidermis called basal layer. New keratinocytes receiving migrate up toward of the epidermis. After keratinocytes reaches the skin surface, they are slowly shed and are replaced by younger cells pushed up from below.*(Tyagi.R.K,et,al., 2011)*

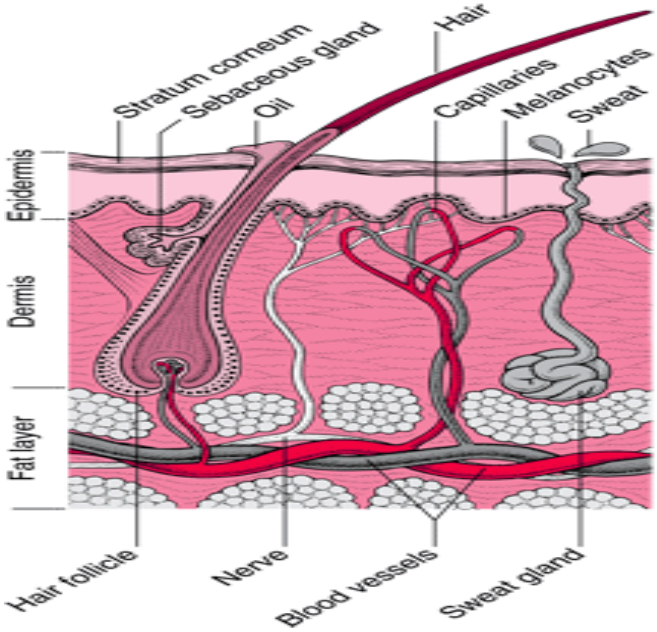


Figure: 7 Anatomy of skin

The outermost portion of the epidermis is called stratum corneum. It is moderately water proof and when undamaged, prevents most bacteria, viruses and other foreign substances from entering the body. The epidermis is defensive the internal organs such as muscles, nerves

and blood vessels against trauma. In some of the body area obligatory superior production (such as palms of the hand and the soles of the feet), outer keratin layer of stratum corneum is much thicker.

Scattered throughout the basal layer of the epidermis cells called melanocytes, which produce the pigment of melanin is one of the main contributor to skin color. The main function of melanin is to filter out ultraviolet radiation from sunlight, which damage DNA, resulting in various had effects, including skin cancer.

The epidermis is also containing Langerhan's cells, which are the part of the skin's immune system. These cells help detect foreign substance and defined the body against infections, they also play a role in the expansion of skin allergies.

Dermis

The dermis is the skin of second layer or next layer of epidermis. It is the thick layer of fibrous and elastic tissues, these are gives the skin its flexibility and strength. The dermis contains nerve ending, sweat gland, oil glands, hair follicles and blood vessels.

The nerve ending is response of sense of pain, tough, pressure and temperature. Some of area is contain more nerve ending than compare to other areas. The dermis contain another important glands are sweat gland. Sweat is composed of water, salt, and other chemicals. As sweat evaporates off the skin, it is help of cool the body.

The sebaceous glands secrete sebum into hair follicles. Sebum is an oil that keeps the skin moist and soft and act as a barrier against foreign substance. The hair follicles generate the various types of hair throughout body. Hair not only contributes to a person's appearance but has number of physical role, including body temperature and proving protection from injury, and enhancing sensation. The creation of hair follicle also contains stem cells capable of regrowing damaged epidermis.

The blood vessels of the dermis provide nutrients to the skin and help control body temperature. The heat makes blood vessels enlarge, allowing large amount of blood to circulate near the skin surface, where the heat is unrestricted. Cool make blood vessels narrow, retaining the body's heat.*(Tyagi.R.K,et,al., 2011)*

Fat layer

Below the dermis lies a layer of fat that fill the body from heat and cold, provides protective padding, and serves as an energy strong area. They contained living cells, called fat

cells, hold together by fibrous tissue. The fat layer varies in thickness, from a fraction of an inch on the eyelids to several inches on the abdomen and some of the body parts.*(Tyagi.R.K,et,al., 2011)*

Functions of the skin

There are many different structures within the skin. Together these structures are important protective properties to the skin that help to avoid damage to the influences. In this way, the skin:

- ***Protection:*** an anatomical barrier from pathogens and damage between the internal and external environment in bodily defense; Langerhans cells in the skin are part of the adaptive immune system.
- ***Sensation:*** contains a variety of nerve ending that react to heat and cold, touch, pressure, vibration, and tissue injury; see somaticsensory system and hap tics.
- ***Heat regulation:*** the skin contains a blood supply far greater than its requirements which allows precise control of energy loss by radiation, convection and conduction. Dilated blood vessels increase perfusion and heat loss, while constricted vessels greatly reduce cutaneous blood flow and conserve heat.
- ***Control of evaporation:*** the skin provides a relatively dry and semi impermeable barrier to fluid loss. Loss of this function contributes to the massive fluid loss in burns.
- ***Aesthetics and communications:*** others see our skin and can assess our mood, physical state and attractiveness.
- ***Storage and synthesis:*** act as a strange centre for lipid and water, as well as a means of synthesis of vitamin D by action of UV on certain parts of the skin.
- ***Excretion:*** sweat contains urea; however its concentration is $1/130^{th}$ that of urine, hence excretion by sweating is at most a secondary function to temperature regulation.
- ***Absorption:*** the cells comprising the outermost 0.25-0.40mm of the skin thickness almost exclusive supplied by external oxygen", although the "contribution to the total respiration is negligible". In addition, medicine can be administered through the skin, by ointments or by means of adhesive patch, such as the nicotine patch or iontophoresis. The skin is an important site of transport in many other organisms.
- ***Water resistance:*** the skin act as a water resistance barrier so essential nutrients aren't washed out of the body.

DISEASE PROFILE

Introduction of diabetes mellitus

Diabetes mellitus is a disease caused by defective functioning of the cells of the islets of Langerhans in the pancreas. The secretion made by the pancreas is known as insulin. Insulin's first is to help the body use glucose or sugar and when there is inadequate supply of insulin, the function of the body gets affected and very soon diabetes follows. The body loses its ability to metabolized sugar or it may develop because the body is producing too much of sugar. Diabetes is not a disease but a kind of disorder caused by inadequate supply as well as utilization of insulin in the body.

Anatomy and physiology of Pancreas

Pancreas an exocrine and endocrine gland of about 12-15cm long and 2.5cm thickness connected by two small ducts to duodenum. The pancreas divided into three parts such as head, body and tail.It is the primary organ involved in sensing the organism's dietary and energetic states via glucose concentration in the blood. The pancreas is soft, glandular organ.

The endocrine function is performed by clusters of cells the pancreatic islets, or islets of Langerhans that secrete the hormone insulin and glucagon into the blood. The exocrine tissues secretes digestive enzymes, these enzyme are secretes into a network of ducts that join the main pancreatic duct, which runs the length of the pancreas.

After a meal, Carbohydrated in food are converted into glucose in the intestine and liver and enters the blood stream- cells sense the rising the blood glucose level and secretes insulin into the blood to breakdown the glucose molecules. (*Vivek Kumar Sharma et al.,2010*)

Once it reaches the blood stream, insulin helps glucose to enter the body's cells, where it can be "burned" by the liver and muscles for energy. Liver and muscles can also convert glucose to glycogen, a reverse form of energy that is stored there for future use. All three hormones are polypeptides.

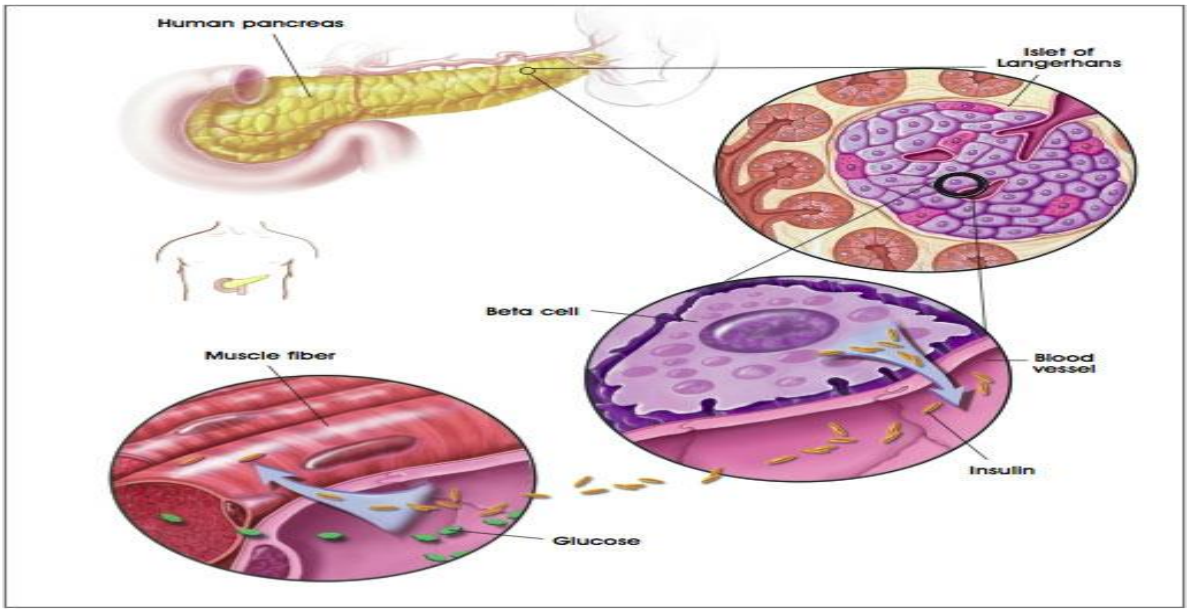


Figure: 8 Physiology of Pancreas

Types of diabetes

There are three types of diabetes

- Type 1 diabetes
- Type 2 diabetes
- Gestational diabetes

Type 1 diabetes (Insulin dependent diabetes mellitus)

The result from the body's failure to produce insulin, and a presently requires the person to inject insulin. It is otherwise called insulin dependent diabetes mellitus. In this type characterized by loss of the insulin producing beta cells of Langerhans in the pancreas leading to insulin deficiency. This type of diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes medicated nature, where beta cells loss T-cell mediated autoimmune attack.

Type 2 diabetes (non insulin dependent diabetes mellitus)

In this type characterized by insulin resistant this may combined with relatively reduced insulin secretion. The responsiveness of body tissue to insulin is believed to involve the insulin receptors. In this type of diabetes the most common type. It is also called as non-insulin dependent diabetes mellitus.

Maturity-Onset diabetes of the young

When present in the youngsters, non insulin dependent diabetes mellitus is often referred to as maturity onset diabetes of youth. This is the type of spontaneous diabetes and may be due to genetics of β cell function.

In this group, a ketosis-resistant, non insulin dependent, generally asymptomatic form of diabetics is present in individuals before age of 25.

Gestational diabetes mellitus

This is resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%-5% of all pregnancies and many improve or disappear after delivery. It is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%- 50% of affected women develop type 2 diabetes later in life.

It may be transient, untreated gestational diabetes can damage the health of the fetus or mother. This is risk to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system a nomalies and skeletal muscle malformations. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyper bilirubinemia may result forms red blood cells destruction. (*Vivek Kumar Sharma et al., 2010*)

Signs and symptoms

The classical symptoms of diabetes are

- **Polyuria** (frequent urination),
- **Polydipsia** (increased thirst),
- **Polyphagia** (increased hunger).
- **Diabetic keto acidosis (**Diabetic coma**)**

Ketoacidosis of different grades generally occurs in insulin dependent diabetes. The most common cause is infection. Others are trauma, stroke, pancreatitis, stressful conditions and inadequate doses of insulin.(*www.rxlist.com)*

The other symptoms of diabetes mellitus are such as dehydration, weight loss, nausea, vomiting and infections of the bladder.

Blood glucose level

Blood glucose i.e is the amount of glucose present in the blood. It is otherwise called as serum glucose level. The amount of glucose present in the blood is expressed in milli mol/liter. Normally blood glucose level is higher in time of after meal and lowers at morning.

Normal blood glucose level

Before meal: 4 mmol/L or 72mg/dl

After meal: 7.8 mmol/L or 140mg/dl

If the person suffering with diabetics Mellitus has the blood glucose level out of this range.

Drugs used for anti diabetic

Insulin

Insulin is consisting of two polypeptide disulfide bonds. Insulin was the first of these hormones to be discovered. Insulin in diabetes mellitus was immediately recognized, and clinical use of insulin in the treatment of this disease began almost immediately after its discovery. Diabetic patients are depending on insulin for the management for diabetics. Without insulin, they develop degenerative complications like microangiopathy, nephropathy, retinopathy. (*Leonard Tedong et.al.,2006*).

Major role of insulin are as follows:

- It facilities the passage of glucose through cell barriers into the cells.
- It effects the phosphorylation of glucose.
- It also plays role in oxidative phosphorylation.
- It is essential to lipid and protein catabolism.

Oral hypoglycemic agents

Sulfonyl urea

These are dived into two types:

First generation Drugs	Tolbutamide
	Chlorpropamide
Second generation drugs	Glipizide
	Gliclazide
	Glimepiride

Biguanides	Phenformin
	Metformin
Meglinitides analogues	Repagilinide
	Nateglinide
Thiazolidinediones	Rosiglitazone
	Pioglitazone
α-Glucosidase inhibitors	Acarbose
	Miglitol

Sulfonylureas

The act to force the pancreas to produce more insulin which then lowers the blood sugar level. For this medication the pancreas should at least produce some insulin. If pancreas not making insulin then this type of medication is not suitable and if patients suffering from allergy to sulpha drug then sulfonylureas have to be stopped.

The principle mechanism is decreased hepatic glucose output and increased uptake of glucose in muscles. High affinity receptors for sulfonylureas are present on the K_{ATP} channel activation causes depolarization,Ca^{2+} entry and insulin secretion.

Side effects

- Hypoglycemia
- Stomach upset
- Skin rash and itching
- Weight gain

Biguanides

It works by inhibiting the production and release of glucose from the liver. One of the benefits of biguanides is to reduce the weight gains and which helps to the lowering the blood glucose level. Enhance the peripheral tissue and in skeletal muscle. It also reduce the low-density lipoproteins.

Side effects

- Metal taste in mouth
- Nausea

- Stomach problem

Meglinitides

They help to make more insulin by the pancreas right after meal. The very good thing about they act very fast and the body uses it quickly to reduce the blood sugar level.If one medicine alone does not control the blood sugar, doctor prescribe it along with Metformin to have good therapeutic effect.

Side effects:

- Weight gain
- Low blood sugar level

Thiazolidiendiones

This medication works by making the cells more sensitive to insulin thus insulin can help to move glucose from the blood stream to the body cells for the energy production.

They also reduce the peripheral insulin resistance leading to reduction of blood glucose concentration. While taking this medication the enzyme level should be checked regularly. The reduction in blood glucose is often accompanied by reductions in circulating insulin and free fatty acids. Triglycerides may decline with little alteration in LDL: HDL ratio.

Side effects:

It affects the liver function and leads to nausea, vomiting, tiredness

- Yellowing of skin or whiteness of eye
- Dark colored urine
- Weight gain
- Swelling in legs or ankles

α-Glucosidase inhibitors

This medication blocks the enzymes in the digestive system that is responsible for the breakdown of starch that we eat. The sugar produced is absorbed slowly and is responsible for the prevention of rise in blood sugar level throughout the day.

Side effects:

- Loose stools
- Abdominal pain and bloating
- Flatulence

Alternative therapy to the current modern pharmacotherapy of Diabetes Mellitus is urgently required, because of the inability of existing to control all the pathological aspects of the disorder.

Literature Review

Literature review of proniosomes

Ankurguptha *et al*., has investigated proniosomal carriers system used for the treatment of anti hypertension activity. These carriers having able delivering entrapped drug over period of long time. The potential of proniosomes were introduced in transdermal drug delivery system was investigated by encapsulating the drug of proniosomal gel composed of different ratio of sorbiton fatty acid esters, cholesterol, lecithin prepared by phase conservation method. The formulated proniosomal gel was characterized in vitro studies such as size, vesicle count, drug entrapment, drug release profile and vesicular stability at different storage conditions. Stability study for pronisomal gels were carried out for four weeks. Resulted proniosomes in a encapsulation yield of 66.7-78.7 %. Proniosomes were characterized by transmission electron microscopy. In vitro studies showed prolonged release of entrapped captopril. At cool or refrigerated condition, higher drug retention was observed.

Chandra *et al*., has investigated in piroxicam used as potent non steroidal anti-inflammatory drug, with due potential for dermal delivery. Permeation activity of piroxicam was resolute from proniosome based reservoir type transdermal gel formulation across excised rat abdominal skin by using keshery chein diffusion cell. There was extensive improvement Influx over the control gel formulation. The lipid vesicle was investigated entrapped drug and vesicle size of niosomes was formed. In this study observed span 60 based formulation produced vesicle smallest in size but higher entrapment efficient while those of span 80 produced vesicle least entrapment efficiency. Proniosomes were prepared by conventional technique and used maltodextrin and sorbital as base. The morphology of proniosomes was studied by scanning electron microscopy. Maximum flux achieved for transdermal system based on proniosomal gel compared to control gel.

SanjulaBaboota *et al.,* has developed a low dose of proniosomal gel celecoxib was used in the treatment of osteoarthritis. All the prepared formulations were concerned to physicochemical evaluations and anti inflammatory studies. The efficient entrapment was >90%. The vesicle shape was determined by transmission electron microscopy. The vesicle size, size distribution and poly dispersive studies were performed by photon correlation spectroscopy. Anti inflammatory studies were performed using the rat hind –paw oedema

induced by carrageenan (1%w/w). The particular proniosomal gel produced 100% inhibition of paw oedema in rats upto 8 hours after carrageenan injection. It produced 95% and 92% inhibition after 12 and 24 hours respectively. These results indicate that proniosomes were a promising carriers for the transdermal delivery of celecoxib. The large dose of proniosomal gel was produce adverse effect.

Ibrahim Alssara *et al*., has evaluated the transdermal potential of niosomes bearing a potent anti inflammatory piroxicam. Piroxicam loaded niosomes were prepared and characterized for surface morphology and entrapment efficiency. The *in-vitro* evaluation of different proniosomal gel was carried out by the Franz diffusion cell. The different non ionic surfactants were used to produce optimum encapsulation efficiency. The prepared proniosomes were significantly enhanced drug permeation and reduced lag time ($p<0.05$). The piroxicam prepared with span60 produced higher permeation flux across the skin than compare to the tween 80. The span60 produced higher release rate than compare to span20 and span80. But niosomes prepared by Tween produced higher release rate than compare to span. This result indicates lipophilicity and hydrophilicity of surfactant has main role release of piroxicam. The particle size of proniosomes was determined by scanning electron microscopy. The encapsulation efficiency of proniosomal gel was evaluated by High performance liquid chromatography method. Niosomes formed from span and tween exhibit very high encapsulation efficiency.

Rishukakar *et al.*, has investigated a number of novel drug delivery systems had emerged encompassing various route of administration to produced controlled and targeted drug delivery. Encapsulations of the in vesicular form to produce prolong the existence of drug release in systemic circulation and reduced toxicity. In this study to developed number vesicular drug delivery system such as liposomes, niosomes, Transferosomes, ethosomes and proniosomes etc. In this study proniosomes are water soluble carrier that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation on hot water. In this study, review the proniosomes were prepared and evaluate the characterization of proniosome and study of penetration and transport of various drug though skin.

***Walve* et al.,** has developed proniosomes are formed by using suitable carrier coated with nonionic surfactant and can be converted into niosomes immediately before use by hydration.

These types of proniosomes minimize the problem of niosomes physical stability such as aggregation, leakage and fusion, and provide convenience of transportation, distribution, storage and dosing. This proniosomes derived niosomes are so good as than compare to conventional niosomes. In this review bring out proniosomes are preparation, characterization, entrapment efficiency, in-vitro drug release application and merit.

Thejaswi *et al*., has developed proniosomes derived niosomes form, niosomes are made from nonionic surfactant vesicle entrap a solute in manner analogous to liposomes. They are osmatically active, stable and increase the stability of the entrapped drugs. In this describe the formulation and evaluation of proniosomes.

Hanan Ei-Laithy *et al*., has developed novel sustained release proniosomal system designed using the sugar esterase as non-ionic surfactant in which proniosomes converted to niosomes upto hydration following topical application under occlusive condition. All formulae exhibited high entrapment efficiencies, regardless of the surfactant HLB. Vesicle size within range from 0.63µm-2.52µm these are effect for the transdermal drug delivery system. The extant absorption proniosomes was larger when compare to oral tablet the bioavailability also increase. Histopathological evaluation revealed only moderate skin irritation when using SE_s compared to the skin inflammation when using Tween 80.Sugar esterase proniosomes may be effective carrier for vinpocetine.

Sudhamani *et al*., has investigated ibuprofen loaded maltodextrin based proniosomes .These were prepared by slurry method with different surfactant and carrier ratio.The formulation and evaluation for FT-IR study and scanning electron microscopy. The niosomal dispersion was further evaluated for entrapment efficiency, in-vitro study, kinetics data analysis, stability study. The result from SEM analysis has given smooth surface of proniosomes. The formulation F4 which showed higher entrapment efficiency of 96.57±1.08% and *in-vitro* cumulative drug release of 92.16% at the end of 12 hr was found to be best among the all 9 formulations. Release was best explained by the zero order kinetics. Kinetics analysis showed that the release follow non-fickian release. Proniosome formulation has showed appropriate stability for 60 days by formulations at different condition.

Ajay solanki *et al*., has developed preparation, optimize and characterize ketoprofen proniosomes. The niosomes were prepared using a slurry method followed by *in vitro* evaluation after embedding the proniosomes derived niosomes into a carbopol matrix. The

central composite box-wisondesing was used for the optimization with the total lipid concentration(X1), surfactant loading9(X2), and amount of drug(X3) as the independent variables. Prepared proniosomes were characterized for percentage entrapment and mean volume diameter. Multiple regression analysis and contour picts were used to relate the dependent and independent variables. Checkpoint batches were also preparaed to prove the validity of the evolved mathematical model and contour plots. The optimizations predict the levels of X1, X2, X3 for a maximized response of PDE witjconsrians of ≤ 5 μm on MVD. Optimized batch was used to prepare a niosomal gel, which showed significantly higher cumulative amount of drug permeated and steady state transdermal flux compare to pain gel. This work has demonstrated the use of the central composite Box wlson design, regression analysis and contour plots in optimizing ketoprofen proniosomes. Niosomal gel formulation has also demonstrated permeation enhancement ketoprofen compared to pain gel.

IntakhabAlam *et al*., has developed low dose of proniosomal gel containing celecoxib used in the treatment of osteoarthritis.The prepared formulations were subjected to physiochemical evaluation and anti- inflammatory studies. The entrapment studies were carried out > 90%.The vesicle shape can be determined by transmission electron microscopy. The vesicle size, size distribution and poly dispersity studies were performed using photon correlation spectroscopy. Anti inflammatory studies were performed using the rat hind-powoedema induced by carrageen injection. The selected proniosomal gel was produced 100% inhibition of powoedema in rat's upto 8 hours after carrageen injection. It induced 95% and 92% inhibition after 12 hours and 24 hours respectively. These result was effective for pronisomal transdermal preparation of celecoxib. Thus celecoxib can be formulated into a low dose proniosomal gel that can save the recipient from the adverse effect of large dose.

Deenanathjhade *et al*., has investigated formulation and evaluation of vesicular drug delivery carrier system proniosomal gel for transdermal delivery of antifungal agent, griseofluvin. Proniosomal gel formulations of griseofluvin were prepared and characterized for vesicular shape, size, entrapment efficiency and drug permeation across pig ear skin. The optimized proniosomal gel formulation showed enhanced in vitro skin permeation greater as compared to plain drug solution in water. The result was optimized proniosomal gel formulation of griseofluvin better skin permeation potential than plain drug solution in water.

Jia- You Fang *et al*., has investigated estradiol from different proniosomal gel formulations across excised rat skin. The encapsulation efficiency and size of niosomal vesicles formed from pronisomes by hydration. The encapsulation of proniosomes with span surfactant showed very high value. Proniosomes with surfactant the permeation estradiol across the skin. Both permeation enhancer effect of non ionic surfactant and vesicle- skin interaction may produce to the mechanism for proniosomes to enhance estradiol permeation. Niosomal suspension and proniosomal gel showed different behavior in modulating transdermal delivery of estradiol across the skin. Presence or absences of cholesterol in lipid bi layers of vesicle did not reveal difference in encapsulation and permeation of the associate estradiol. The types and content of non ionic surfactant proniosomes are important factor affecting the efficiency of transdermal estradiol delivery.

Mahmoud Mokhar Ahmed Ibrahim *et al*., has investigated to formulate and evaluate proniosomal transdermal carrier system for flurbiprofen. Proniosomes were prepared by various non- ionic surfactants such as span 20,span 40, span 60, and span 80 without and with cholesterol at percentage ranging from 0%to 50%.The effect of cholesterol and surfactant type and drug content were investigated. Drug release through cellophane membrane and rabbit skin. Drug release from the prepared system was compared to that from flubiprofen suspension in distilled water and HPMC gel. By addition of span 20, span 80 into the amount of cholesterol affected the preparation type to be either proniosomal alcoholic solutions or liquid crystalline gel system. And other type span 40, span 60 produced gel system in presence or absence of cholesterol. The proniosomal composition controlled drug diffusion rate to either faster or slower than prepared flurbiprofen suspension in HPMC gel or distilled water, respectively.

Nand Kishore *et al*., has developed proniosomal gel as non-ionic surfactant based vesicle system which exits in different liquid crystalline phase. The formation proniosomal gel by mixing of surfactant in alcohol and limited hydration with aqueous phase.The various phases of liquid crystalline structure can be utilized as such for topical/transdermal applications or can be used after further hydration to form niosomes. Interaction studies between proniosome components and reports the delivery of therapeutic agents through topical/dermal route, but cosmetic application were not much explored.

Rishukakkar *et al*., has developed valsartan proniosmal gel prepared by phase coacervation method. The prepared formulations were characterized for encapsulation efficiency, vesicle size, shape and in vitro release. Stability study was carried out to investigate the leaching of drug from the proniosomal system during storage. The result showed that valsartan in all the formulation was successfully entrapped and a substantial change in release rate and an alteration in the encapsulation efficiency of drug from proniosomes were observed upon varying the type of cholesterol content. The encapsulation efficiency of proniosomes prepared with span 60 is very effective for span40.Apreparation with 9:2:9 ratio of span 60, cholesterol, lecithin gave maximum encapsulation efficiency and release report also highest then compare to other compositions. Proniosomal formulations showed fairly high retention of valsartan inside the vesicles at refrigerated temperature upto one month.

Sankar *et al*., has approach to stabilize niosomal drug delivery system without affecting its properties of merits have resulted in the development of the promising drug carrier, proniosomes. Proniosomes is dry formulation using suitable carrier coated with non ionic surfactant can be converted into niosomes immediately before hydration. These proniosomes derived form of niosomes are as good as or even better conventional niosomes.

Akhilesh *et al*., has developed based on nanotechnology is one of the advancement in nanotechnology is the preparation of pronisomes –derived niosomes are solid colloidal particles which may be hydrated immediately before use to yield aqueous noisome dispersion similar to those produced by more cumbersome conventional methods. These proniosomes are more physical stable than compare to niosomes. The physical stability such as aggregation, fusion and leaking and provide additional convenience in transportation, distribution, storage and dosing. The addition of proniosomes-derived to niosomes are described in terms of their morphology, particle size, particle size distribution and drug release. A slurry method has to be produced proniosomes using maltodextrin as the carrier. The encapsulation is dependent on the amount of maltodextrin used.

Kiran Yadav *et al*., has developed proniosomal gel as a provesicular approach for transdermal drug delivery. The skin has a very tough diffusion barrier that is lipid bilayer in the stratum corneum inhibiting penetration of drug moiety which is rate limiting barrier for penetration barrier. They may act as vehicle or as permeation enhancer for bioactive materials to enhance their penetration via stratum corneum. Proniosomal gel are semisolid

liquid crystal product of nonionic surfactant 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 drug and increased therapeutic effectiveness. Proniosomes can entrap both hydrophilic and hydrophobic drugs.

Literature review of Transdermal patchs

PandyaNarendra *et al*., has investigated glipizide transdermal patchs of matrix type using the Eudragit RL 100 and Eudragit RS 100 by the mercury substrate method. This were evaluated various in vitro parameters (Thickness, Folding Endurance, Moisture content, Moisture uptake, drug content, drug permeation, scanning electron morphology).Drug content of patchs had more than 98%.In vitro permeation study was found to be Franz diffusion cells. Variations in drug permeation profile were observed among various formulations. The SEM of patch showed the formation of porous surface after in vitro permeation study. The drug and polymer interaction results suggested on interaction between drug and polymer was observed. From formulations, formulation M3 was selected for the best formulation and formulation was stable for period of 90 days stability study.

Arijit das *et al*., has developed prepare and evaluate transdermal drug delivery of metformine HCL. The drug undergoes rapid first pass metabolism which necessitates its frequent dosing by oral route. Transdermal drug delivery system of the drug was prepared using combination of a hydrophobic polymer, ethyl cellulose and hydrophilic polymer, polyvinyl pyrrolidine in different ratios by solvent evaporation technique. Polyvinyl alcohol was used to prepare the backing membrane and dibutyl phthalate as plasticizer. The prepare patches were characterized for various physiochemical parameters like film thickness, tensile strength, moisture content, moisture uptake, water vapor transmission rate. Permeation studies were carried out for patch through commercial semi permeable membrane as well as rat abdominal skin using keshary-chein diffusion cell and selected ex vivo skin permeation and drug release from the patch and release data of selected patch showed good fit into higuchi equation.

Debjit Bhowmik *et al*., has developed transdermal delivery system produce sustained release as well as reduced the intensity of action and reduce the side effects associate with oral therapy. It delivers the drug through intact the skin at a controlled rate into the systemic circulation. The deliver rate of drug is controlled by the skin or membrane in the delivery system. Formulated drug to meet specific biopharmaceutical and functional characteristics. The material of

construction, configuration and combination of the drug proper cosolvent, excipient, penetration enhancer and membrane are carefully selected and matched to optimize adhesive properties and drug delivery required. Transdermal drug delivery-an approach used to deliver drugs through skin for therapeutic use as an alternative to oral, intravascular, subcutaneous and transmucosal routes. Transdermal delivery system used for different treatment of disorder of hormone replacement therapy, management of pain, angina pectoris, smoking cessation and neurological disorder such as Parkinson's disease. It should not cause any skin irritations and sensitization. Enhancing the bioavailability via bypassing first pass metabolism.

Ashok kumar *et al*., has investigated 74% of drug are taken orally and are not to be as effective as desired so to improve such character for the transdermal drug delivery system. This system is very effective than compare to the traditional topical drug delivery. TDDS are dosage involves drug transported to viable epidermal and dermal tissue of the skin for local therapeutic effect while a very major fraction of drug is transport into the systemic blood circulation. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. This system is more advantage than compare to other dosage system such as limitation of hepatic first pass metabolism, enhancement of therapeutic efficacy and maintain of steady plasma level of drug. In this article provide an overview of types of transdermal patch, method of preparation and its physicochemical methods of evaluation.

Sharavani *et al*., has to be developed formulate and characterized Fulvestrant reservoir type transdermal drug delivery. It is very effective for breast cancer cells by down regulates the ER Protein in human breast cancer cells. It has demonstrated the drug can be administrated though transdermal application with predetermined targeted release. The formulation was evaluate by FT-IR study and evaluate *in vitro* study also. The data obtained from *in vitro* skin permeability studies is fitted with kinetics models to determine drug release mechanism and it was find about drug release pattern follow zero order kinetics. It has been demonstrated that targated concentration has been achieved in the in one of the formulation tested and conducted *in vivo* test also.

Roongnapa Suedee *et al*., has to be developed a transdermal patch for selective controlled delivery of the active S-enantiomer from racemic proponolol. The drug was added to the chitosan gel, This was exhibit high flux and had the ability to encaustic selective delivery S-

propranolol across excised rat skin. The reservoir patch for enantiomer controlled delivery of propranolol was therefore fabricated by incorporating the chitosan gel formulation containing racemic proparnolol HCL into the MIP composite membrane Laminated backing. From this formulation, evaluate the pharmacokinetic parameters in rats. S-propranolol enantiomer plasma concentration profiles for the transdermal in the *in vivo* study were comparable to data for the gel formulations that were applied directly to skin, and containing a single S-enantiomer of propranolol. The results demonstrate that the transdermal patch based on MIP composite membrane controlled release system may have potential in the enantio selective controlled delivery of the S-isomer of racemic propranolol.

Geeta aggarwal *et al*., has to be investigated in Transdermal drug delivery established itself as an integral part of novel drug delivery system. Transdermal delivery is polymeric formulations which when applied to skin delivery the drug at a predermined rate across dermis to achieve systemic effects. Transdermal patch dosage form is costly than compare to conventional formulation, but it is very popular because of their unique advantages. The discontinue drug administration by simply removing the patch from the skin are some of the potential advantage of transdermal drug delivery.

Srinivas Mutalik *et al*., has developed the membrane moderated transdermal system were prepared using drug containing carbopol gel as reservoir and different rate controlling membranes. The possible drug interaction between drug and polymer was studied by IR spectroscopy, DSC and HPTLC analysis. *In vitro* release, histopathological test and pharmacokinetics evaluation were carried out in mice.

Divyesh patel *et al*., has improve characters of transdermal drug delivery system. Drug achieve systemic effect differs from traditional topical drug delivery to transdermal drug delivery system. In this delivery system drug transport viable epidermal to dermal tissue of the skin for local therapeutic effect while a very major fraction of drug is transported into systemic circulation. The adhesive of the transdermal drug delivery system critical to the safety, efficacy and quality control of the product.IN this system having several advantages such as limitation of hepatic first pass metabolism, enhancement of therapeutic efficacy and maintenance of steady state.

Kuan-Hung *et al*., has developed reservoir type fentanyl transdermal drug delivery system using ethanol, in this ethanol acting as a skin permeation enhancer and an important quality control component. Samples were extracted with water by ultrasonic vibration using acetone as the

internal standard. This method was fully validated according to the ICH Q2A and Q2B guidelines. The robustness and system suitability testing were conduct. A validated method for the assay of ethanol in reservoir-type fentanyl transdermal patchs was applied to quality control practices.

Literature Review of vesicular system

Kavitha *et al*., has investigated various type lipid based vesicular system having in controlled and targeted drug delivery system. Pharmacosomes bearing more advantages over liposomes and niosomes have come up as potential alternative to conventional vesicles. These were the amphiphilic phospholipids complexes of drug active hydrogen bind phospholipids. In this method is very useful delivery of drug directly to the site of infection, reduced toxicity, no adverse reaction and effective Biopharmaceutical properties of the drug and improved bioavailability of poorly soluble drugs. This system used in non-steroidal anti-inflammatory, cardiovascular and anti neoplastic drugs.

Rishu Kakar *et al*., has investigated the number of novel drug delivery system have emerged encompassing various routes of administration to achieve controlled and targeted drug delivery. Encapsulated of the drug used in vesicular structure can produced to prolong the existence of the drug in systemic circulation and reduced the toxicity. The number of vesicular system such as liposomes, niosomes, transferosomes, ethosomes and proniosomes were developed. Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous solutions.

Parthiban *et al*., has developed colloidosome drug delivery the focus on the types, properties, fabrication techniques, characterization and stability of collodosomes. It is one of the type of vesicular system. The other recent developments number of lipid based system like liposomes, liposheres, niosomes, ethosomes, transferosomes are developed. The collodosomes are also solved the problem of insolubility, instability, rapid degradation, and widely used in specialized areas like proteins delivery, gene delivery, targeting to brain, tumour targeting. The more advanced system than compare to other vesicular system. The vesicular system reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drug. In this system have a great, encapsulation efficiency with a wide control over size, permeability, mechanical strength and compatibility.

Biju *et al*., has investigated about novel drug delivery system to deliver the drug at a rate directed by the needs of the body during the periods of treatment and channel the active entity to ths site of action. The number of novel drug delivery system is used as a controlled and targeting drug delivery. Encapsulation vesicular system in a drug vesicular structure which can predict prolonged and existence of the drug in systemic circulation, and reduce the toxicity. Liposomes, Niosomes, Proniosomes, transfersomes, pharmacosomes were developed. Advances have been made in the area of vesicular drug delivery, leading to development allow drug targeting and sustained or controlled release of conventional medicines.

Satishshilpi *et al*., has developed colloidal and nanoparticulate carrier system in the biochemical field used in diagnosis, treatment, and disease management. Carrier system (liposomes, polymeric particles, micro emlusion droplets) are used for sustained release of drugs. These systems are used in the area of targeting to brain, tumor targeting and oral vaccine formulation problems associated stability and permeability.

Surendar verma *et al*., has developed nanoparticle vesicular system like liposomes, niosomes etc. A nanomaterial is a material with one or more external dimensions or an internal structure, on the nano scale which could exhibit novel characteristic. These micro or nano structures are containers loaded with drugs which are ideal for sustained and targeted release of drug. Drug efficacy depends upon the drug loaded into vesicle, temperature, drug solubility P^H, release characteristics, additives and most significantly, the vesicle morphology.

Literature review of drugs

Kajal ghosal *et al*., has investigate the effect of chemical enhancers on the release of glipizide through transdermal patch using different chemical enhancers. L – menthol, oleic acid and n – octanol were used in glipizide matrix patch. These were used in different ratios. To prepare the transdermal matrix patch, ethyl cellulose and poly vinyl pyrrolidone were used as polymer. Di – butyl phthalate was used as plasticizer at 30% concentration of the total polymer weight. These transdermal patches were evaluated for drug release.

Shankar *et al*., has developed the membrane controlled transdermal system of glipizide and to evaluate with respect to various in vitro parameters. The membrane moderate transdermal system were prepared using drug containing carbopol gel as a reservoir and Eudragit RS-100(ERL), Eudragit RL-100(ERS) and poly(ethylene-co-vinyl acetate rate controlling membranes. The

membrane was prepared by solvent evaporation mercury subtract method. The drug permeation is depending upon the different rate controlling membrane.

Subash *et al*., was formulate transdermal patch of glipizide which is a potent antidiabetic drug by using different ratio of polymers like hydroxyl methyl cellulose and Eudragit. These patches were prepared by solvent casting method. The polymers were prepared by different ratio with the drug was determined. The prepared transdermal patches were uniform in shape and white in color which was calculated for physicochemical characteristics, *in-vitro* release and *in-vivo* drug release in mice.

Narasimha Rao *et al*., has investigated transdermal route is advantages over conventional modes of drug administration. It should be avoid hepatic first pass metabolism and improves patient compliance. The highly organized structure of stratum corneum forms effective barrier to the permeation of drug, which must be modified if poorly penetrating drugs to be administered. The use of chemical penetration enhancers would significantly increase the number of drug molecules suitable for transdermal delivery.

Sampath kumar *et al*., in this formulation developed the hydrodynamic balanced controlled drug delivery system of glipizide. Ii should be increased the bioavailability and reduction of dosing frequency. The can added to the different polymers such as carbopol, HPMC, citric acid. These tablets were prepared by the direct compression method and evaluated to the drug content, invitro drug release dissolution. Buoyancy.

Biraju patel *et al*., has developed direct compression method. Two superdisintegrants viz crospovidone and croscarmellose sodium with different binders viz PVP k-30 and pregelatinized were used. The formulation was evaluated by hardness, friability, disintegration, wetting time, drug content and *invitro* dissolution study. The selected formulation was compared to the conventional formulation. The stability study on the optimized formulation indicated that there is no significant changes found in physical appearance, disintegration time and wetting time of the tablets.

Shivalingam *et al*., has developed poorly water soluble drug used in solid dispersion technique by solvent evaporation method. The drug and carrier were in different ratios like 1:1, 1:2, 1; 3 by keeping constant weight. The prepared formulations were evaluated by phase solubility, *in-vitro* dissolution study ad evaluate drug and polymer interactions by FTIR method.

Bhosale Ashok *et al*., has investigated to enhace the solubility and impart a controlled release in a single formulation. The formulation was prepared by drug complex with β-cyclodextrin. Phase solubility studies were performed according to method reported by Higuchi and Connors. Inclusion complex of glipizide with cyclodextrin is prepared by kneading and evaluated for in-vitro release and FTIR spectroscopy. Glipizide was increasing concentration of polyethylene oxide and evaluated various tablet properties and *invitro* dissolution studies.

DRUG PROFILE

Name: Glipizide

Synonym: Glipizida, Glydiazinamide

Chemical name

1- cyclohexyl-3-[[p-[2-(5-methyrpyrazine-carboxamido)ethyl]phenyl]sulfonyl]urea.

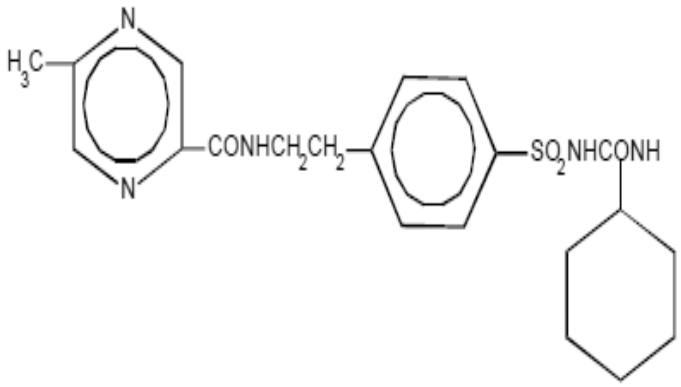
Molecular formula

$C_{21}H_{27}N_5O_4S$

Molecular weight

445.55

Structural formula



Structure of Glipizide

S.NO	PHYSICAL PROPERTIES	DESCRIPTION
1.	Description	Whitish, odorless powder
2.	Solubility	Insoluble in water and alcohol Soluble in 0.1N NaOH Freely soluble in dimethyl foramide
3.	Melting point	208^0-209^0C

Chemical property

P^{Ka}- 5.9

Categories

Hypoglycemic agent

Half life:

2-5 hours

Dose:

2.5-5 mg (*www.drugbank.com*)

Mechanism of action

Glipizide to produce lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. On the pancreatic cell membrane is cause depolarization by reducing conductance of ATP sensitive K^+ channels. This enhances Ca^{2+} influx degradation. (*www.drugbank.com*). The rate of insulin secretion at any glucose concentration is increased. Extrapancreatic effects also may play a part in the mechanism of action of sulfonylurea hypoglycemic drugs. Two extrapancreatic effects shown to be important in the action of glipizide are an increase in insulin sensitivity and a decrease in hepatic glucose production. However, the mechanism by which glipizide lowers blood glucose during long-term administration has not been clearly established. Stimulation of insulin secretion by glipizide in response to a meal is of major importance. The insulinotropic response to a meal is enhanced with Glipizide administration in diabetic patients. The postprandial insulin and C-peptide responses continue to be enhanced after at least 6 months of treatment.

Pharmacokinetic

Elimination half life:	2-5 hr
Duration of action:	12-18 hr
Clearance route:	Liver
Daily dose:	5-20mg
No of dose per day:	1-2
Elimination ranges:	2-4 hr
Peak plasma level:	1-3 hr
Apparent volume of distribution:	11 li
Bioavailability:	98%
Bound to plasma protein:	98-99%

Side effect

Diarrhea, Headache, Constipation, Sore throat, Fever, chills, Dizziness, Fainting, Rash, Itching, heart palpitations, shortness of breath, chest pain. (*www.alldrugs.com,* www.rxlist.com)

Drug interactions

Glipizide interaction with other drug have some fatal effects to the body.

- Seizure medicines
- Steroids
- Isonoazid
- Phenothiazines
- Birth control pills and others hormones
- Thyroid medicines
- Niacin
- Medicines to treat asthuma, colda or allergies
- Diet pills
- Heart or blood pressure medication such as nifedipine, verapamil, ditiazem. *(www.alldrugs.com)*

Overdose

Over dose of glipizide, can produce hypoglycemia. Mild hypogilycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Severe hypoglycemic reactions with coma, seizure or neurological impairment occur infrequently. www.alldrugs.com

SURFACTANT PROFILE

Synonym

Sorbitan mono octadecanoate, Sorbitan stearate

Chemical name

Sorbitan mono stearate (Span60)

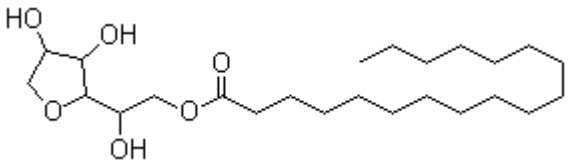
Molecular formula

$C_{24}H_{46}O_6$

Molecular weight

430.62

Structural formula



Description

Pale yellowish waxy solid

Slightly odour

Bland taste

Physical property

Density-0.98 - 1.031

Melting point- 57^0C HLB value-4.7

Flash point- > 110^0C

Category

Emulsifying agent, Nonionic surfactant, Solubilizing agent, Wetting agent and dispersing agent.

Applications

It is used for cosmetic product, food products, and pharmaceutical formulations.

It is mainly used as an emulsifing agent in the preparation of creams, ointment and emulsion.

Stability and Storage Condition

Gradual soap formation occurs with strong acid or bases, sorbitan esters are stable in weak acids or bases. Keep container tightly closed. Keep container in a cool, well ventilated area. Do not store above 24^0C (72.2^0F).

Solubility

Insoluble in cold water, soluble in ethanol, isopropanol, mineral oil, and vegetable oil. Insoluble in propylene glycol.

Method of manufacture

Sorbitol is dehydrated to form hexitan(1,4- sorbitan), which is then esterified with the desired fatty acid.

Handling Precaution

1. Keep away from heat and sources of ignition.
2. Avoid contact with eyes.
3. Wear suitable protective clothing, in case of insufficient ventilation.
4. Wear suitable respiratory equipment. (*Handbook of pharmaceutical excipients. Edited by Raymond C Rowe,Paul J Sheskey*)

CHOLESTEROL PROFILE

Synonym

Cholesterin

Chemical name

Cholest 5-en3β-ol

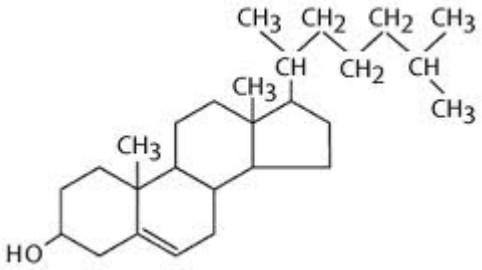
Molecular formula

$C_{27}H_{46}O$

Molecular weight

386.67

Structural formula



Description

White or faintly yellow colour, almost odourless, pearly leaftlets,

Needles, powder granules.

Insoluble in water, soluble in vegetable oil.

Physical property

Boiling point : 360^0C

Melting point: 147^0C-150^0C

Density :1.052g/cm^2

Dielectric constant: 5.41.

Category

Emollient, emulsifying agent.

Application

It is mainly used in cosmetic and pharmaceutical formulations.

It is used in the ointment preparation for emollient activity.

Cholesterol additionally has a physiological role.

Stability and storage

Cholesterol is stable and should be stored in a well closed container, protected from light.

Safety

1. Cholesterol is generally regarded as an essentially non toxic and non irritant material at the level employed as an excipient.
2. Cholesterol is often derived from animal sources and must be done so in accordance with the regulation for human consumption.

HANDLING PRECAUTION

1) May be harmful following inhalation or ingestion of large quantities,or over prolonged period of time, due to the possible involvement of cholesterol in atherosclerosis and gallstone.
2) It may also causes irritation to eyes.
3) Observe normal precautions appropriate to the circumstances and quantity of material handle.
4) Rubber or plastic gloves, eye protection and a respirator are recommended. (*Handbook of pharmaceutical excipients. Edited by Raymond C Rowe,Paul J Sheskey*)

POLYMER PROFILE

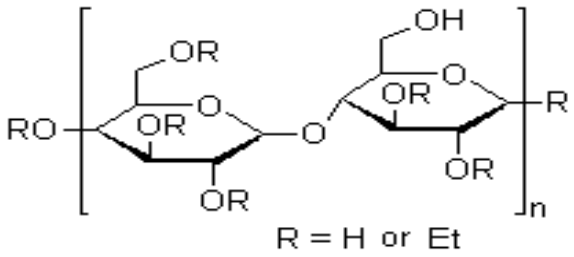
ETHYL CELLULOSE

Synonym: Aquacoat ECD, Aqualon

Chemical name: Cellulose ethyl ether

Molecular formula: $C_{12}H_{23}O_6$

Structural formula



Description

It is tasteless.

Free flowing

White to light tan colour powder.

Freely soluble in chloroform, ethanol, ethyl aceate.

Practically soluble in glycerin, propylene glycol.

Physical property

Density: 0.4gm/cm^3

Glass transition temperature: 129-133^{0}C

Refractive index: 1.14

Category

Coating agent, flouring fixative, tablet binder, tablet filler, viscosity increasing agent.

Application

It is used as a hydrophobic coating agent for tablet and capsules.

It is used to increase stability of formulations.

High viscosity ethyl cellulose are used in drug encapsulation.

In topical formulations it is used as a thickening agent. (*Handbook of pharmaceutical excipients. Edited by Raymond C Rowe,Paul J Sheskey*)

AIM AND OBJECTIVE

AIM

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.

OBJECTIVE

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 pancrease 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.(*www.pfizer.com*) 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. (*KiranYadav et al., 2010*).

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.

PLAN OF WORK

- **Review of Literature**
- **Selection of drug and exicipients**
- **Preformulation Studies**
  - Confirmation of Drug
  - Determination of Drug Solubility
  - Color, Odor, Taste and Appearance
  - Determination of Melting Point
  - Determination of drug interaction by FT-IR
  - Determination of DSC
- **Formulation and Preparation methods**

  Preparation of Proniosomal gel

  (Phase Coacervation separation Techniques)

  Preparation of transdermal patches

  (Reservoir type transdermal patches)
- **Characterization of Proniosomal gel**
  - P^H Determination
  - Viscosity Determination
  - Entrapment efficiency
  - Drug Content
  - Vesicle size analysis
- **Evaluation of transdermal patches**
  - In-vitro drug Release Study
  - In-vitro Skin Permeation study
  - Drug Release Kinetic Data Analysis
  - In-vivo Drug Release Study
  - Skin Irritation Study
  - Stability Study

Result and Discussion

Summary and Conclusion

MATERIALS AND INSTRUMENTS

Materials Used

The following materials were used for the preparation of proniosomal gel transdermal patches and their evaluation in their best quality available.

Table no 1.

Materials used for the research work

S.No.	Name	Grade	Company Name
1.	Glipizide	Parma	Wanbury Limited, India
2.	Cholesterol	L.R	Loba Chem Pvt. Ltd., Mumbai
3.	Span 60	L.R	Loba Chem. Pvt. Ltd., Mumbai
4.	Lecithin	L.R	Loba Chem. Pvt. Ltd., Mumbai
5.	Isopropyl alcohol	L.R	S.D.FineChem Ltd., Mumbai
6.	Glycerol	L.R	Loba Chem Pvt. Ltd., Mumbai
7.	Chloroform	L.R	Loba Chem Pvt. Ltd., Mumbai
8.	Ethyl cellulose	L.R	Hi Media Laboratories Ltd, Mumbai.
9.	Poly ethylene glycol 400	L.R	Loba Chem Pvt. Ltd., Mumbai
10.	Alloxan	L.R	Sigma chemicals, Bangalore
11.	Potassium di-hydrogen phosphate	L.R	S.D.FineChem Ltd., Mumbai
12.	Sodium hydroxide	L.R	S.D. Fine Chem Ltd., Mumbai
13.	Distilled water	L.R	Leo Scientific, Erode

Table no 2.

Instruments Used For the Research Work

S.No.	Name	Company Name
1.	Franz diffusion cell	Natural Scientific, Erode.
2.	Magnetic stirrer	Remi industries, Mumbai
3.	Electronic digital balance	Schimadzu, Japan.
4.	Cooling centrifuge	Remi industries, Mumbai
5.	US 800 Double beam UV/VIS Spectrophotometer.	Shimadzu, Mumbai
6.	Glucometer	Contour TS, Bayer poly chem. Limited, Thane
7.	FT-IR- 8400	Shimadzu, Mumbai.
8.	Sonicator	Growell Instruments, Bangalore.
9.	Desicator	Natural Scientific, Erode.

EXPERIMENTAL WORK

Preformulation studies

Preformulation testing was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The useful of Preformulation parameters maximizes the changes in formulation an acceptable, safe, efficacious and stable product and at same time provides the basis for optimization of the drug quality.

Confirmation of Drug

Conformation of Drug was carried out by using UV spectroscopy. 2mg of drug dissolved in methanol and diluted with the same solvent. When UV spectrum of gilipizide solution in methanol was scanned at 200-400 nm, maxium was observed.

Determination of Drug solubility

The solubility of glipizide was determined in water, dimethyl formamide, and 0.1N NaOH was assayed. Excess of drug was added to known volume of the solvent system, vortex mixed for 2 minutes and then equilibrated at 37±0.5^{o}C in more than 24 hrs. The contents were filtered and analyzed by uv visible spectrometer.

Color, odor, taste and appearance

The drug sample was evaluated for its color and odor and results have been noted down.

Melting point determination

Melting point of the drug sample was determined by capillary method using melting point apparatus. Taking a small amount of drug in a capillary tube closed at one end. The capillary tube was placed in the electrically operating melting point apparatus and temperature at which the drug melt was recorded. The observed melting point was noted down.

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 f 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 aluminium pan, the lid was pierced and the DSC thermogram was recorded at heating rate of 20^{o}C/min from 60 to 240^{o}C 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 phospate 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 10,15,20,25,30,35,40µg/ml were prepared by withdrawing 1,1.5,2,2.5,3,3.5,4,4.5ml respectively. Absorbance of eachsolution was measured at276nm. (*Avinashsingh et al.,2011*)

Preparation of proniosomal gel

Proniosomal gel was prepared by phase coacervationmethod. The weighed amount of surfactant (span 60), lipid (cholesterol), protein(egg lecithin) 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 with a 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^{o}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 air tight container and stored in a dark place.(*Ankurguptha et al.,2007, Chandra.A et al., 2008, IntakhabAlam et al., 2010.*).

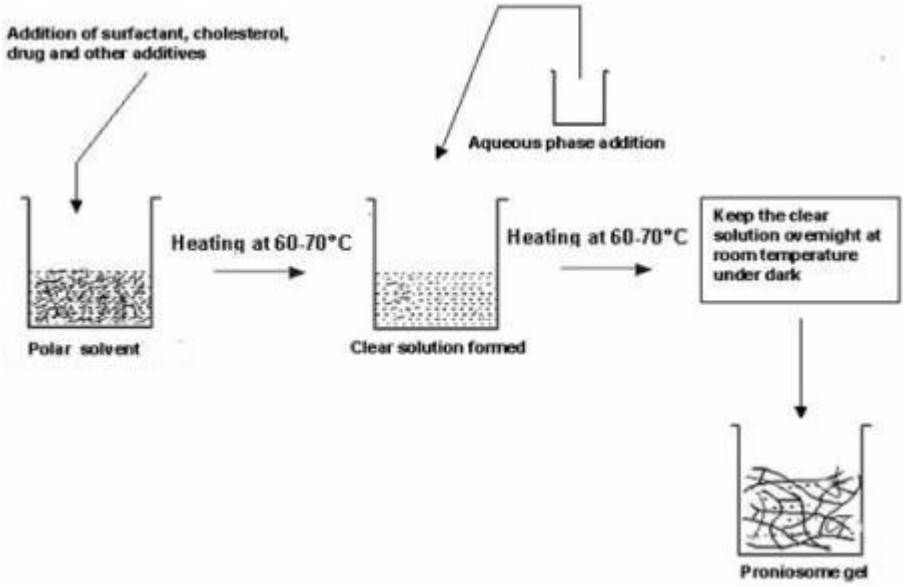


Figure no: 9Method of Preparation of Proniosomal Gel

S.NO	FORMULATION	DRUG (mg)	SPAN 60 (mg)	CHOLESTROL (mg)	LECITHIN (mg)
1	F_1	10	180	10	200
2	F_2	10	180	20	190
3	F_3	10	180	40	180
4	F_4	10	200	50	140
5	F_5	10	200	60	130
6	F_6	10	200	70	120
7	F_7	10	220	90	80
8	F_8	10	220	100	70
9	F_9	10	220	110	60
10	F_{10}	10	240	120	30

Table No: 1 Formulation of Different Proniosomal Gels

Preparation of rate controlling membrane

Rate controlling membrane was prepared by solvent evaporation method. 0.5 mg of ethyl cellulose polymer weighed anddissolved in 10ml of chloroform with Poly ethylene glycol asplasticizers. Then the solution is poured on the horizontal surface of Petridis and left for evaporation of solvent in order to obtain a thin film. (*GeetaArrarwal et al., 2009*).

Preparation of drug reservoir and of transdermal patch

The prepared proniosomal gels were fabricate by encapsuling within a shallow compartment of drug impermeable backing membrane(laminatedaluminum foil). A micro porous tape of larger area was 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*)

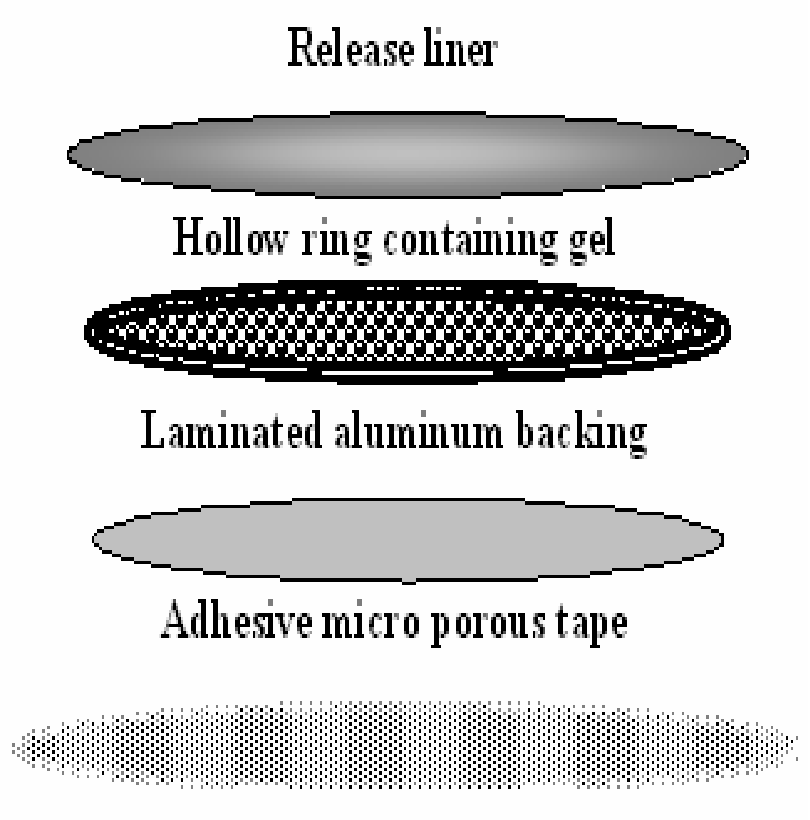


Figure No: 10 Fabrication design of reservoir type transdermal drug Delivery of glipizide

Evaluation

P^H Determination

The P^H of each proniosomal gel was determined using P^H meter. The Electrode first calibrated with P^H 4.0 and P^H 7.0 solution, then reading were 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 very important characteristic. The surface morphology (round, smoothness, and formation of aggregates) and the size analysis was performed by Scanning electron microscopy. 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 20^{o}C for 30 minute. 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:

$$\%EE = \frac{\text{Total drug concentration} - \text{concentration of free Drug}}{\text{Total drug concentration}} \times 100$$

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*)

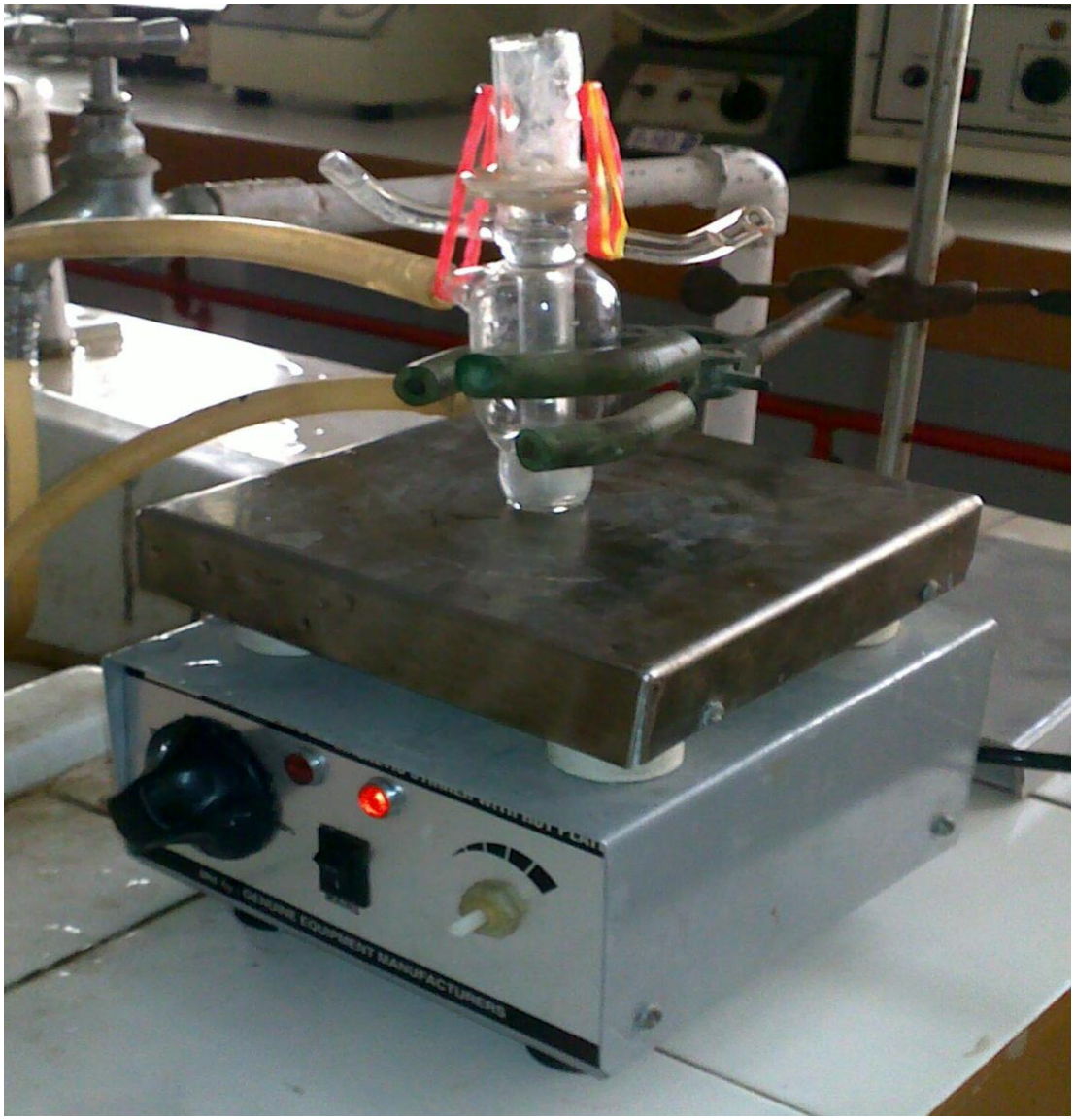


Fig No: 13 *In-vitro* skin Permeation study

***In-vitro* Drug Release Study**

In-vitro drug release studies were performed on a Franz diffusion cell with an effective diffusional area of 3.12 cm^2. 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 P^H 7.4. The receptor compartment was surrounded by water jacket to maintain the temperature at 37±1^oC. 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, sampleswere withdrawn and replaced 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 against time.*(Kiranyadev et al., 2010).*

***In-vitro* skin Permeation Study**

In-vitro skin permeation studies were performed on a Franz diffusion cell with an effective diffusional area of 3.465 cm^2, properly thawed porcine skin was mounted between the compartments of the franz diffusion cell with the stratum corneum side facing the donor compartment and dermal side facing the receptor compartment. The patch to be tested was placed on the skin i.e in donor compartment. Phosphate buffer solution of P^H7.4 was used as receptor phase and the entire assembly was kept on a magnetic stirrer with continuous stirring of the solution in the receive compartment. Samples were withdrawn at regular periods through the sampling port and replaced by an equal volume of fresh buffer solution maintained at 37^{o}C. The samples were filtered through a 0.2 µm filter membrane, absorbance of sample was measured UV-Visible spectrophotometer at 276nm against blank. The amount of drug permeated was plotted against time. (*Shankar S.J et al.,2011, Shankar V 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 v_s time, Higuchi model as log cumulative % drug release v_s square root of time.r^2 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 that do not disaggrated andrelease the drug slowly, assuming the area does not change and no equilibrium conditions are obtained can be represents by the following equation:

$$At=A_0-k_0t$$

Where, At= amount of drug dissolved in time t. A_0 is the initial drug concentration.K_0 is zero order rate constant (hr-1) when the data is plotted as cumulative percent drug release versus time, if plot is linear then the data obeys zero-order equal to K_0. K_0 zero order in units of conc/time and t is time in hours.

First order Kinetics:

Predicted by equation;

$$\text{Log } C = \log C_0 - Kt/2.30$$

Where, C is the amount of drug remained at time t, C_0 is initial amount of drug and K is the first order rate constant (hr-1). When the data is plotted as log cumulative percent drug remaining v_s time yields a straight line indicated that the release follow first order kinetics. The constant k can be obtained by multiplying 2.303 with the slope values.

Higuchi model:

Higuchi developed several theoretical models to study the release of water soluble and low soluble drug incorporated in semi solid or solid matrixes.

Mathematical expression were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media and equation is

$$Qt = KH.t_{1/2}$$

Where, Qt = amount of drug release in time t, KH = Higuchi constant.

Krosmeyer and Peppas release model:

To understand the release mechanism in-vitro data was analyzed by Peppas model. As log cumulative drug release $v_s$log time and exponent n was calculated through the slope of the straight line.

$$Mt/M\alpha = bt^n$$

Where, Mt is amount of drug release at time t, M is the overall amount of the drug, b, is constant and n is release exponent indicative of the drug release mechanism. (*Shamsheer Ahmad et al., 2011, Chitta Suresh kumar et al., 2010*).

***In-vivo*drug release study**

Animal approval

The study was conducted after obtaining the approval from Institutional animal ethics committee (IAEC), and the experimental procedures were in accordance to the guidelines of IAEC (688/02/c/CPCSEA).

Selection of Animals

The mice weighing around 25-30gm was selected for the experiment. The animals were checked for the free of any disease, only the healthy rodent is accepted for the experiments. The male rodents are preferred so that there occur no interference between the experiments because of the pregnancy. The rodents were collected from the animal house of NandhaCollege of pharmacy and research institute, Erode 52.

Maintenance of animals

The selected male swiss albino mice were brought to the laboratory two days before the commencement of the experiment and provided with standard laboratory rodent chow diet obtained from (Pranav Agro Industries Ltd, Bangalore) and free access of water, 12 hrs day/dark cycle and room temperature is maintained 27^{o}C. The night before the commencement of the experiment food is withdrawn but free access of water was provided.

Induction of diabetics

Adult male swiss albino mice were fasted for 24 hours with water and the initial blood sugar levels were checked. The animals were made diabetic by single intraperitoneal injection ofalloxan 200mg/kg of body weight and the blood glucose level was raised this condition was observed at the end of 48 hours after alloxan injection.(*ZhengweiZhoet al 2009.,)*

Groupingsof animals

Group I =Control

Group II = Diabetic control

Group III =Alloxan + Drug patch

Group IV =Alloxan + Standard drug

The drugs were dissolved in normal saline and it was administered orally via a standard gastric cannula. Anti-hyperglycemic activity in diabetic mice was assessed by fall in fasting blood glucose level (*S.K.Guptha et al., 2009*) Blood samples were collected from the tip on 0th, 1st, 2nd, 3rdupto 24 hrs.(*V.Vats et al., 2002*). By without scarifying the animal, from the tail vein by snipping off the tip of the tail and blood glucose was checked by glucometer.

For evaluating the hypoglycemic activity of glipizide loaded transdermal patches in mice. The hair on the posteriors abdomen of the mice was removed with an electric hair clipper. On the before three days were treated with standard drug and group treated with test patches on the fasted mice skin whose hair previously removed. Blood samples were collected from the tip on 0th, 2nd, 4th, 6th, 8th,10th, 16thup to 24 hrs. By without scarifying the animal, from the tail vein by snipping off the tip of the tail and blood glucose was checked by glucometer. (*Manoj K mishra et al., 2009*)

Skin irritation Study

The mice were divided into 3 groups (n=3). On the previous day of the experiment, the hair on the backside area of mice was removed. The animals of group I was served as normal, without any treatment. One group of animals (Group II) was applied with Test patch. A 0.8%

v/v aqueous solution of formalin was applied as a standard irritant (Group III). The animals were applied with new patch/formalin solution each day upto 7 days and finally the application sites were graded according to a visual scoring scale, always by the same investigator. The erythema scale was as follows: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, scar formation. The edema scale was: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, severe can be done by after visual evaluation of skin irritation. (*SrinivasMutalik et al.,2005*)

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 (4-8^{o}C), Room temperature (25±2^{o}C) and oven (45±2^{o}C). Throughout the study, proniosomal formulations were stored in aluminum foil-sealed glass vials. The samples were withdrawn at different time interval 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*)

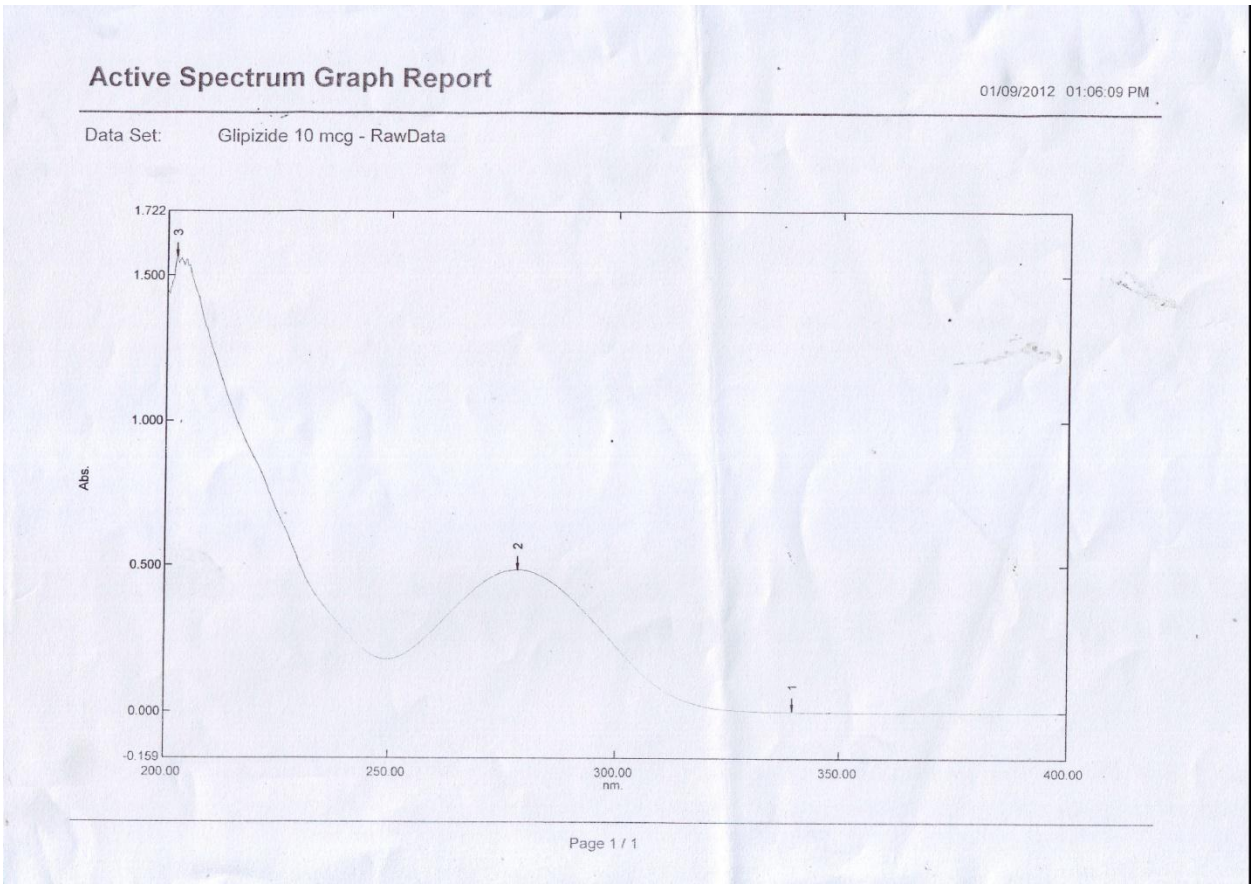
RESULTS AND DISSCUSION

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 lucidprogress. 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 thechanges in formulating an acceptable, safe, efficacious and stable product and at same time provides the foundation for optimization of the drug product quality.

Confirmation of drug

Glipizide in methanol solution was scanned at 200nm to 400nm, Maxima observed at 276 nm in methanol as showned in Spectra No:1 . This is confirmed with reported UV spectrum ofGlipizide.



Spectra No: 1 UV- Visible Spectrum of Glipizide

Color, Odor, Taste and Appearance

S.No	Parameter	Drug
1.	Color	White
2.	Odor	Odorless
3.	Taste	Tasteless
4.	Appearance	Crystalline

Table No: 2 Results of identification tests of drug

Determination of Solubility

The solubility of glipizide was determined and found to be freely soluble in Dimethyl formamide and slightly soluble in 0.1N NaOH, poorly soluble in water.

Melting point determination of Glipizide

The melting Point of Pure drug of glipizide was determined by capillary method. The melting point drug was found to be 208^0C. The melting point compared with standards that was found to be within a standard limits.

Reported melting point	Observed melting point
208-209^0C	209^0C

Table No: 3Melting point of Pure Drug

Drug – Excipients Compatibility Study

FT-IR spectra of glipizide, and physical mixture of drug were recorded to check the interaction between drug and physical mixture. The peak obtained due to pure glipizide at 2941.5cm^{-1} (C-H alkane), 3324.42cm^{-1} (O-H Phenolic),1159.26 cm-^{1} (C-O Ether), 1689.70cm^{-1} (C=O Ketone Stretching), 1033.88 cm^{-1} (S=O Sulfoxide Stretching), 1333.82 cm^{-1} (C-N Amine Stretching), 686.68 cm^{-1} (C-H Bending), which is shown in Table No:4 .

All these peaks have appear in spectra of Glipizide and Surfactant representing no chemical interaction between Drug and Surfactant without any markable change in the position and also not affected of transition temperature on indensity of peak appeared. It also confirmed that the stability of drug formulations.

Transition	Standard I.R range of Glipizide	Observed value of Glipizide
C-H (aromatic)	3050-3250	3251.13
C=C (aromatic)	1450-1600	1527.67
C-H (alkane)	2850-3000	2943.47
C-N (amine)	1000-1350	1332.86
C=O (ketone)	1650-1750	1689.70
S=O (Sulphoxide)	950-1050	1033.88

Table No:4Interpretation of FT-IR of Glipizide

Transition	Standard I.R range of Span 60	Observed value of Span 6o
O-H (alcoholic)	3200-3400	3258.84
C-H (alkane)	2850-3000	2917.43
C-O (ether)	1000-1300	1178.55

Table No:5 Interpretation of FT-IR of Span 60

Transition	Standard I.R range of Cholesterol	Observed value of Cholesterol
O-H (alcoholic)	3200-3400	3427.62
C-H (alkane)	2850-3000	2901.04
C=C (alkene)	1600-1700	1671.37

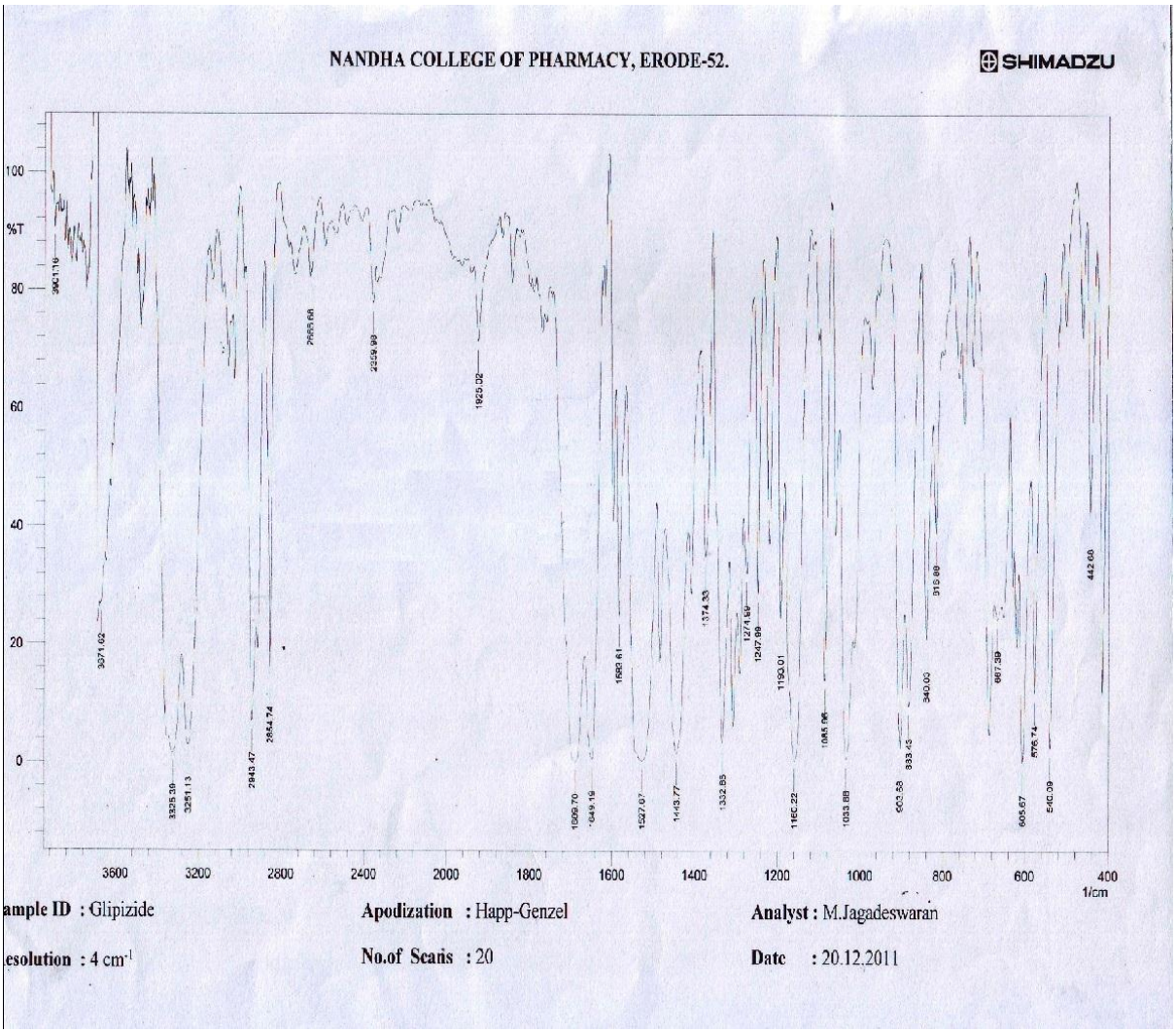
Table No: 6Interpretation of FT-IR of Cholesterol

Transition	Standard I.R range of Ethyl cellulose	Observed value of Ethyl Cellulose
C-O (ether)	1000-1300	1242.20
C-H (alkane)	2850-2950	2888.24

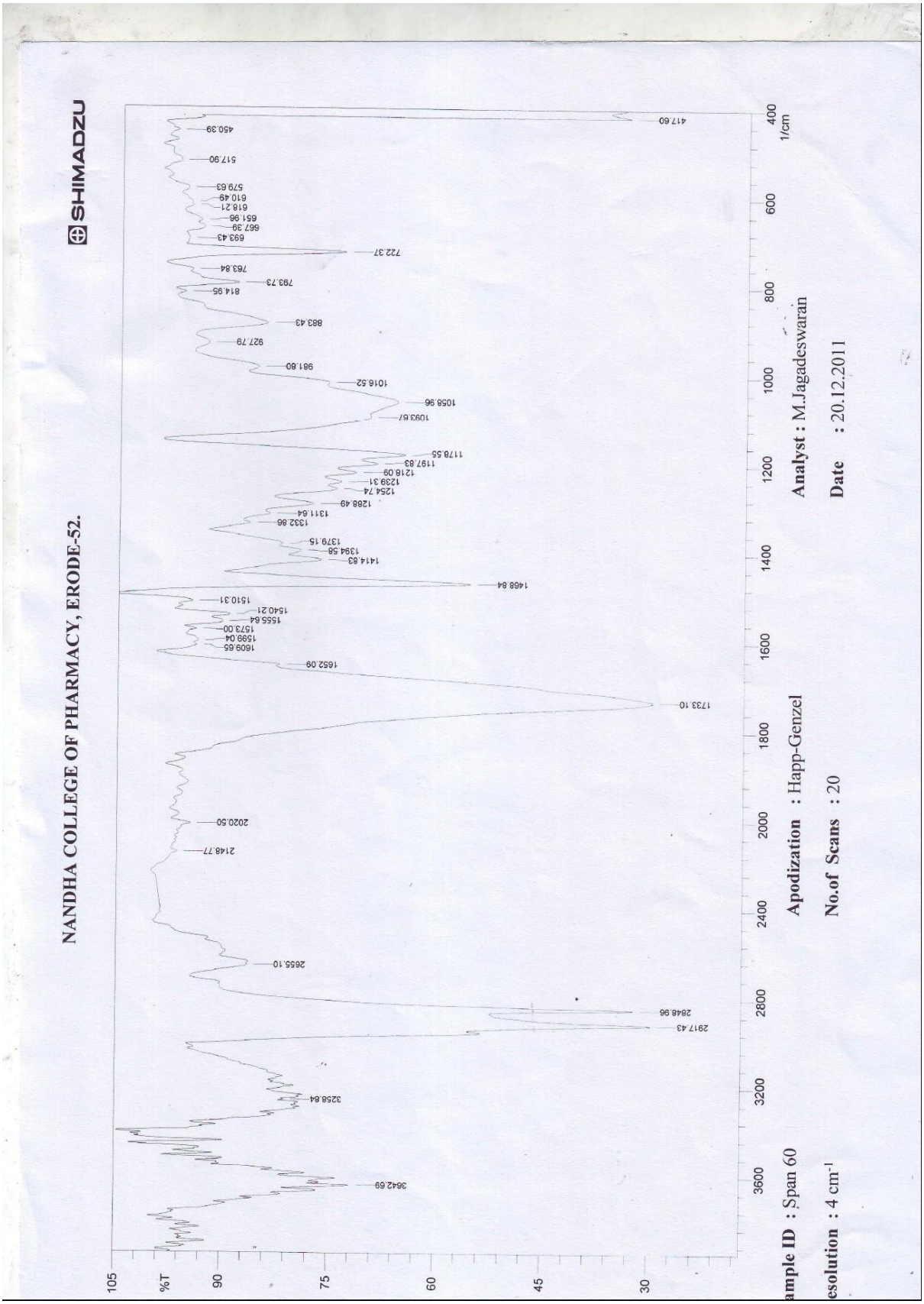
Table No: 7 Interpretation of FT-IR of Ethyl Cellulose

Transition	**Standard I.R range**	**Observed value of Physical Mixture**
O-H (Phenolic)	3200-3400	3324.42
C-H (alkane)	2859-3000	2941.54
C-O (ether)	1000-1300	1159.26
C=O (ketone)	1650-1750	1689.70
S=O (sulphoxide)	950-1050	1033.88
C-N (amine)	1000-1350	1333.82

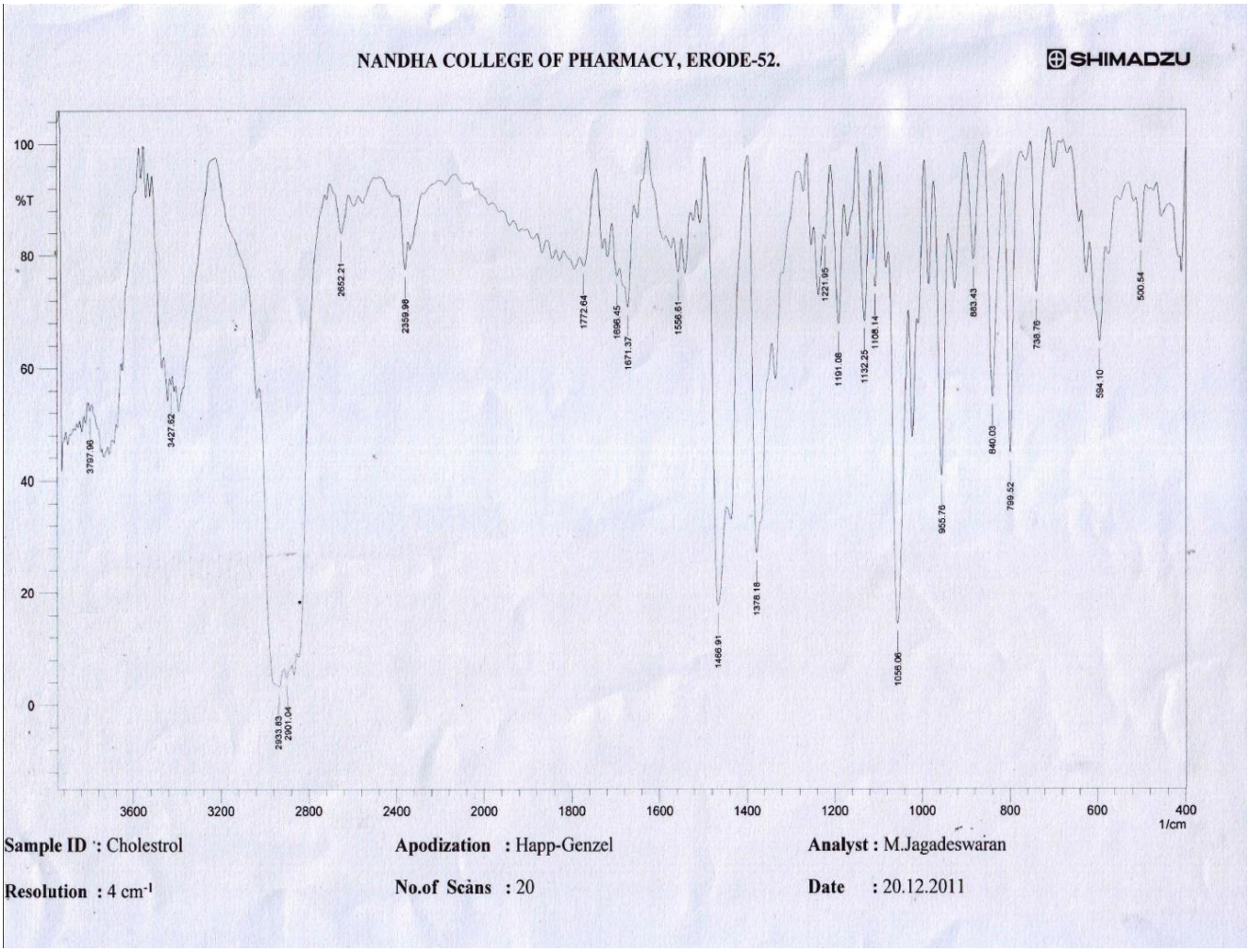
Table No: 8 Interpretation of FT-IR Physical Mixture



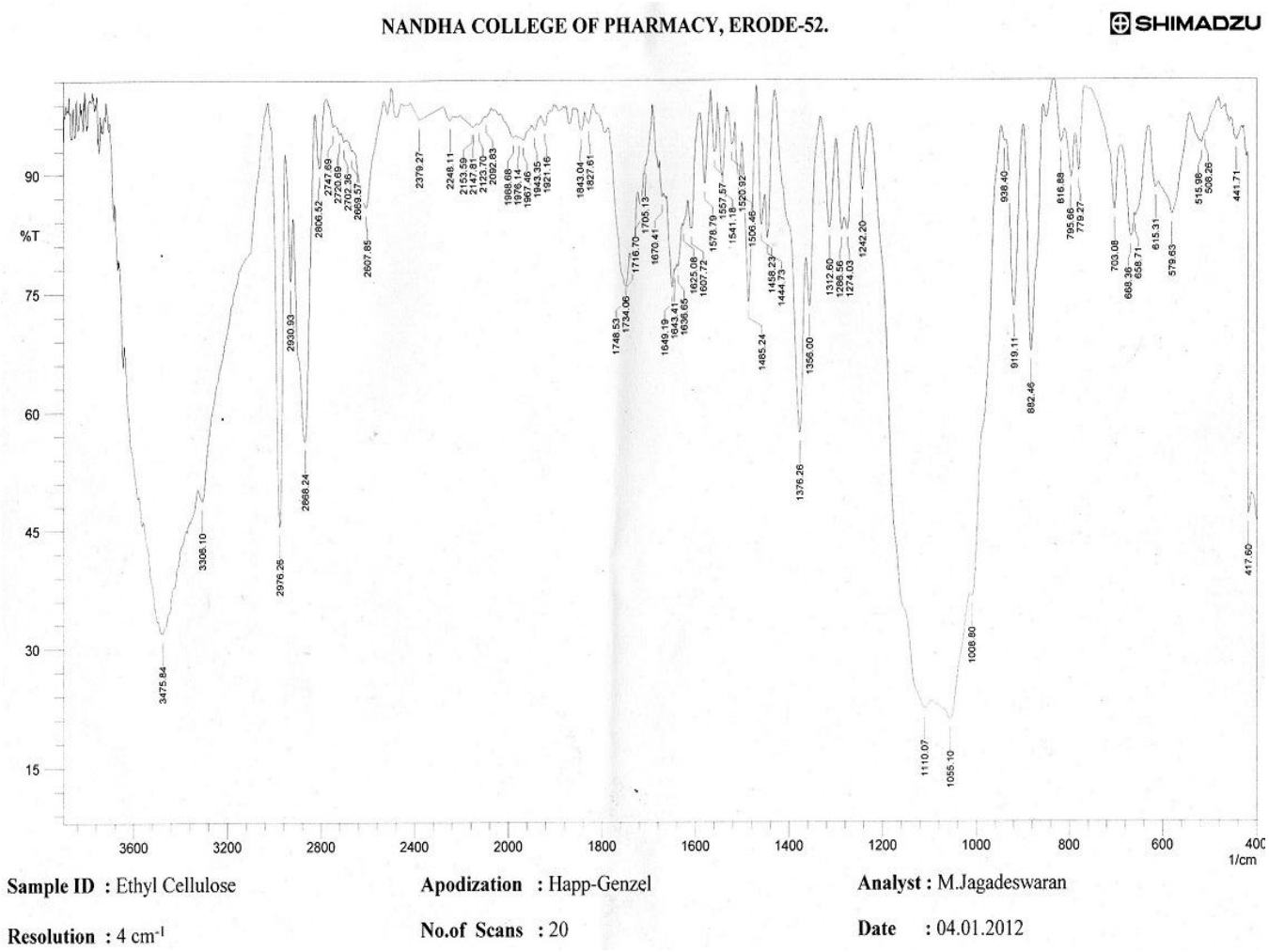
Spectra No:2 IR Spectram of Pure Drug of Glipizide



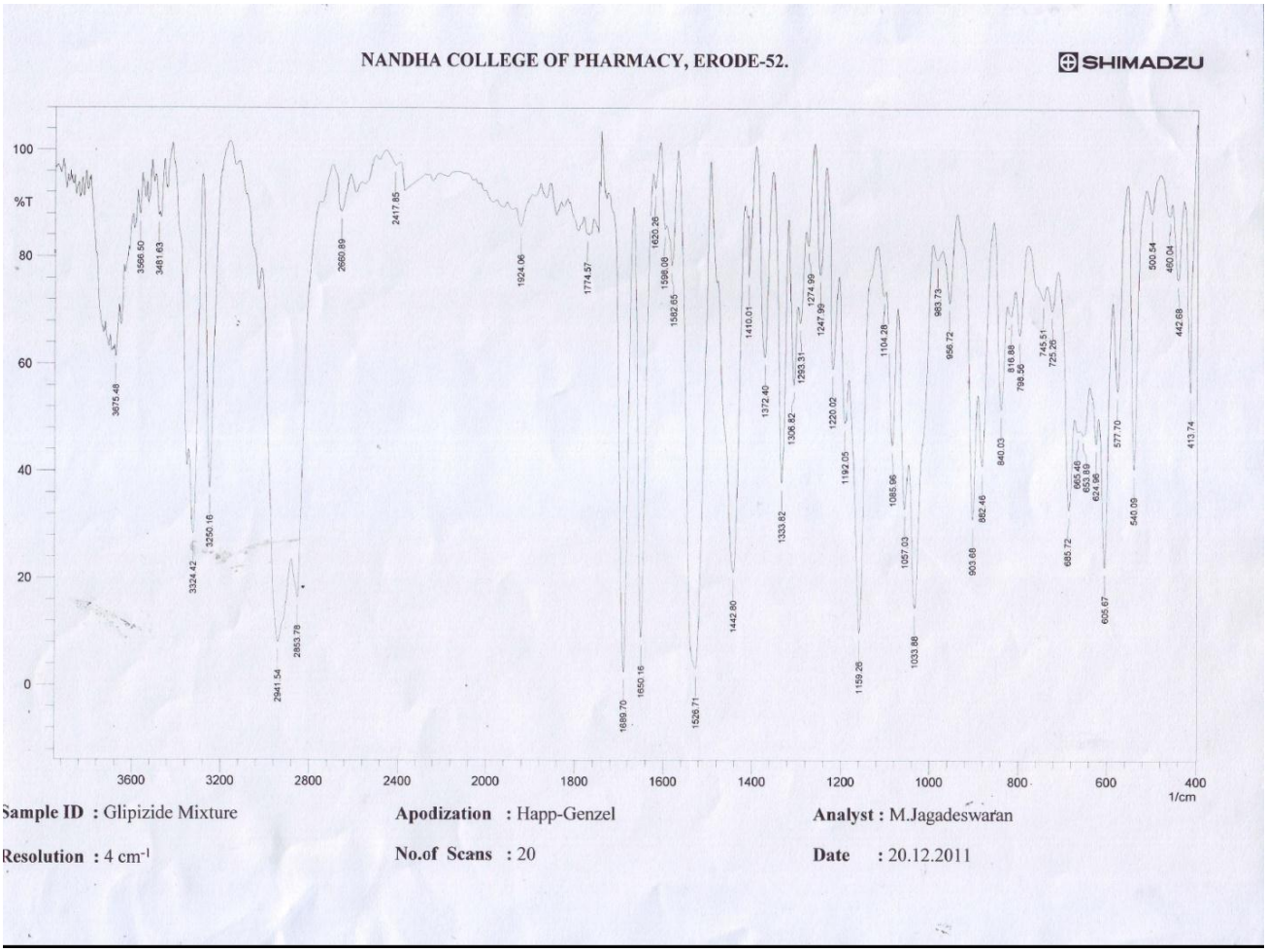
Spectra No: 3IR Spectrum of Span 60



Spectra No: 4IR Spectrum of Cholesterol



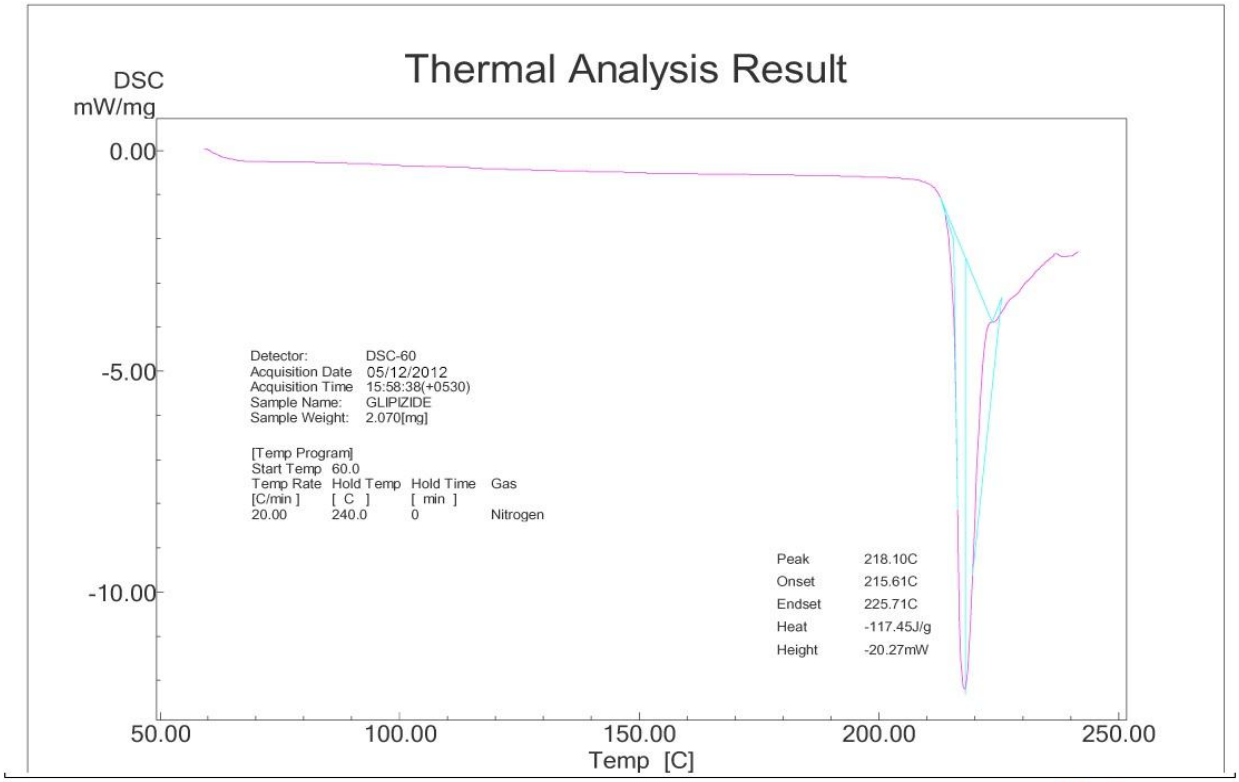
Spectra No: 5 IR Spectra of Ethyl Cellulose



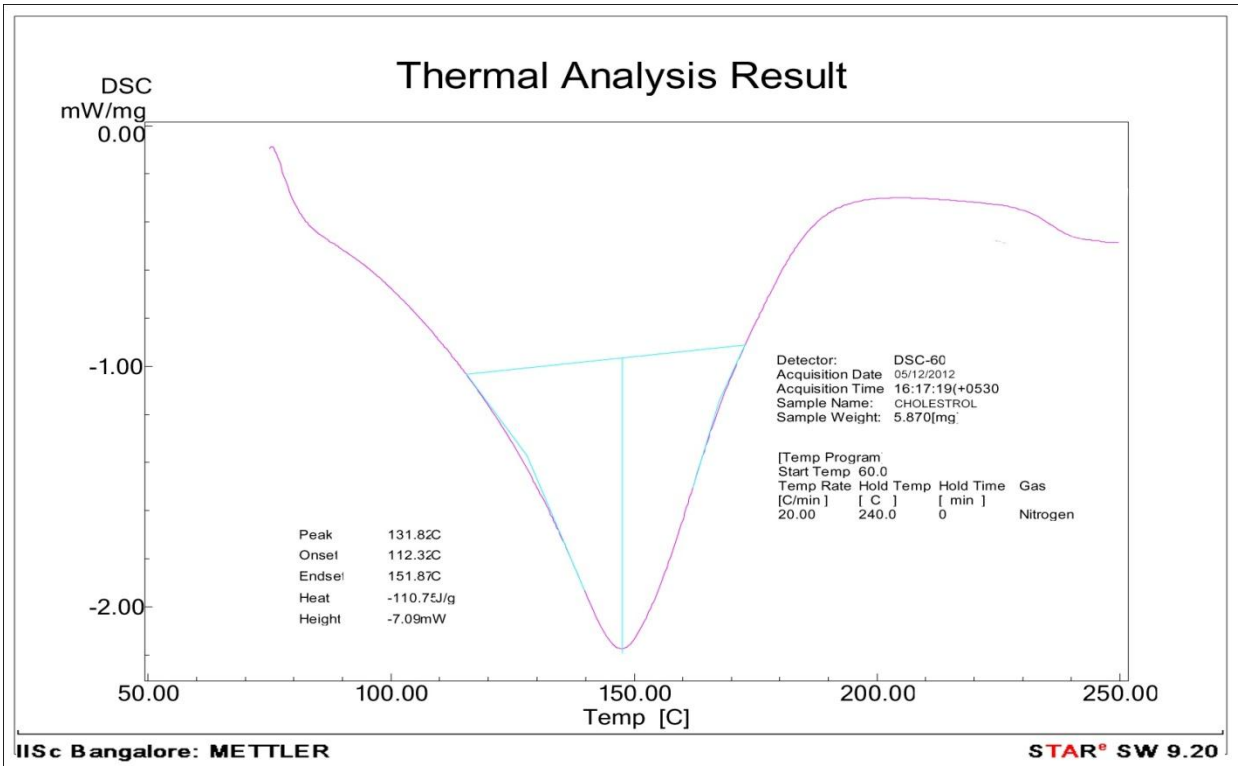
Spectra No: 6 IR Spectra of Physical Mixture

Differential Scanning Calorimetry

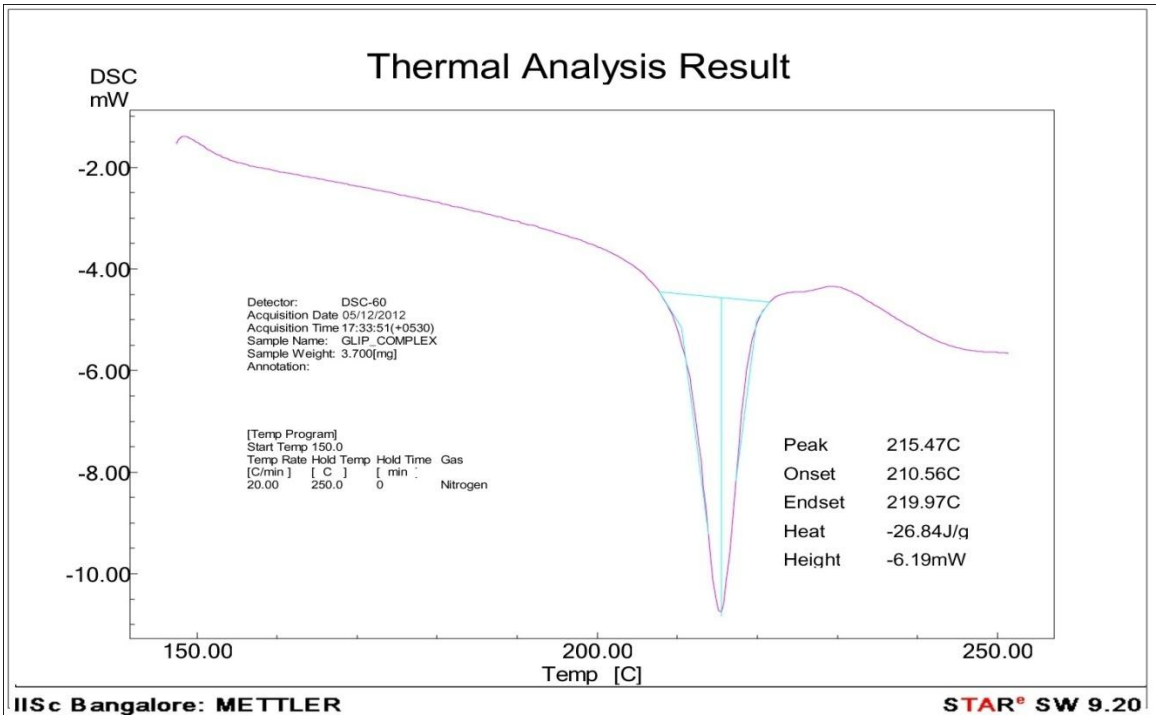
The thermal behavior of Glipizide with cholesterol complex was studied using DSC in order to confirm the formation of semi solid complex. DSC thermograms of Glipizide complex are shown in spectra no:6. DSC thermograms of glipizide exhibited an endothermic peak at 210.11^{o}C corresponding to its melting point. DSC curves revealed that both cholesterol and Glipizide exhibited an endothermic peak with onset temperature of 148^{o}C and 210.11^{o}C respectively. These melting peaks indicated the crystalline nature of both components. Thethermograms of formulation complex are different from the pure drug, which gives clear evidence that there is formation of the complexes.



Spectra No: 7 DSC Spectra of Glipizide pure drug



Spectra No: 8 DSC Spectra of Cholesterol



Spectra No: 9 DSC Spectra of infusion Glipizide formulation

Standard graph of Glipizide

Standard curve of Glipizide in PBS P^H 7.4

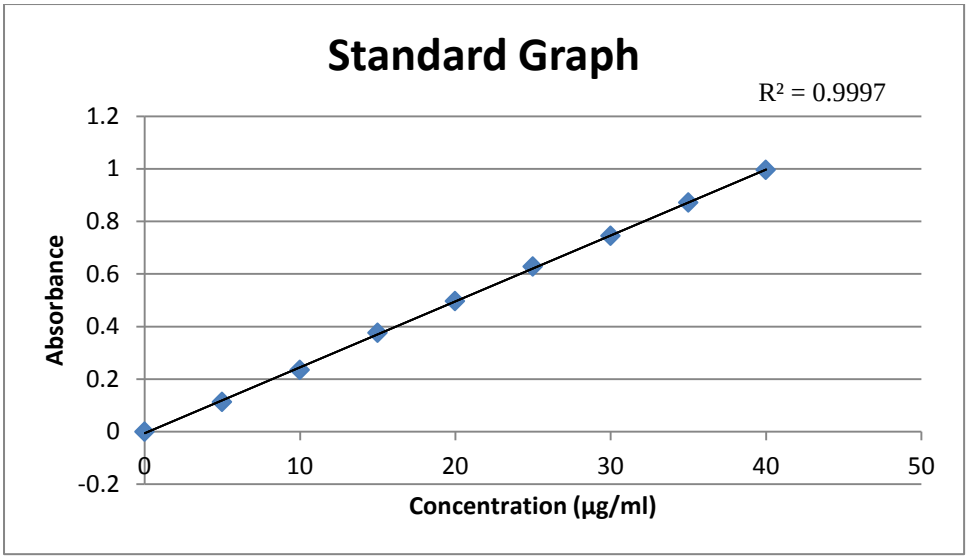
Standard graph was prepared for concentration of 5µg/ml- 40µg/ml at 276 nm. The graph of absorbance v_s concentration was plotted and data were subjected to linear regression analysis. The standard graph of drug in phosphate buffer show in table no: 9

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: 9 Standard Graph of Glipizide

R^2= 0.999

Slope=0.0252



Graph No: 1 Standard Graph of Glipizide

Different Formulation categories of Proniosomal Gel:

S.NO	F. NO	DRUG (mg)	SPAN60 (mg)	CHOLESTROL (mg)	LECITHIN (mg)	OBSERVATION
1	F_1	10	180	10	200	Pale Yellowish Gel
2	F_2	10	180	20	190	Yellowish Gel
3	F_3	10	180	40	180	Yellowish Gel
4	F_4	10	200	50	140	Yellowish cream
5	F_5	10	200	60	130	Yellowish semi solid
6	F_6	10	200	70	120	Yellowish semi solid
7	F_7	10	220	90	80	Yellowish semi solid
8	F_8	10	220	100	70	Yellowish semi solid
9	F_9	10	220	110	60	Yellowish semi solid
10	F_{10}	10	240	120	30	Yellowish semi solid

Table No: 10 Different State of Proniosomal Gel Preparations

FigureNo:12ProniosomalgelFormulations

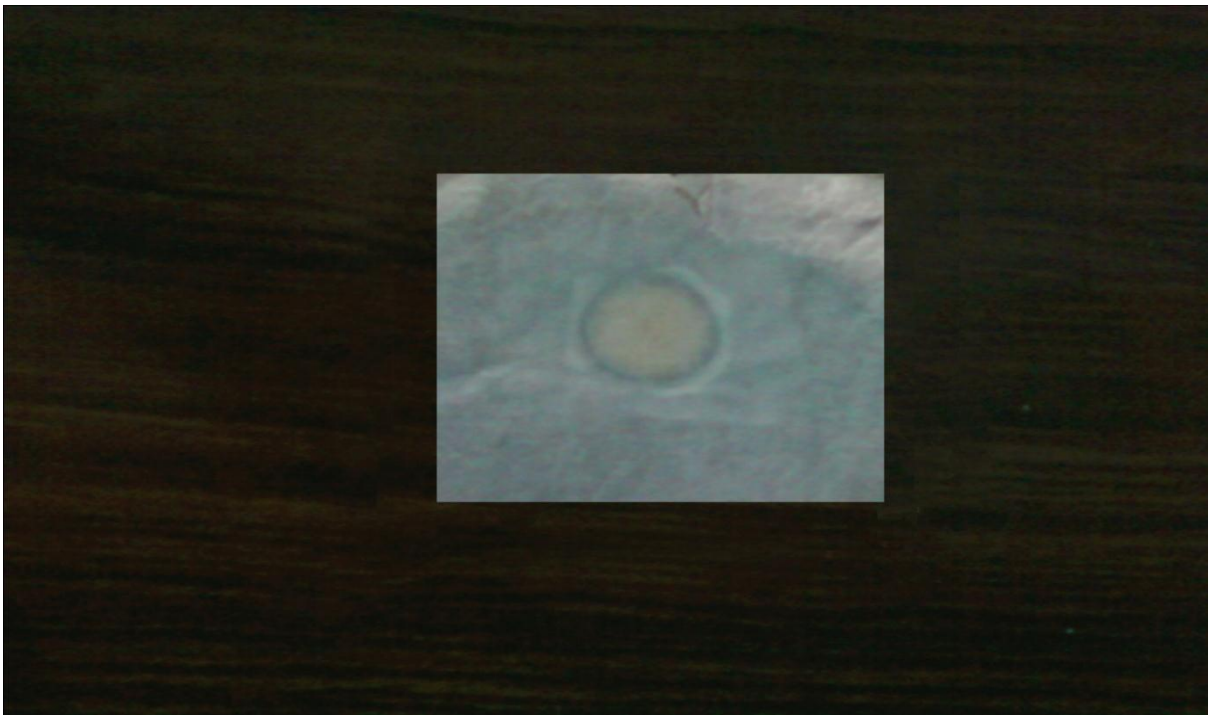


Figure no: 12 Proniosomal gel used in transdermal patch

P^H Determination

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

S.NO	Formulation Code	P^H
1.	F_1	6.90±0.14
2.	F_2	6.98±0.32
3.	F_3	6.89±0.57
4.	F_4	6.91±0.41
5.	F_5	6.93±0.58
6.	F_6	6.87±0.36
7.	F_7	6.90±0.78
8.	F_8	7.07±0.27
9.	F_9	7.11±0.58
10	F_{10}	7.18±0.63

n=3 ±S.D***Table No: 11 P^H of Proniosomal Gel**

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:11

Viscosity Determination

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

S.No	Formulation Code	Viscosity
1.	F_1	46127
2.	F_2	45773
3.	F_3	43672
4.	F_4	42019
5.	F_5	41371
6.	F_6	38674
7.	F_7	36096
8.	F_8	35885
9.	F_9	33098
10.	F_{10}	32633

n=3 ±S.D*

Table No: 12 Viscosity Determinations

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 ofEncapsulationEfficiency. 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 EncapsulationEfficiency.

Effect on Cholesterol:

Cholesterol molecules are accommodate itself as vesicular observation in the molecule cavities formed monomers are assembled into bilayers to form Proniosomal membranes. This space filling action was in charge for higher inflexibility and less permeability of cholesterol containing membranes compared to cholesterol free membranes and improved percentage Encapsulation Efficiencyi.e very low level of cholesterol content to produce deceased EncapsulationEfficiency. In dissimilarity very high level cholesterol content decreased percentageEncapsulationEfficiency F_3,F_4,F_5,F_6 respectively 86.75 ±0.288, 87.75± 0.803,87.25 ± 0.629,86.75 ± 0.381. This could be due to the information that cholesterol beyond a certain level starts disrupting the regular bi layered structure leading to loss of drug entrapment. The higher entrapment may be explained by high cholesterol content.In F_2cholesterol level was responsible for producing higher (92.75± 0.520%) encapsulation efficiency.

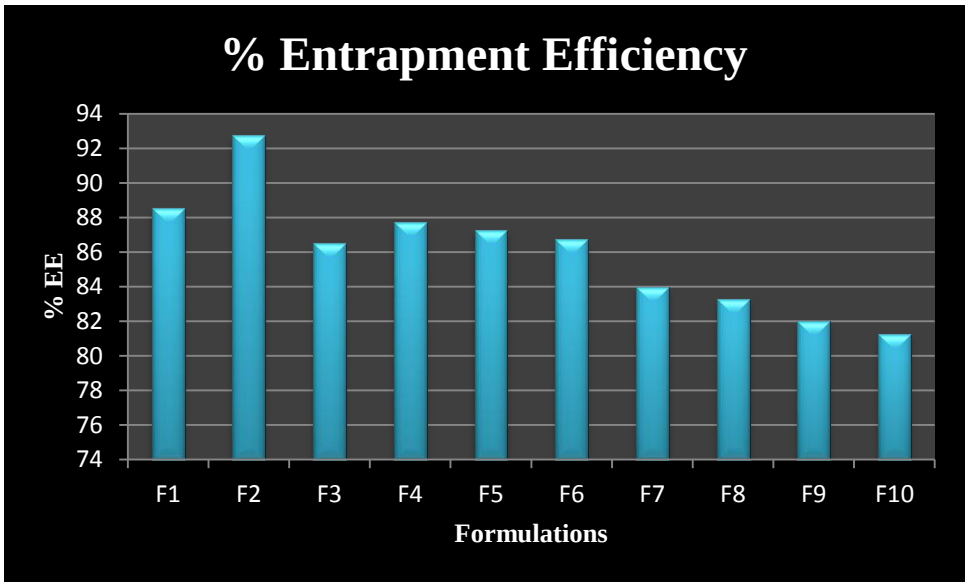
Effect of lecithin:

Incorporation of lecithin is larger amount to produce higher percentage Encapsulation Efficiency which is commonly used to system stability.

S.NO	FORMULATION CODE	ENCAPSULATION EFFICIENCY* (%)
1.	F_1	88.5 ± 0.250
2.	F_2	92.75 ± 0.520
3.	F_3	86.75 ± 0.288
4.	F_4	87.75 ± 0.803
5.	F_5	87.25 ± 0.629
6.	F_6	86.75 ± 0.381
7.	F_7	84.50 ± 0.381
8.	F_8	83.50 ± 0.629
9.	F_9	82.00± 0.750
10.	F_{10}	81.75 ± 0.500

n=3 ±S.D*

Table No: 13 Encapsulation Efficiency Proniosomal Gel



Graph No: 3 Entrapment Efficiency of Proniosomal Gel

Drug Content

Uniformity in content of proniosomal gel (F_1 to F_{10}) were confirmed to assure Uniformity in dosage. The results were reported in following table no:14

S.NO	Formulation Code	Drug Content
1.	F_1	87.50± 0.144%
2.	F_2	90.00± 0.25%
3.	F_3	80.0±0.866 %
4.	F_4	82.5± 0.520%
5.	F_5	85.0±0.866%
6.	F_6	75.0± 0.381%
7.	F_7	70.0±0.577%
8.	F_8	72.50± 0.381%
9.	F_9	65.0±1.526%
10.	F_{10}	62.5±1.041%

n=3± S.D*

Table No: 14 Drug Content of Proniosomal Gels

Scanning Electron Microscopy

Shape and surface characteristic of proniosomal gel examined by scanning electron microscopy analysis as shown fig No: .the vesicles are shown smaller in diameter, and produce smooth surface area.

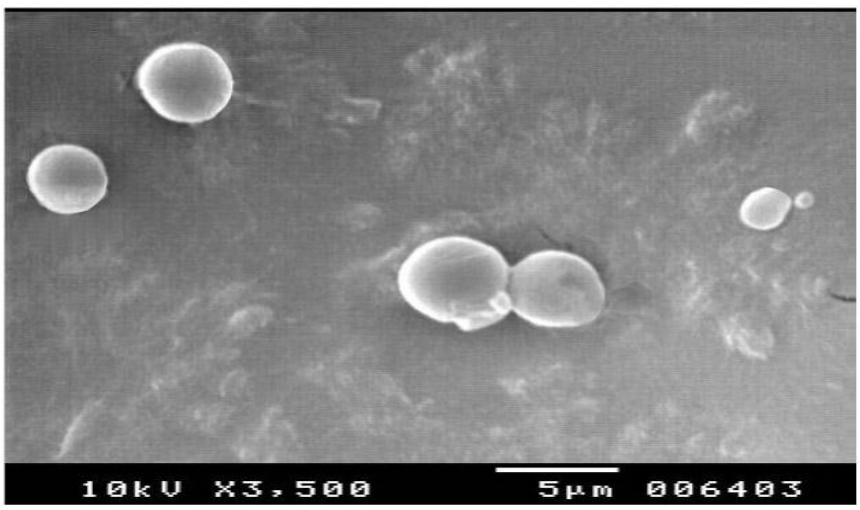


Fig No: 14 SEM image of F_2 *In-Vitro* studies

***In-Vitro* Drug Release of F_1**

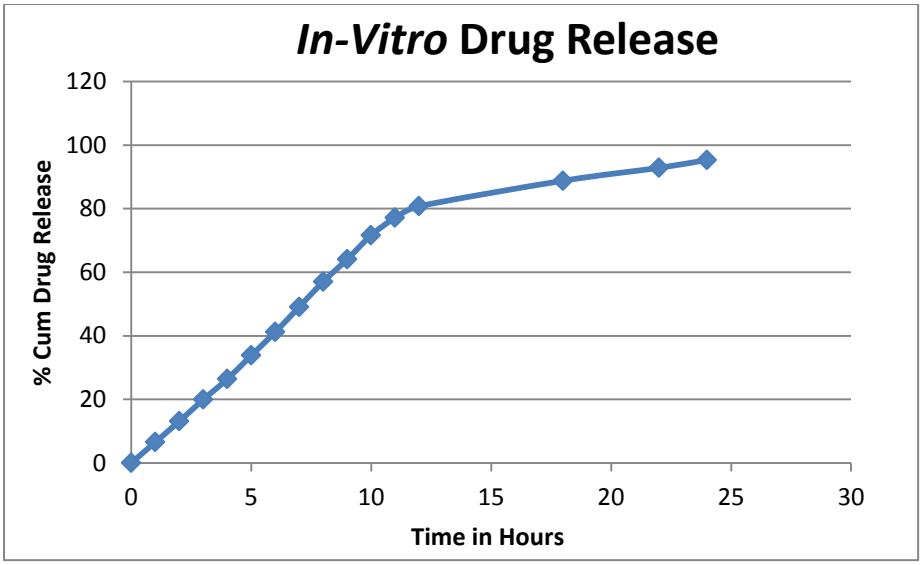
Time	Log time	Sq.rt of time	Absorbance	conc µg/ml	conc mg/ml	% release	cum % release	log cum % release
0	0	0	0	0	0	0	0	0
1	0	1.000	0.066	2.619	0.655	6.548	6.548	0.816
2	0.301	1.414	0.132	5.238	1.309	13.095	13.095	1.117
3	0.441	1.732	0.201	7.976	1.994	19.940	19.940	1.299
4	0.602	2.000	0.266	10.556	2.639	26.389	26.389	1.421
5	0.699	2.236	0.341	13.532	3.383	33.829	33.829	1.529
6	0.778	2.449	0.415	16.468	4.117	41.171	41.171	1.615
7	0.845	2.645	0.495	19.643	4.911	49.107	49.107	1.691
8	0.903	2.828	0.527	20.913	5.228	52.281	52.282	1.718
9	0.903	2.828	0.575	22.818	5.704	57.044	57.044	1.756
10	0.954	3.000	0.646	25.635	6.409	64.087	64.087	1.807
11	1.000	3.162	0.727	28.849	7.212	72.123	72.123	1.858
12	1.071	3.316	0.814	32.302	8.075	80.754	80.754	1.907
18	1.342	3.464	0.886	35.159	8.789	87.897	87.897	1.944
22	1.380	4.242	0.995	39.484	9.871	98.710	98.71	1.994
24	1.380	4.899	0.998	39.603	9.901	99.008	99.008	1.996

Table no: 15 *Invitro* Drug Release Study of F_1

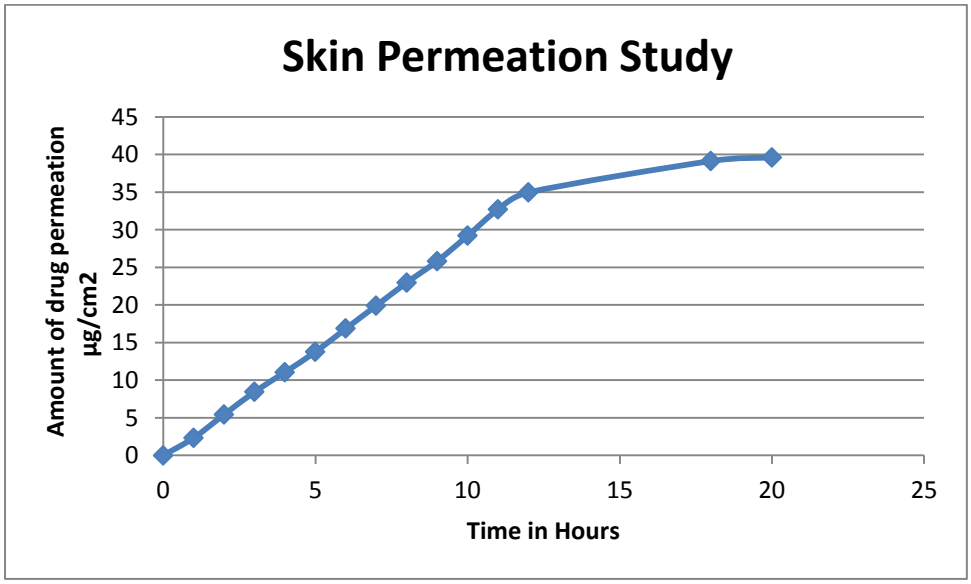
***In-Vitro* Skin Permeation Study**

S. No	Time	Absorbance	Conc µg/cm^2
1	0	0	0
2	1	0.059	2.341
3	2	0.137	5.437
4	3	0.213	8.452
5	4	0.279	11.071
6	5	0.347	13.769
7	6	0.425	16.865
8	7	0.502	19.921
9	8	0.579	22.976
10	9	0.651	25.833
11	10	0.736	29.206
12	11	0.824	32.698
13	12	0.881	34.960
14	18	0.893	35.861
15	22	0.986	39.127
16	24	0.998	39.603

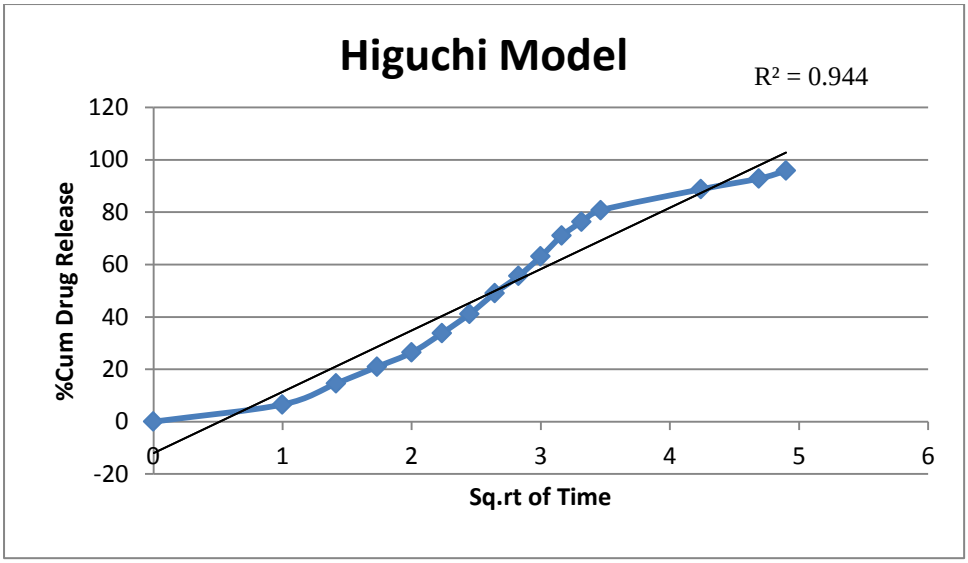
Table No:16*In-vitro* Skin Permeation Study of F_1



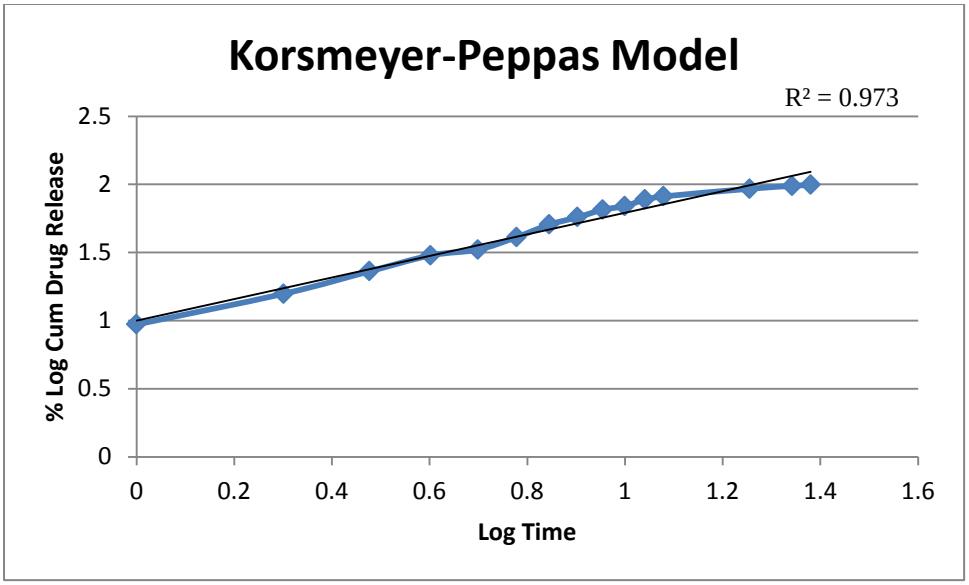
Graph No: 4 *In-vitro* Drug Release of F_1



Graph No: 5 *In-vitro*skin Permeation Study of F_1



Graph No: 6 Higuchi Model of F_1



Graph No: 7Korsmeyer-PeppasModel of F_1

Formulation: 2

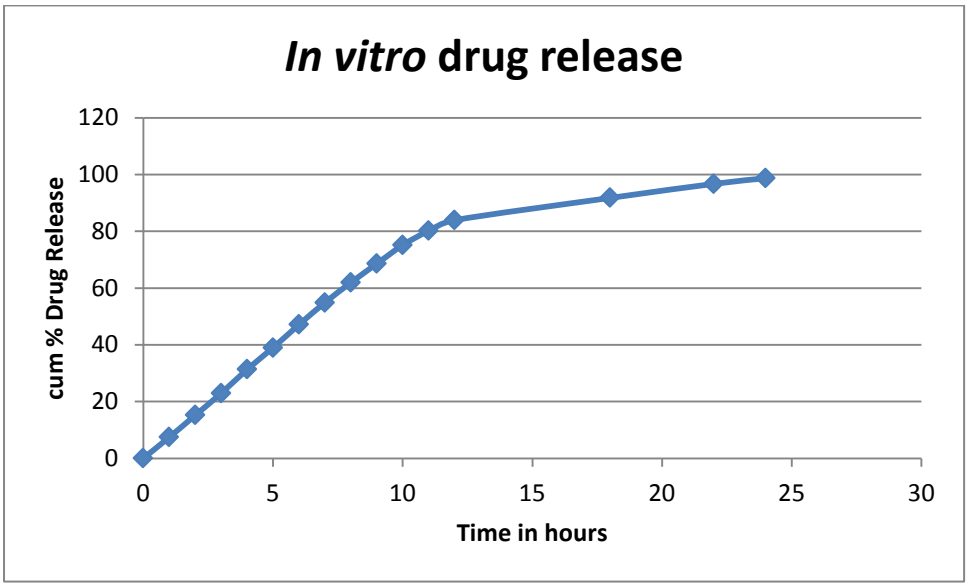
S.No	Time	Sq.rt of time	Absorbance	Conc µg/ml	Conc mg/ml	Cum % Release	Log Cum % Release
1	0	0.000	0.000	0.000	0.0000	0.000	0.000
2	1	0.000	0.075	2.976	0.744	7.44	0.872
3	2	0.301	0.153	6.071	1.518	15.178	1.181
4	3	0.441	0.231	9.167	2.292	22.917	1.360
5	4	0.602	0.316	12.539	3.135	31.349	1.496
6	5	0.699	0.389	15.437	3.859	38.591	1.591
7	6	0.778	0.475	18.849	4.712	47.123	1.673
8	7	0.845	0.553	21.944	5.486	54.861	1.739
9	8	0.903	0.624	24.762	6.190	61.905	1.792
10	9	0.954	0.691	27.421	6.855	68.552	1.836
11	10	1.000	0.757	30.039	7.509	75.099	1.876
12	11	1.041	0.808	32.063	8.016	80.158	1.904
13	12	1.071	0.846	33.571	8.393	83.929	1.963
14	18	1.255	0.925	36.706	9.177	91.769	1.986
15	22	1.342	0.975	38.690	9.673	96.726	1.994
16	24	1.380	0.986	39.125	9.781	98.710	1.990

Table No: 17*In-Vitro* drug Release of F_2

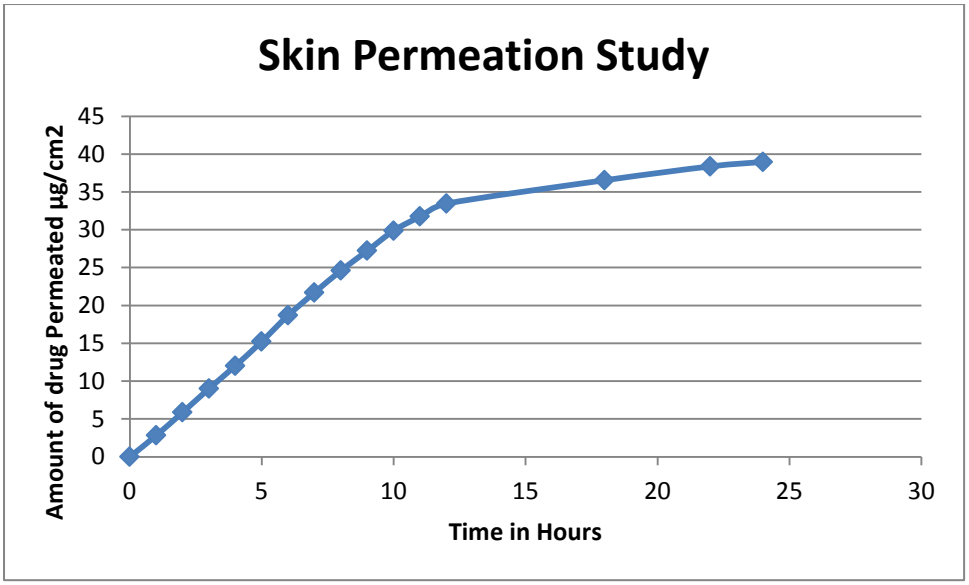
In-Vitro Skin Permeation

S.No	Time	Absorbance	Conc µg/cm^2
1	0	0	0
2	1	0.071	2.817
3	2	0.148	5.873
4	3	0.227	9.008
5	4	0.303	12.024
6	5	0.384	15.238
7	6	0.471	18.690
8	7	0.547	21.706
9	8	0.62	24.603
10	9	0.686	27.222
11	10	0.753	29.881
12	11	0.8	31.746
13	12	0.843	33.452
14	18	0.921	36.548
15	22	0.967	38.373
16	24	0.991	39.325

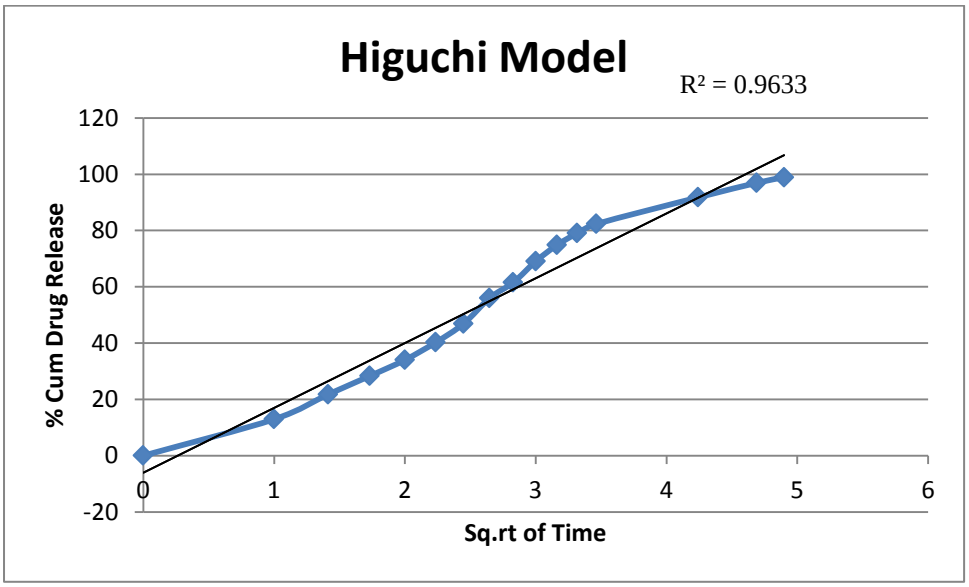
Table No:18_In-Vitro_ Skin Permeation Study F_2



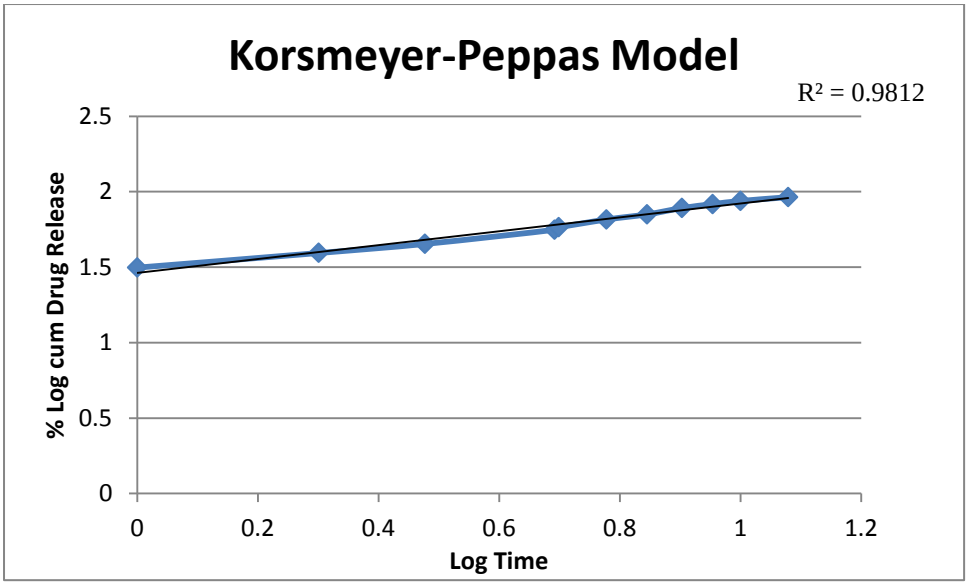
Graph No: 8_In-Vitro_ Drug Release of F_2



Graph No: 9 In-Vitro Skin Permeation Study of F_2



Graph No: 10 Higuchi Model of F_2



Graph No: 11Korsmeyer-PeppasModel of F

Formulation: 3

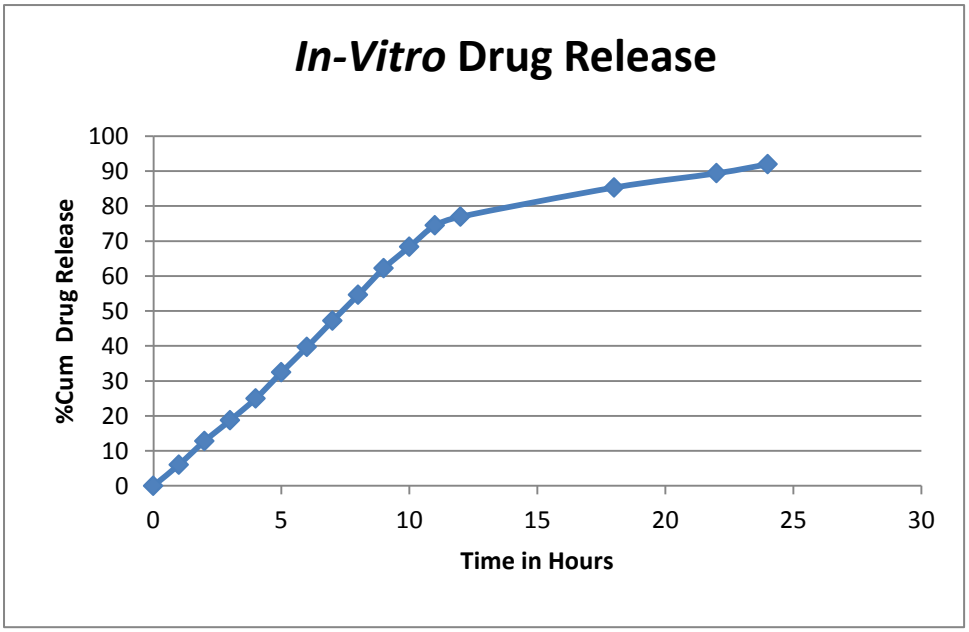
S.No	Time	Log time	Sq.rt of time	Absorbance	Conc µg/ml	Conc mg/ml	% Cum Drug Release	Log % Cum Drug Release
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	0.000	1.000	0.061	2.421	0.605	6.052	0.782
3	2	0.301	1.414	0.129	5.119	1.279	12.798	1.107
4	3	0.044	1.732	0.189	7.500	1.875	18.750	1.273
5	4	0.602	2.000	0.252	10.000	2.500	25.000	1.398
6	5	0.699	2.236	0.327	12.976	3.244	32.44	1.511
7	6	0.778	2.449	0.400	15.873	3.968	39.683	1.598
8	7	0.845	2.646	0.476	18.889	4.722	47.222	1.674
9	8	0.903	2.828	0.554	21.984	5.496	54.603	1.737
10	9	0.954	3.000	0.633	25.119	6.279	62.198	1.794
11	10	1.000	3.162	0.689	27.341	6.835	68.353	1.835
12	11	1.041	3.317	0.751	29.802	7.450	74.504	1.872
13	12	1.072	3.464	0.776	30.794	7.698	76.984	1.886
14	18	1.255	4.242	0.86	34.127	8.532	85.317	1.931
15	22	1.342	4.690	0.901	35.754	8.938	89.385	1.951
16	24	1.380	4.899	0.927	36.786	9.196	91.964	1.964

Table No: 19 *In-vitro* drug Release of F_3

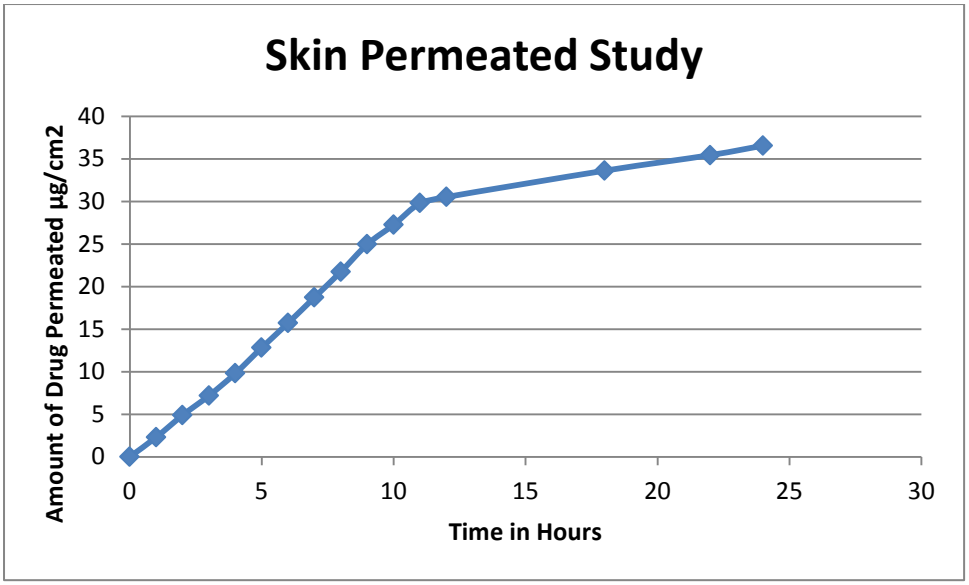
***In-Vitro* Skin Permeation Study**

S.No	Time	Absorbance	Concµg/cm^2
1	0	0	0
2	1	0.058	2.302
3	2	0.123	4.881
4	3	0.181	7.183
5	4	0.247	9.802
6	5	0.323	12.818
7	6	0.396	15.714
8	7	0.472	18.730
9	8	0.548	21.746
10	9	0.629	24.960
11	10	0.687	27.262
12	11	0.751	29.802
13	12	0.769	30.516
14	18	0.847	33.611
15	22	0.893	35.437
16	24	0.921	36.548

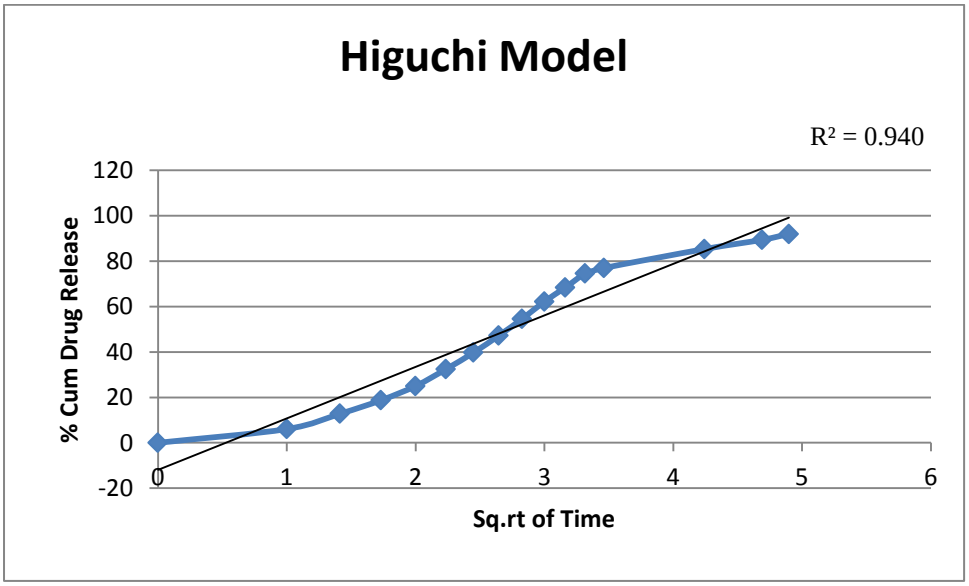
Table No: 20 *In-vitro* Skin Permeation Study of F_3



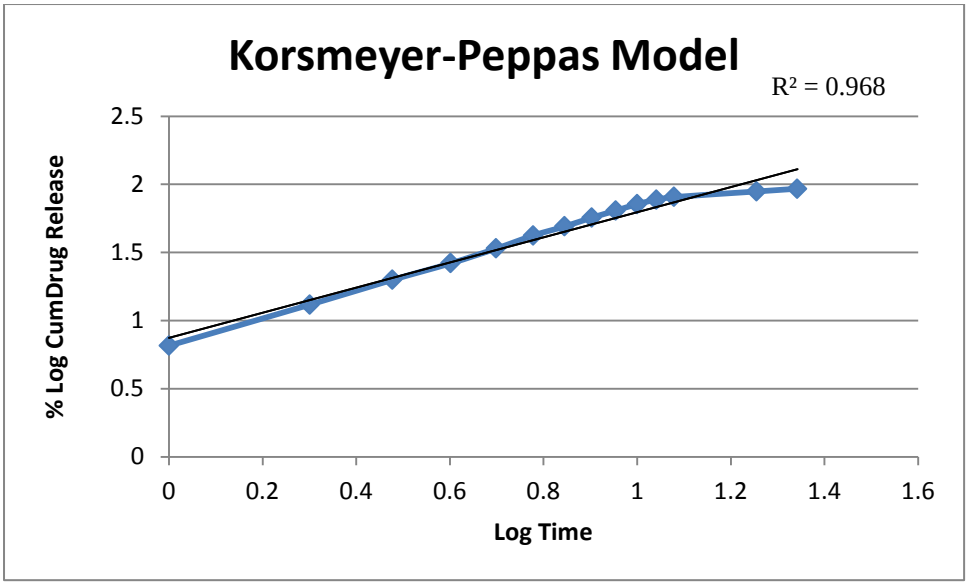
Graph No: 12In-vitro drug release of F_3



Graph No: 13 *In-vitro* Skin Permeation of F_3



Graph No: 14 Higuchi Model of F_3



Graph No: 15Korsmeyer-PeppasModelof F_3

Formulation: 4

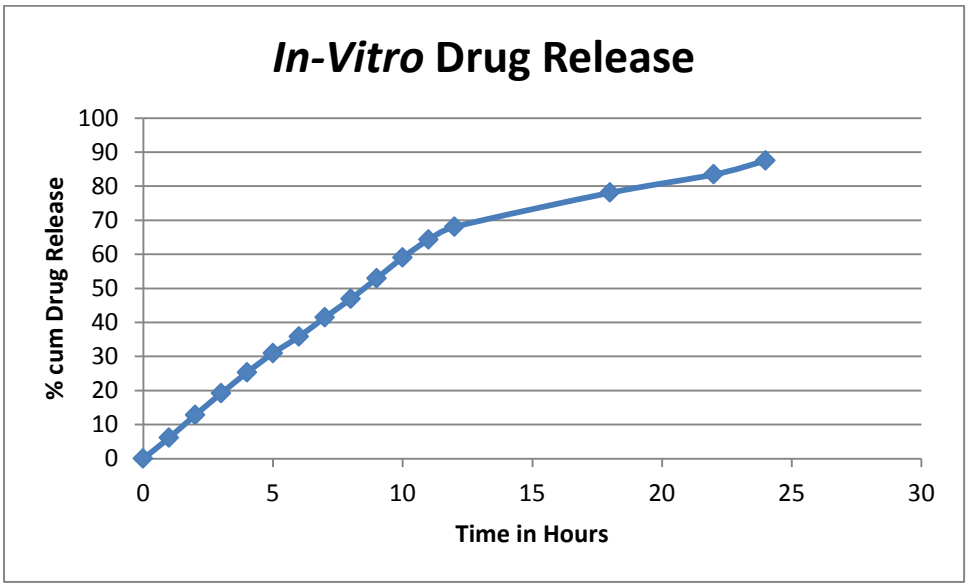
S.No	Time	Log Time	Sq.rt of Time	Absorbance	Conc µg/ml	Conc mg/ml	Cum % drug Release	Log Cum % Drug Release
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	0.000	1.000	0.062	2.460	0.615	6.151	0.789
3	2	0.301	1.414	0.129	5.119	1.279	12.798	1.107
4	3	0.477	1.732	0.193	7.659	1.915	19.146	1.282
5	4	0.602	2.000	0.255	10.119	2.529	25.298	1.403
6	5	0.698	2.236	0.312	12.381	3.095	30.952	1.491
7	6	0.778	2.449	0.361	14.325	3.581	35.813	1.554
8	7	0.845	2.646	0.418	16.587	4.147	41.468	1.618
9	8	0.903	2.828	0.473	18.769	4.692	46.925	1.671
10	9	0.954	3.000	0.534	21.190	5.298	52.941	1.724
11	10	1.000	3.162	0.595	23.611	5.903	59.0278	1.77
12	11	1.041	3.317	0.648	25.714	6.429	64.286	1.808
13	12	1.079	3.464	0.686	27.222	6.806	68.056	1.833
14	18	1.255	4.242	0.787	31.230	7.808	78.0754	1.892
15	22	1.342	4.69	0.841	33.373	8.343	83.433	1.921
16	24	1.380	4.899	0.882	35.000	8.750	87.500	1.942

Table No: 21*In-vitro* Drug Release of F_4

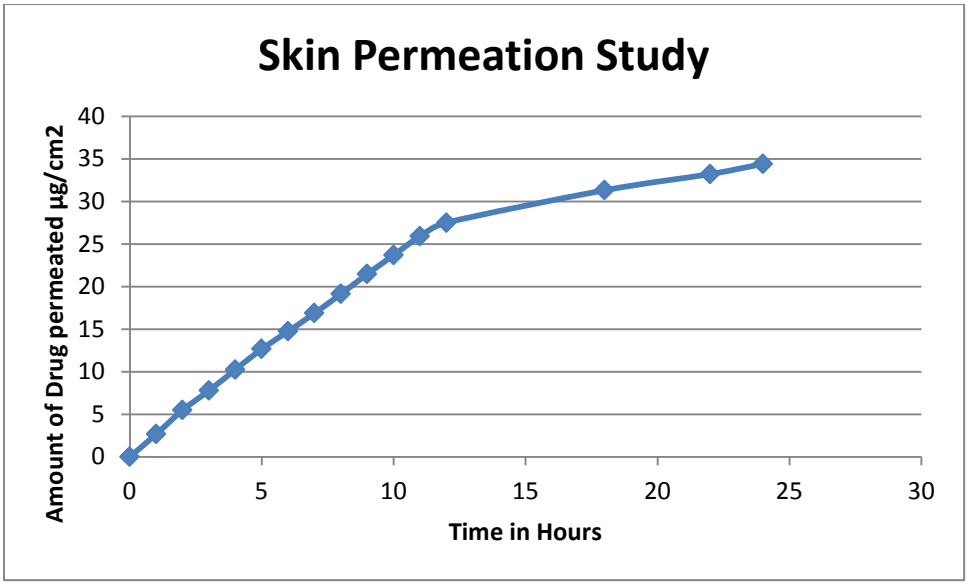
***In-Vitro* Skin Permeation Study of F_4**

S.No	Time	Absorbance	Conc µg/cm^2
1	0	0	0
2	1	0.067	2.659
3	2	0.138	5.476
4	3	0.196	7.778
5	4	0.258	10.238
6	5	0.319	12.659
7	6	0.371	14.722
8	7	0.425	16.865
9	8	0.482	19.127
10	9	0.541	21.468
11	10	0.597	23.690
12	11	0.653	25.913
13	12	0.693	27.500
14	18	0.789	31.309
15	22	0.837	33.214
16	24	0.867	34.405

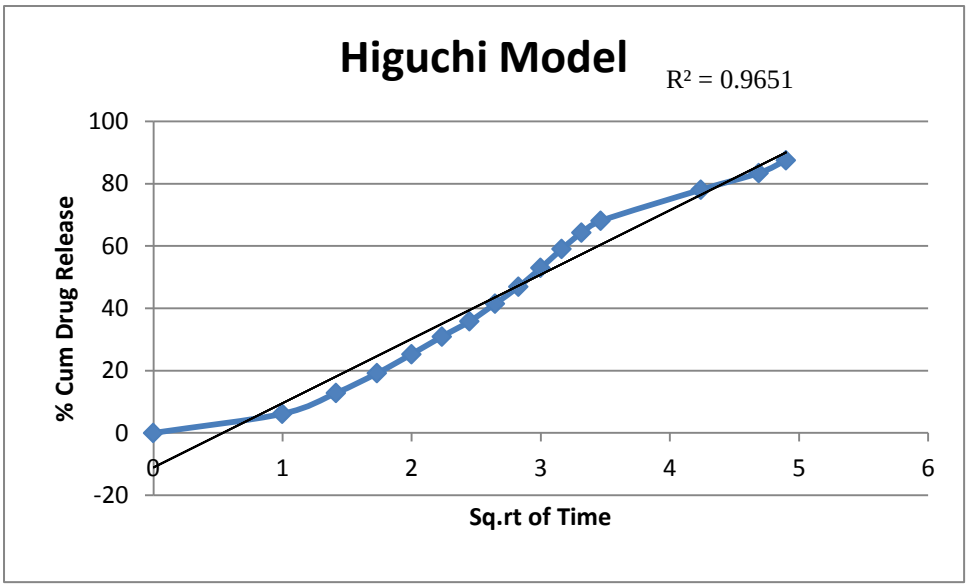
Table No: 22*In-Vitro* Skin Permeation Study of F_4



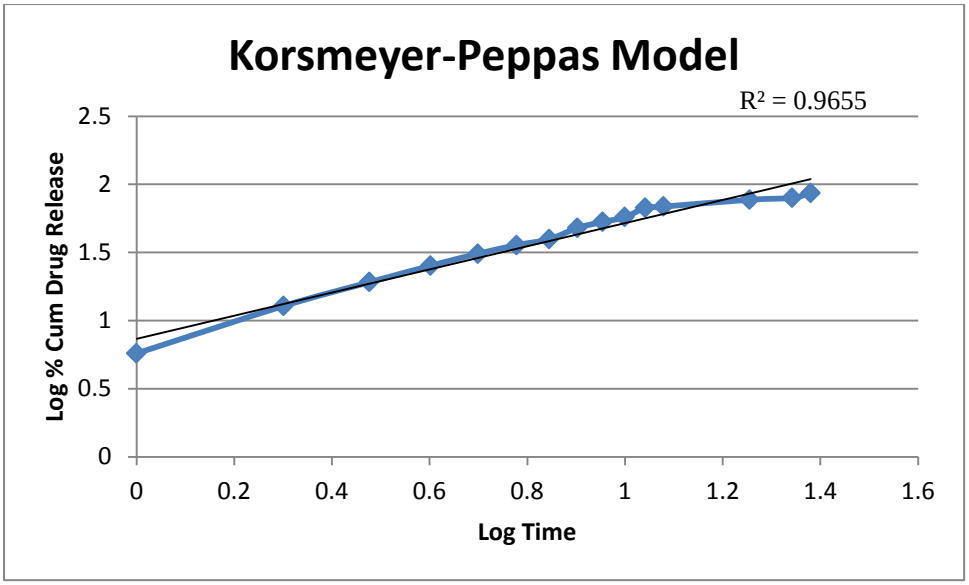
Graph No: 16 In-vitro Drug Release of F_4



Graph No: 17 *In-vitro* Skin Permeation Study of F_4



Graph No: 18 Higuchi Model of F_4



Graph No: 19Korsmeyer-Peppas Model of F_4

Formulation:5

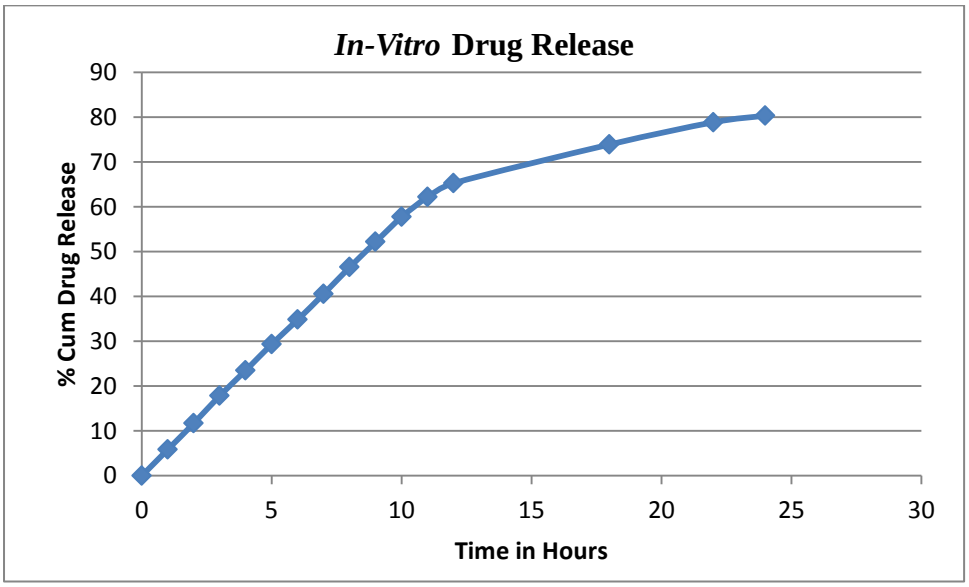
S.NO	Time	Log time	Sq.rt of time	Absorbance	Conc µg/ml	Conc mg/ml	% Cum Drug release	Log Cum % Drug Release
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	0.000	1.000	0.059	2.341	0.585	5.853	0.767
3	2	0.301	1.414	0.118	4.683	1.171	11.706	1.068
4	3	0.044	1.732	0.18	7.143	1.786	17.857	1.252
5	4	0.602	2.000	0.237	9.405	2.351	23.512	1.371
6	5	0.699	2.236	0.296	11.746	2.937	29.365	1.468
7	6	0.778	2.449	0.351	13.929	3.482	34.821	1.542
8	7	0.845	2.646	0.409	16.230	4.058	40.575	1.608
9	8	0.903	2.828	0.469	18.611	4.653	46.528	1.668
10	9	0.954	3.000	0.526	20.873	5.218	52.183	1.718
11	10	1.000	3.162	0.582	23.095	5.774	57.738	1.761
12	11	1.041	3.317	0.627	24.881	6.220	62.202	1.794
13	12	1.072	3.464	0.658	26.111	6.528	65.278	1.815
14	18	1.255	4.242	0.745	29.563	7.391	73.909	1.869
15	22	1.342	4.690	0.795	31.548	7.887	78.869	1.897
16	24	1.380	4.899	0.810	32.143	8.036	80.357	1.905

Table No: 22*In-vitro* Drug Release of F_5

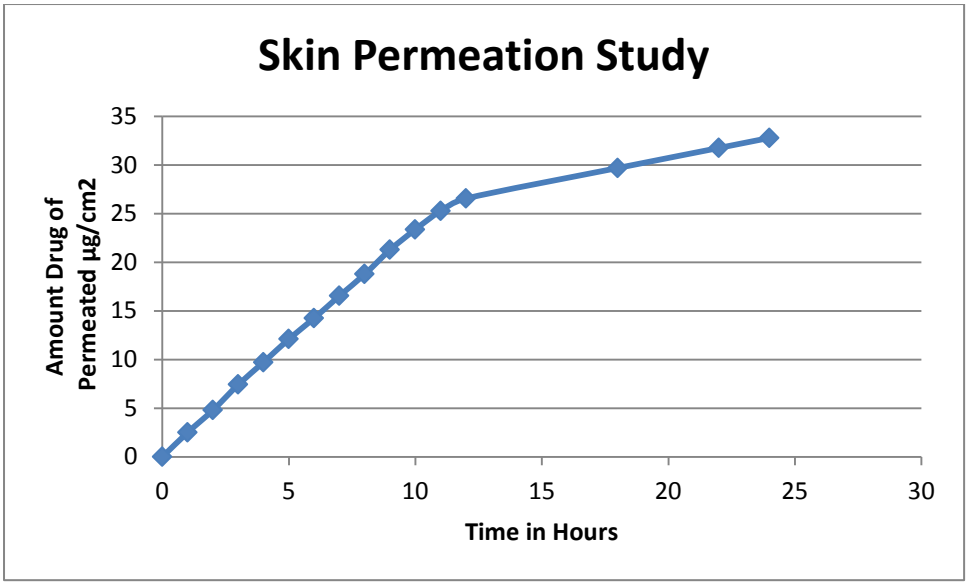
***In-Vitro* Skin Permeation Study of F_5**

S.No	Time	Absorbance	Conc µg/cm^2
1	0	0	0
2	1	0.063	2.5
3	2	0.121	4.802
4	3	0.187	7.421
5	4	0.245	9.722
6	5	0.305	12.103
7	6	0.359	14.246
8	7	0.417	16.548
9	8	0.473	18.769
10	9	0.536	21.269
11	10	0.589	23.373
12	11	0.637	25.278
13	12	0.669	26.548
14	18	0.748	29.683
15	22	0.8	31.746
16	24	0.826	32.778

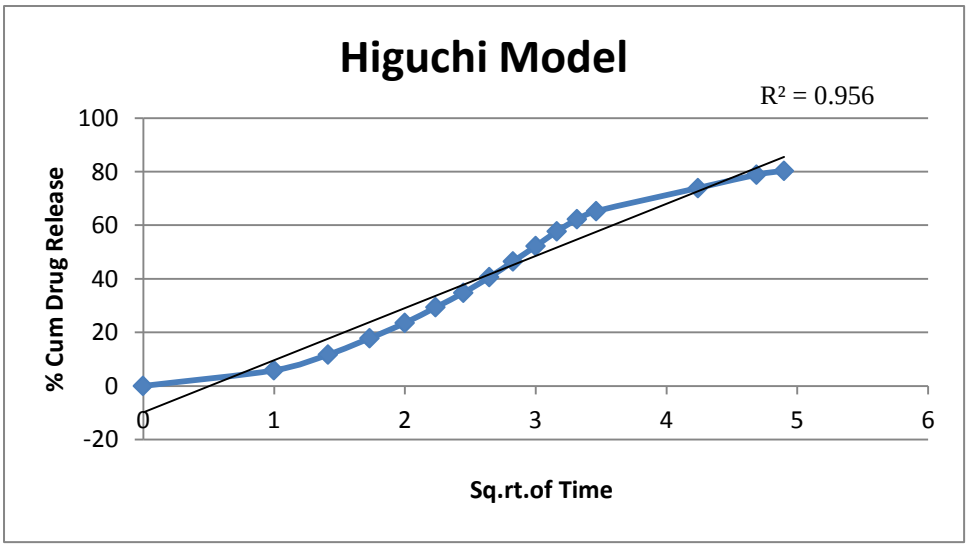
Table No: 23 *In-Vitro* Skin Permeation Study of F_5



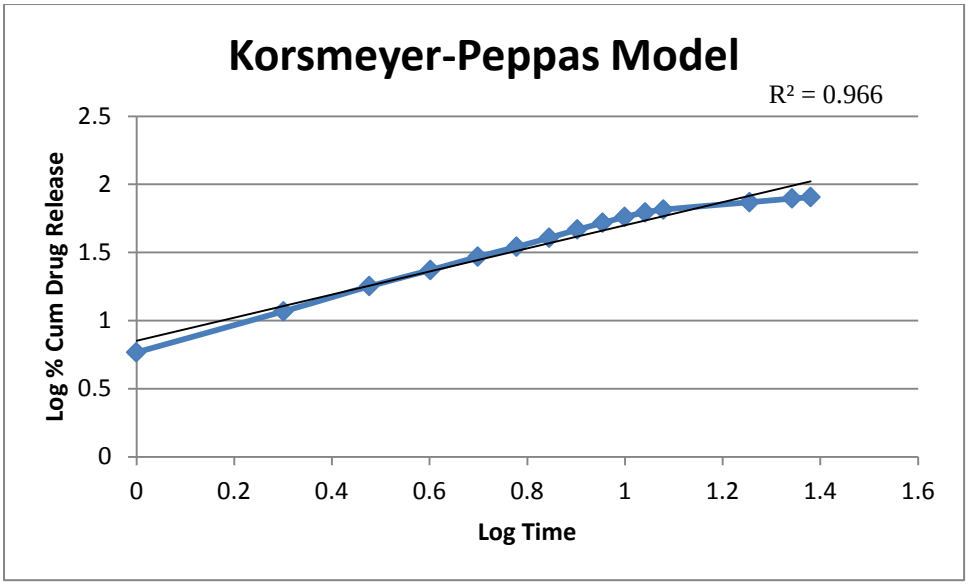
Graph No: 20 In-vitro Drug Release of F5



Graph No:21*In-vitro* Skin Permeation Study of F_5



Graph No:22 Higuchi Model of F_5



Graph No:23Korsmeyer-Peppas Model of F_5

Formulation: 6

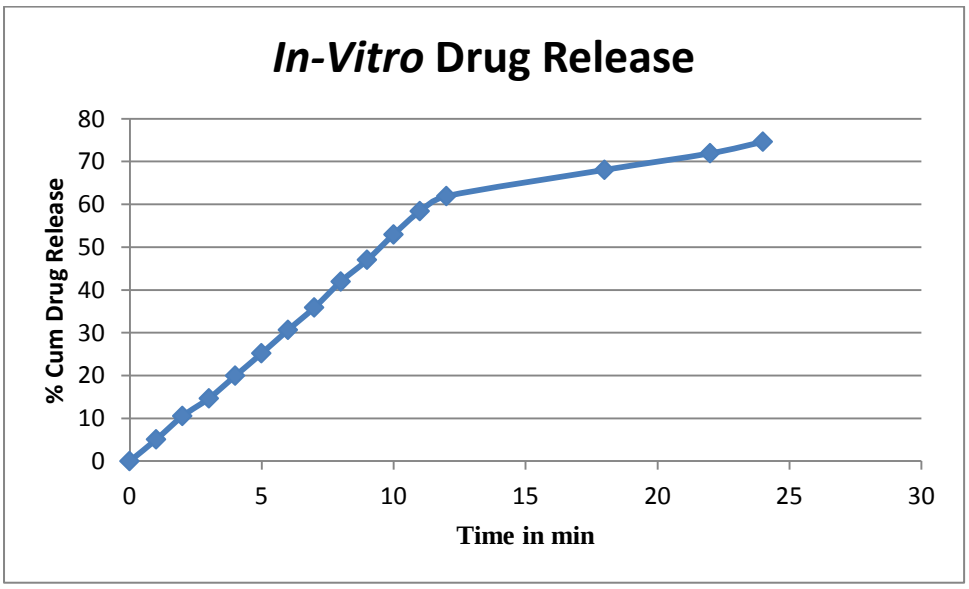
S.No	Time	Log time	Sq.rt of time	Absorbance	Conc µg/ml	Conc mg/ml	% Cum Drug Release	Log % Cum Drug Release
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	0.000	1.000	0.051	2.024	0.506	5.059	0.704
3	2	0.301	1.414	0.106	4.206	1.052	10.516	1.022
4	3	0.044	1.732	0.148	5.873	1.468	14.682	1.167
5	4	0.602	2.000	0.201	7.976	1.994	19.940	1.299
6	5	0.699	2.236	0.254	10.079	2.519	25.198	1.401
7	6	0.778	2.449	0.309	12.262	3.065	30.654	1.486
8	7	0.845	2.645	0.362	14.365	3.591	35.913	1.555
9	8	0.903	2.828	0.423	16.785	4.196	41.964	1.623
10	9	0.954	3.000	0.474	18.809	4.702	47.024	1.672
11	10	1.000	3.162	0.534	21.190	5.298	52.976	1.724
12	11	1.041	3.316	0.589	23.373	5.843	58.433	1.766
13	12	1.071	3.464	0.624	24.762	6.190	61.905	1.792
14	18	1.255	4.242	0.686	27.222	6.806	68.056	1.833
15	22	1.342	4.69	0.725	28.769	7.192	71.925	1.857
16	24	1.380	4.899	0.752	29.841	7.460	74.603	1.873

Table No: 23*In-vitro* Drug Release of F_6

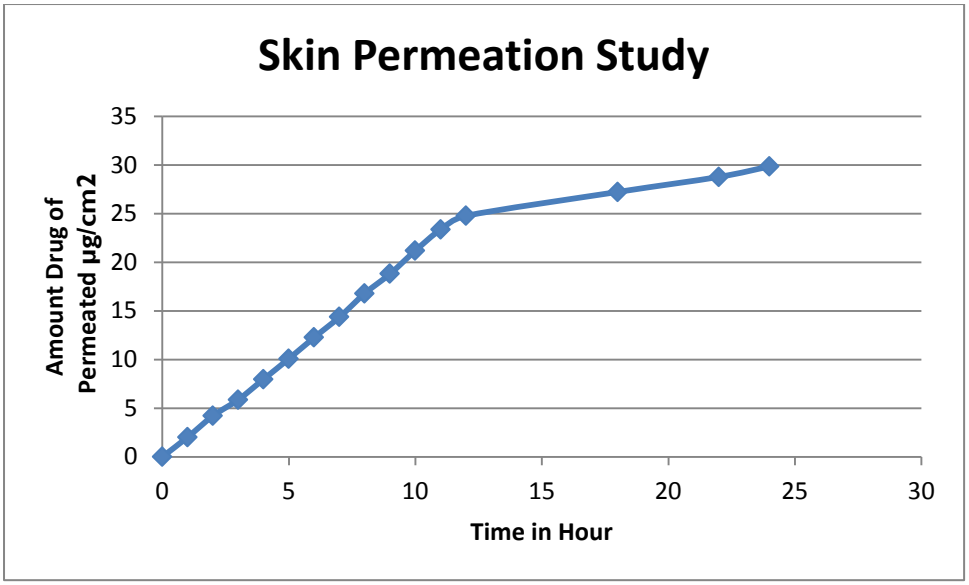
***In-Vitro* Skin Permeation Study of F_6**

S.No	Time	Absorbance	Conc µg/cm^2
1	0	0	0
2	1	0.051	2.024
3	2	0.106	4.206
4	3	0.148	5.873
5	4	0.201	7.976
6	5	0.254	10.079
7	6	0.309	12.262
8	7	0.362	14.365
9	8	0.423	16.786
10	9	0.474	18.809
11	10	0.534	21.190
12	11	0.589	23.373
13	12	0.624	24.762
14	18	0.686	27.222
15	22	0.725	28.769
16	24	0.752	29.841

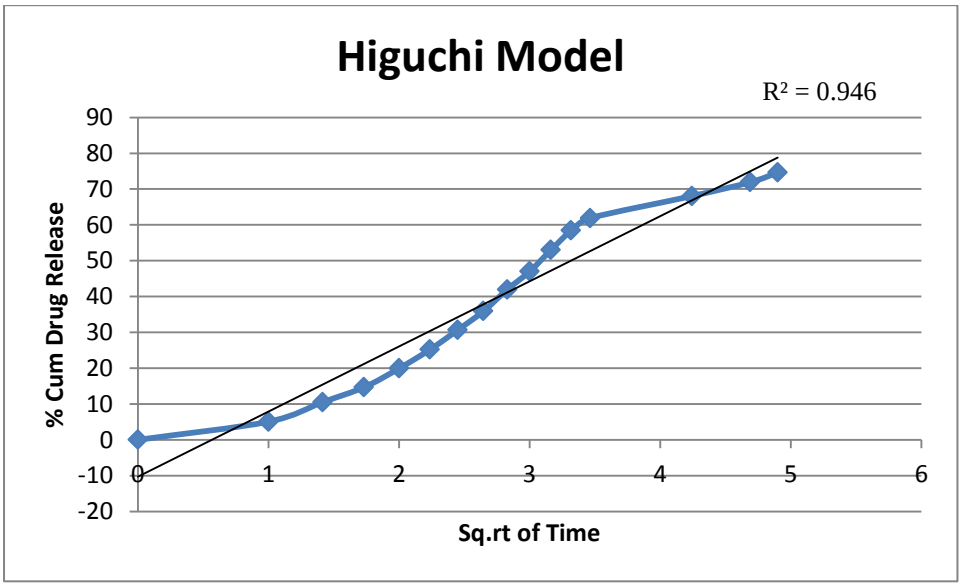
Table no: 24*In-vitro* Skin Permeation Study of F_6



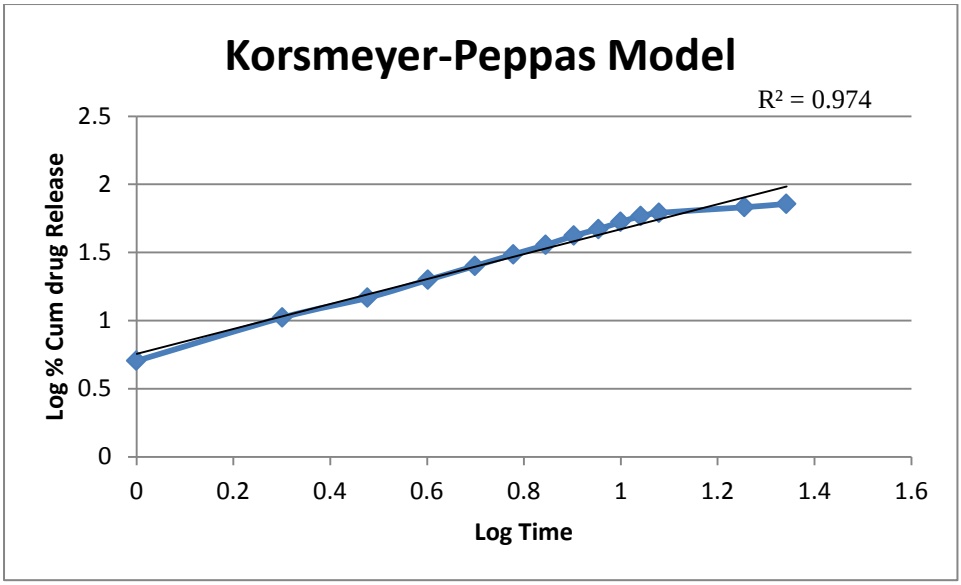
Graph No: 24*In-vitro* Drug Release of F_6



Graph No: 25 *In-Vitro* Skin Permeation Study of F_6

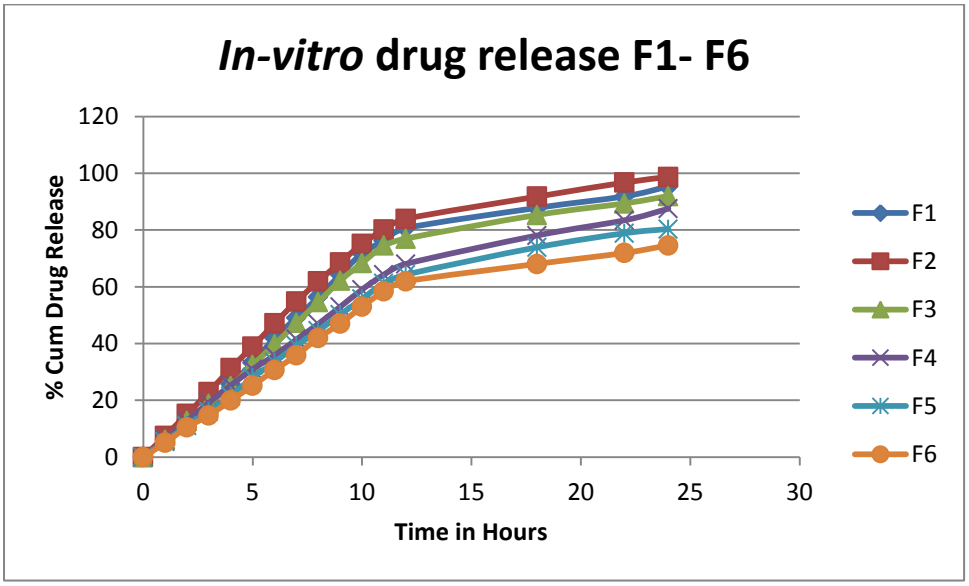


Graph No: 26 Higuchi Model of F_6



Graph No: 27Korsmeyer-PeppasModelof F_6

***In-Vitro* Drug Release [F_1-F_6]**

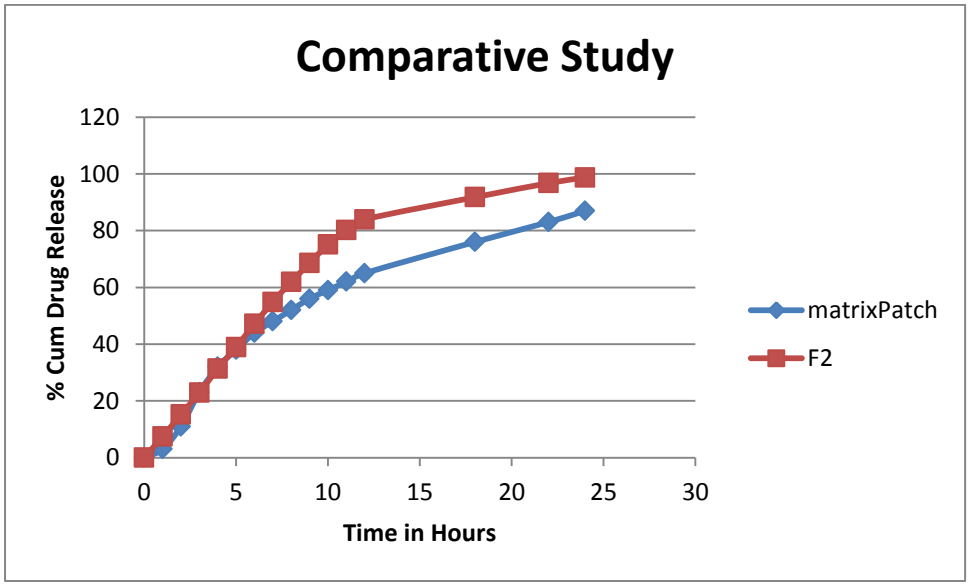


Graph No: 28*In-Vitro* Drug Release of F_1-F_6

In-vitro percentage drug release studies were performed to the release of the drug from different sixproniosomal gel converted to transdermal patches formulations. Most of the formulations were found to have linear release and the formulations were found to provide approximately 90% (F_2, F_3) release within a period of 24 hours. The formulations which have higher concentration of cholesterol level were found to the sustained release but percentage drug release was decreased.

In-vitro skin permeation studies were found to the six different proniosomal gel transdermal patches exhibits the greatest amount of drug permeation were followed 39.325µg/cm^2,36.548µg/cm^2 (F_2,F_3) at the end of 24 hours.

Comparative Study for Glipizide Matrix Patch and Formulation F_2



Graph No: 29 Comparative Studies of Matrix Patch

The formulation F_2 was Show better percentage Cumilative drug release than compared to matrix patch of glipizide.

Pharmacokinetics drug release

Diffusion release exponent	**Overall solute diffusion mechanism**
0.5	Fickian Diffusion
0.5<n< 1.0	Anomalous (Non-Fickian) Diffusion
1.0	Case II transport
n>1.0	Super Case II transport

Table No: 25 Pharmacokinetics of Drug Release

F.No	Zero Order	Higuchi Order	KROSMEYER AND PEPPAS RELEASE MODEL	
	R^2	R^2	n	R^2
F1	0.948	0.968	0.980	0.973
F2	0.948	0.982	0.992	0.991
F3	0.979	0.974	0.984	0.983
F4	0.939	0.976	0.979	0.978
F5	0.940	0.978	0.987	0.965
F6	0.941	0.971	0.981	0.966

Table No: 26 Different Release order

The zero order plots showed the zero order release characteristics of the formulation, which was confirm by the correlation value. The release profile of F_1,F_2,F_3,F_4,F_5,F_6 could be best explained by Higuchi Model, as plots showed high linearity, with correlation coefficient (R^2) values 0.968,0.982,0.974,0.976,0.978,0.971respectively. From this result was diffusion mechanism was conformed. The diffusion mechanism of drug release was further confirmed by Korsmeyer-Peppas plots that showed fair linearity than compare to Higuchi diffusion(R^2 values between0.966 to 0.983).According to this correlation valueindicating the mechanism of drug release was diffusion.

***In-Vivo* Drug Release Study**

The *in-vivo* Drug release was optimized formulation (F_2) to produce sustained release and effectiveness than compare to standard drug.

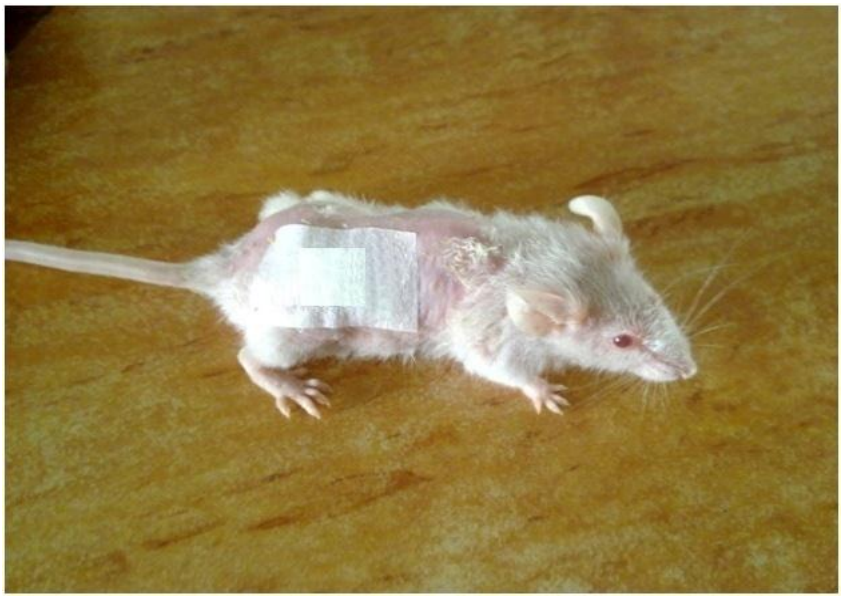
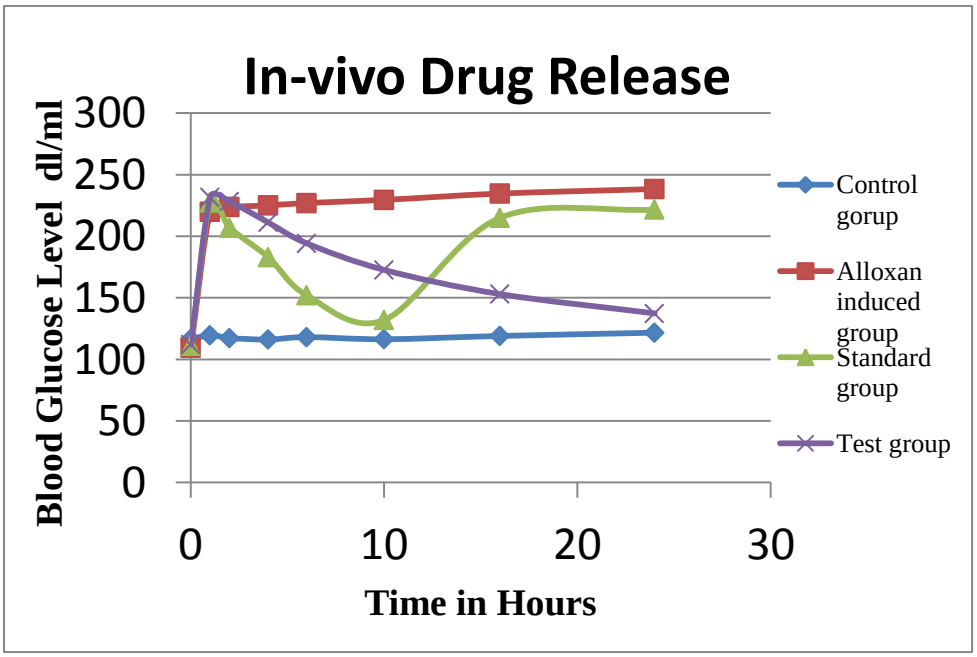


Fig No: 14 *In-vivo* Drug Release Study on Mice

Drug treatment	Initial	After Induction of Alloxan (0hrs)	2 hrs	4 hrs	6 hrs	10 hrs	16 hrs	24 hrs
Control Goup	116.33±2.33	119.66±2.02	117.33±2.4	116.1±1.05	118.1±1.48	116.33±1.28	119.0±2.02	121.66±1.52
Alloxan Induced Group	109.33±1.76	219.8±1.88	223.66±1.1	225±2.47	227.0±1.18	229.5±1.72	234.66±1.84	238.33±1.37
Test (Alloxan+ Test Patch)	112±1.24	231.66±1.55	228.2±1.82	211.2±1.46	194.2±1.89 *	172.66±2.27**	153.11±0.46	132.33±2.42**
Standard Drug (oral administration)	111±1.24	227.33±2.36	207.9±1.14	183.5±1.51 *	137.5±1.51 **	217.33±2.52	215±2.27	221.66±2.27

Data represents mean ± SEM. (n=3); *p<0.05; **p<0.01

Table No : 27 *In-vivo* Drug Release Study



Graph No: 30*In vivo* Drug Release of F_2

Skin Irritation Study

Formulation	Visual observation	
	Erythema	Edema
Normal	0.00±0.00	0.00±0.00
Test Patch	1.16±0.16	1.33±0.40
Formalin (0.8% v/v)	3.64±0.33	3.48±0.22

Table No: 30 Skin Irritation Study

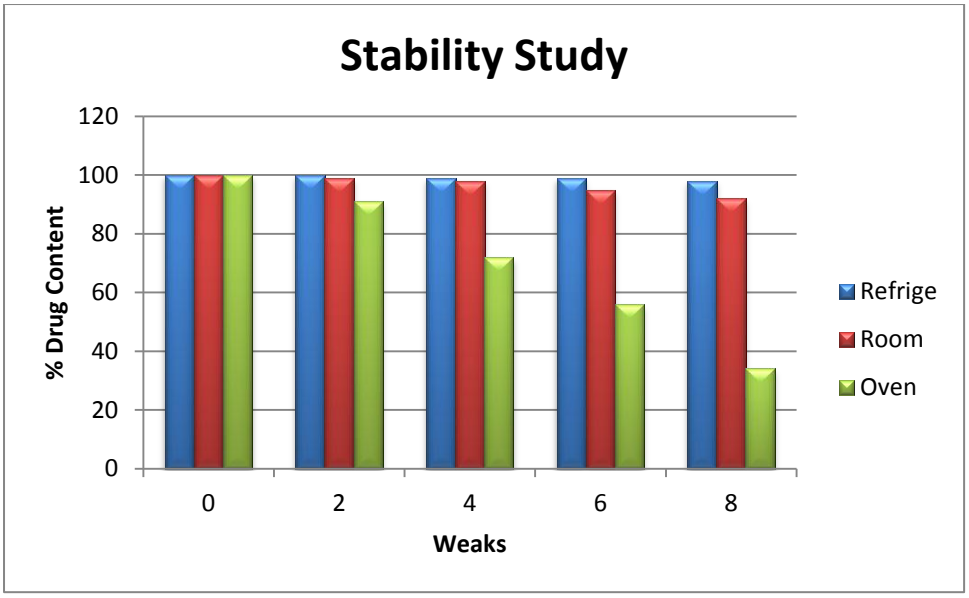
The standard irritant, formalin produced severe erythema and edema. Formalin produced high grade of irritation, indicated by `severe' inflammation and edema besides showing discontinuity in epidermis, thin epidermis, ulceration and hyperplasia. Then compare to formalin the test patch was produce less erythema and edema.

Stability Analysis

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

Weeks	**0**	**2**	**4**	**6**	**8**
Refrigerator Tempt (4-8^{o}C)	100%	100%	99%	99%	98%
Room Tempt (25±2^{o}C)	100%	99%	98%	95%	92%
Oven Tempt (45±2^{o}C)	100%	91%	72%	56%	34%

Table No: 28 Stability Study of F_2



Graph N0: 31 Stability Study of F_2

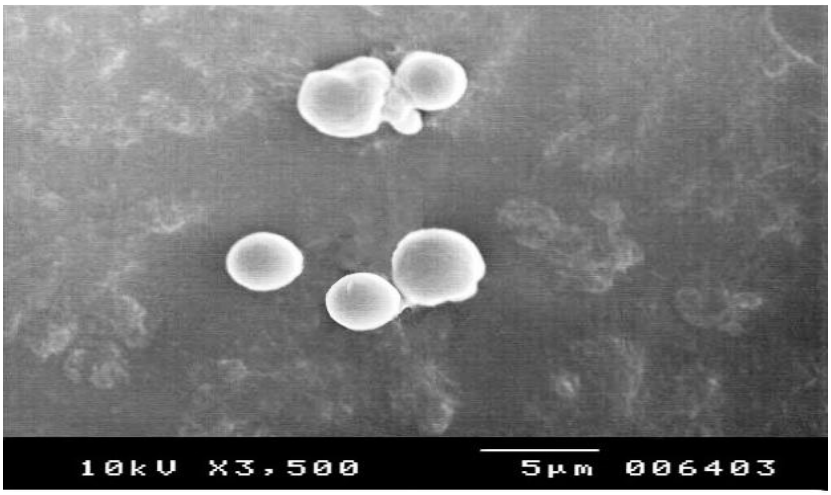


Fig No :15Sem Image of F_2 after two months

The percentage drug retained at evaluated temperature (45^{o}C) 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 (F_2) before 2 months Fig No: 14. Therefore the proniosomal gels were stored in room or refrigeration temperature.

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 thermogram.

The morphology of prepared Proniosomal gel was observed under SEM. It was produce 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 F_7,F_8,F_9,F_{10} cannot be applied to the transdermal patches. So it can be avoid for the further steps.

Remaining formulation F_1,F_2,F_3,F_4,F_5,F_6 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 F_2 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 0.968 to 0.989 which revealed that the mechanism of drug release and further more Korsmeyer-Peppas correlation values ranges from 0.965 to 0.991also confirmed the diffusion mechanism.

The *In-vivo* efficiency tests with compared standard drug (glipizide) to give oral administration and optimized formulation Proniosomal gel converted to transdermal patch formulation (F_2) was performed swiss albino mice by measuring the hypoglycemic effect. Result showed that formulation F_2 had good effectiveness then standard drug solution and also to produce extended hypoglycemic effect may be due to sustained release of

glipizide from Proniosomal gel transdermal patch. In Skin irritation Study, test patches were produce less erythema, edema and negligible side effects.

Based on the entrapment efficiency, Release study, kinetic models and drug content formulation F_2 was subjected for stability studies carried out various storage conditions. The percentage of drug content after a period of two months for 2-8^oC, 25$^oC\pm$ 0.5^oC and 45^oC 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 exicipients and stability of drug during the method of preparations.
- The formulation F_2 which shows higher entrapment efficiency was 92.75%. In-vitro release study of F_2 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 exicipients.
- 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 diabetic patients.

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