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Niosomal Drug Delivery for OralRoute

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Abstract: ***Niosomes are artificial vesicles with potential technological advantages. They are non-ionic surfactant vesicles. As efficient drug delivery systems with a wide range of uses, niosomes have the same potential benefits as phospholipid vesicles (liposomes), including the capacity to hold both water- and lipid-soluble pharmaceutical molecules. Niosomes can also be thought of as more cost-effective, chemically stable, and occasionally physically stable alternatives to liposomes. Simple preparation techniques and commonly used surfactants in pharmaceutical technology can be employed to create niosomes. Numerous studies have covered noisome physicochemical characteristics and their uses as drug delivery vehicles. In this report, a brief and simplified summary of different theories of self-assembly are discussed. Furthermore, manufacturing methods, physical characterization techniques, bilayer membrane additives, unconventional niosomes (discomes, proniosomes, elastic and polyhedral niosomes), their recent applications as drug delivery systems, limitations and directions for future research will be discussed.***

Keywords: Niosomes, Zeta Potential, Proniosome, Bola surfactant, P-glycoprotein, Aspasomes

I. INTRODUCTION

Niosomes are non ionic surfactant vesicles which can entrap both hydrophilic and lipophilic drugs, either in aqueous layer or in vesicular membrane made of lipid materials. Niosomesare either unilamellar or multilamellar vesicles that have a better stability than liposomes. Niosomes are formed on admixture of nonionic surfactant, cholesterol with subsequent hydration in aqueous medium. The addition of cholesterol, gives the rigidity to the bilayer which results in less leaky niosomes. Niosome behave invivo like liposomes prolonging the circulation ofentrapped drug.{1}

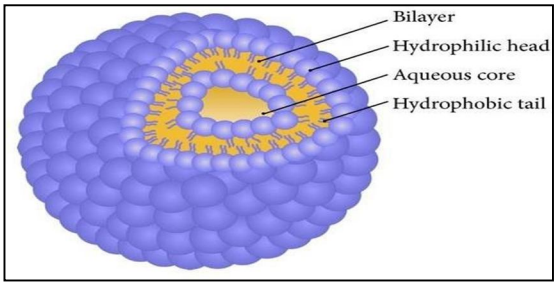
Niosomes offer a versatile vesicle delivery concept with potential for delivering drug via transdermal route. Topically applied niosomes can increase residence time of drug in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. It also improves the horny layer properties both by reducing transepidermal water loss and by increasing smoothness via replenishing lost skin lipids.{2}

Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he investigate a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, & niosomes.{3,4,5}

A. Defination of Niosome

Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionicsurfactants, with or withoutincorporation of cholesterol or other lipids. The sizes of niosomesare microscopic and lie in nanometric scale. Theparticle size ranges from 10nm-100nm.{2}

B. Structure of Niosome



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Structurally, niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes. Most surface active agents when immersed in water yield micellar structures however some surfactants can yield bilayervesicles which are niosomes. Niosomes may be unilamellar or multilamellar depending onthe method used to prepare them. The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while the hydrophobic chains face each other within the bilayer. Hence, the vesicle holds hydrophilic drugs within the space enclosed in the vesicle, while hydrophobic drugs are embedded within the bilayer itself.{7}

The properties of the vesicles can be changed by varying the composition of the vesicles, size, lamellarity,tapped volume, surface charge and concentration. Various forces act inside the vesicle like Vander Waals forces among surfactant molecules, repulsive forces emerging from the electrostatic interactions among charged groups of surfactant molecules, entropic repulsive forces of the head groups of surfactants, short-acting repulsive forces etc. These forces are responsible for maintaining the vesicular structure of niosomes. But, the stability ofniosomes are affected by type of surfactant, nature of encapsulated drug, storage temperature,detergents, use of membrane lipids, the interfacial polymerization of surfactant monomers in situ, inclusion of charged molecule. The geometry of vesicle to be formed from surfactants is affected by its structure, which is related to critical packing parameters. On the basis of critical packing parameters of surfactants, we can predicate geometry of vesicle to be formed.Critical packing parameters can be defined using following equation, CPP (Critical Packing Parameters) v/lc xa0

Where v hydrophobic group volume, le= the critical hydrophobic group length, a0 the area ofhydrophilic head group. From the critical packing parameter value type of miceller structure formed can be ascertained as given, If CPP < ½, then formation of spherical micelles, If ½ < CPP<1, then formation of bilayer micelles, If CPP> 1, thenformation inverted micelles.{3,14}

C. Advantages of Niosomes

1) They are osmotically active and stable.
2) They increase the stability of the entrapped drug
3) Handling and storage of surfactants do not require any special conditions
4) They increasethe oral bioavailability of drugs
5) They enhance the skin penetration of drugs
6) They be used for oral, parenteral as well topical route.
7) The surfactants are biodegradable, biocompatible, and non-immunogenic.
8) Improve the therapeutic performance of the drug by protecting it from the biologicalenvironment andrestricting effects to target cells, thereby reducing the clearance ofthe drug
9) The niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase tocontrol the releaserate of the drug and administer normal vesicles in external non-aqueous phase

D. Disadvantages Of Niosomes

1) Physical instability
2) Aggregation
3) Fusion
4) Leaking of entrapped drug
5) Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion {1}

In niosomes the surface charge determines the behaviour of niosomes in vivo and in vitro uncharged vesicles sometimes caused aggregation and fusion. Vesicle aggregation of niosomes may be prevented by the inclusion ofcompounds that introduce repulsive steric or electrostatic forces. An example of steric stabilization is the inclusion of Solulan C24 (a cholesteryl poly-24- oxyethylene ether) noisome formulations. Examples of electrostatic stabilization are the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein loaded Span 60based niosomes.[46]

HLB value in the range 14-17 is not suitable to produce niosomes so cholesterol must be added to the surfactantin order to form a bilayered vesicle and for lower HLB values,cholesterol enhances stability of vesicles. It is alsoseen that the addition of cholesterol enables more hydrophobic surfactants to form vesicles, suppresses the tendency of the surfactant to form aggregate

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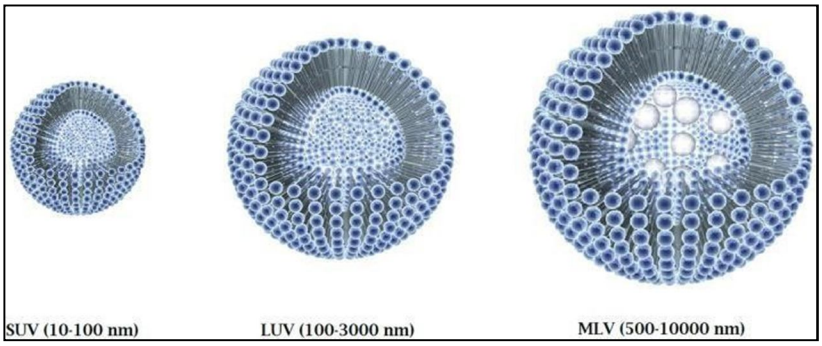
II. COMPOSITIONS OF NIOSOMES

The major components used for the preparation of niosomes are, Nonionic surfactants
The role of surfactants play a major role in the formation of niosomes. The following non-ionic surfactantsare generally used for the preparation of niosomes.
E.g
Spans (span 60, 40, 20, 85, 80)
Tweens (tween 20, 40, 60, 80) and
Brijs (brij 30, 35, 52, 58, 72, 76).
The non ionic surfactants possess a hydrophilic head and a hydrophobic tail.HLB value in therange 14-17 is not suitable to pruduce niosomes so cholesterol must be added to the surfactant in order to form a bilayered vesicle.{1}
Ether linked surfactants These are polyoxyethylene alkyl ethers which have hydrophilic and hydrophobic moieties arelinked with ether. The general formula of this group is (CnEOm), where n can be 12-18 andm can be 3-7. Surfactants with polyhydroxyl head and ethylene oxide units are also reported to be used in niosomes formation. Single alkyl chainsurfactant C16 mono alkyl glycerol ether with an average of three glycerol units is one of the examples of this class of surfactantsused for the preparation of niosomes. Polyoxyethelene 4 lauryl ether (Brij30) has an HLB value of 9.7, phase transition temperature <10°C cannot be used to formulate some drugs and iodides mercury salts, phenolic substances, salicylates, sulfonamides and tannins as it cause ethers (Brij58) and Polyoxyethylene stearyl ethers (Brij72and76) are also used in preparation of niosomes{9}

A. Types Of Niosomes

The niosomes are classified as a function of the number ofbilayer (e.g. MLV, SUV) or as a function of size. (e.g.LUV, SUV) or as a function of the method of preparation (e.g.REV, DRV). The various types of niosomes are described below:

1) Multilamellar Vesicles (MLV)



It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size ofthese vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used niosomes. It is simple to make and are mechanically stable upon storage for long periods. These vesicles are highly suited as drug carrier for lipophilic compounds.thin film hydration method and transmembrane ph gradient method was used for the preparation of multilamellar vesicles.{5,7}

2) Large Unilamellar Vesicles (LUV)

Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materialscan be entrapped with a very economical use of membrane lipids the sizeof large unilamellar vesicles is more than100 nm, Ether injection method and reverse phase evaporation method was used for the preparation of large unilamellar vesicles. {5,7}

3) Small Unilamellar Vesicles (SUV)

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French pressextrusion.the size of small unilamellar vesicles is upto 100 nm i.e 20-50 nm{7

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B. Factors Affecting Niosomes Formulation

1) Drug

Entrapment of drug in niosomes increases vesicle size, probably by interaction of solute with surfactant head groups. In polyoxyethylene glycol (PEG) coated vesicles; some drug isentrapped in the long PEG chains, thus reducing the tendency to increase the size. The hydrophilic lipophilic balance of the drug affects degree of entrapment. The physicochemical properties of encapsulated drug affect charge and rigidity of the niosome bilayer. Here drug interacts with surfactant head group and develops the charge which creates mutual repulsion between surfactant bilayer and hence increase vesicle size [1,14] Another factor to be considered is whether the drug to be encapsulated is amphiphilic. The best example of such a drug is doxorubicin. When encapsulated in niosomes,aggregation occurred and was overcome by the addition of asteric stabilizer. The increase in encapsulation of a drug that occurs when more is added could be the result of saturation of the medium. This suggests that thesolubility of certain poorly soluble drugs can be increased by formulation in niosomes but only upto acertain limit above which drug precipitation will occur. An increase in the encapsulation of flurbiprofen dueto saturation of drug in the hydration medium has been reported. However, when niosomes were prepared using higher amount sof minoxidil,optica Imicro-scopy revealed minoxidil crystals dispersed in between the niosomal particles{11}

2) Amount and Type of Surfactant

The mean size of niosomes increases proportionally with increase in the HLB surfactants likeSpan 85 (HLB 1.8)to Span 20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant.The bilayers of the vesicles are either in the so- called liquid state or in gel state, depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol. In the gel state, alkyl chains are present in a well ordered structure, and in the liquid state, the structure of the bilayers is moredisordered. The surfactants and lipids are characterized by the gel-liquid phase transition temperature (TC). Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60having higher TC, provides better entrapment. HLB value of surfactants affects entrapment efficiency, such as HLB value of 14 to 17 is not suitable for niosomes but HLB value of 8.6 has highest entrapment efficiency and entrapment efficiency decreases with decrease in HLB value from 8.6 to 1.7 [1.4] The maximum amount of surfactant/lipid used to prepare niosomes is generally 10-30mmol/L (1-2.5%, w/w). Alterations in the surfactant:water ratio during the hydration step may affect the structure andproperties of the niosomes produced. As the surfactant/lipid level increases, the amount of drug to been capsulated also increases leading to an increasein the viscosity of the system.{11}

3) Cholesterol Content and Charge

Inclusion of cholesterol in niosomes increased its hydrodynamic diameter and entrapment. In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other, cholesterol decreases the chain order of gel state bilayers. At a high cholesterol concentration, the gel stateis transformed to a liquid- ordered phase. An increase in cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material and therefore an increase of the rigidity of the bilayers obtained. Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.{1}

4) Resistance to Osmotic Stress

Addition of a hypertonic salt solution to a suspension of niosomes brings about reduction in diameter. In hypotonicsalt solution, there is initial slow release with slight swelling of vesicles probablys due to inhibition of eluting fluid from vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress.{1}

5) Effect of Additives

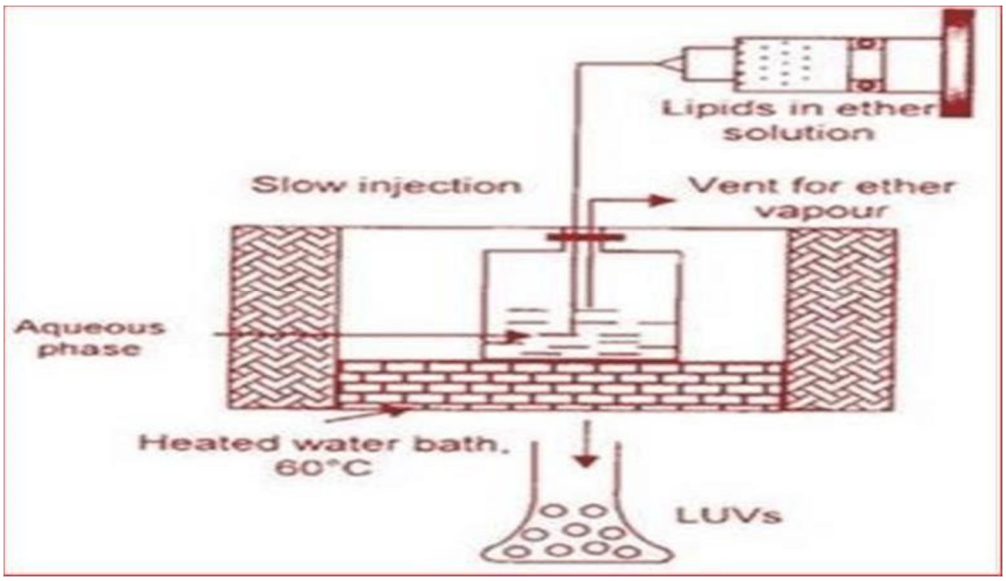
The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. Niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristicsby different additives. In case of polyhedral niosomes formed from C16G2, the shape of these polyhedral noisome remains unaffected by adding low amount of solulan C24 (cholesterol poly-24- oxyethylene ether), which prevents aggregation due to development of stearic hydrance. In contrast spherical Niosomes are formed by C16G2: cholesterol: solution (49:49:2). The mean size of niosomes is influenced by membrane composition such as Polyhedral niosomes formed by C16G2: solution C24 in ration (91:9) having bigger size (8.0+0.03 mm) than spherical/tubular niosomes formed by C16G2: cholesterol: solution C24 in ratio (49:49:2) (6.6+0.2 mm). Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and reduces

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III. METHOD OF PREPARATION

A. Ether Injection Method

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000 nm. {3,4,15}

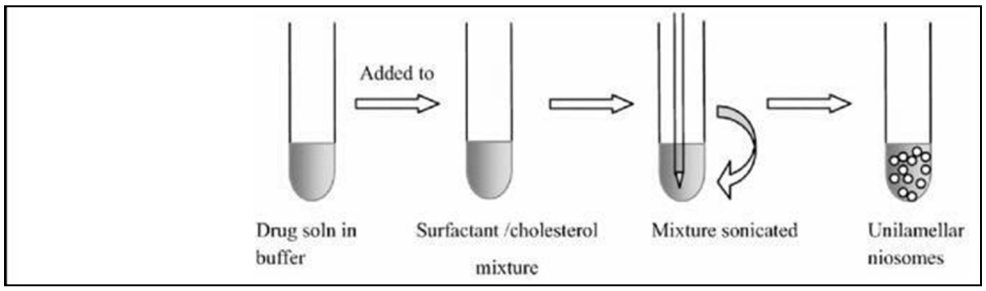


B. Hand Shaking Method (Thin Film Hydration Technique)

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thinlayer of solid mixture deposited on the wall of the flask.The dried surfactant film can be rehydrated with aqueous phase at 0- 60°C with gentle agitation. This process forms typical multilamellar niosomes. Thermosensitive niosomes were prepared by evaporating the organic solvent at 60°C and leaving a thin film of lipid on the wall of rotary flash evaporator. The aqueous phase containingdrug was added slowly with intermittet shaking of flask at room temperature followed by sonication.{3,4,15}

C. Sonication

In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glassvial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.{3,4,}



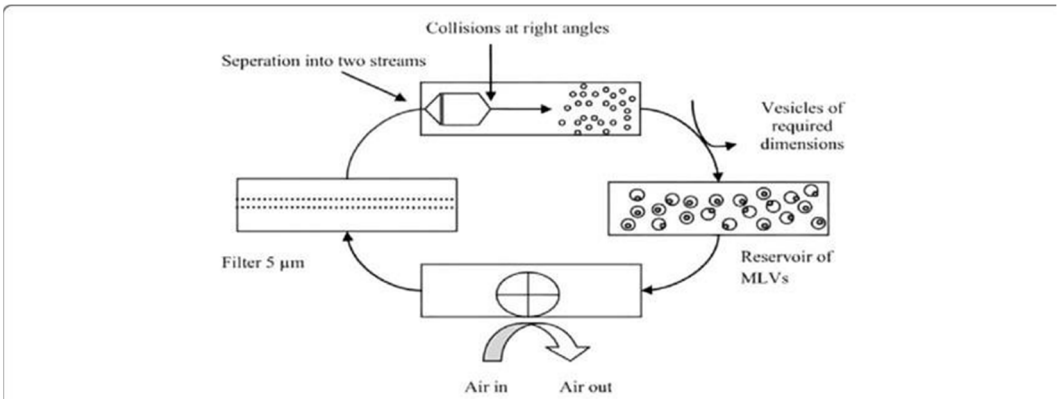
D. Micro fluidization

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The resultis a greater uniformity, smaller size and better reproducibility of niosomes formed.{3,4,}

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E. Multiple Membrane Extrusion Method

Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate membranes, which are placed in series for upto 8 passages. Itis a good method for controlling niosome size.{3,4



F. Reverse Phase Evaporation Technique (REV)

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containingdrug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicatedafter the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes. have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

G. Trans Membrane pH Gradient (inside acidic) Drug Uptake Process (remote Loading)

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydratedwith 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen andthawed 3 times and latersonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with IM disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes.{3,4,}

H. The "Bubble" Method

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supplythrough the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.{3,4,}

I. Formation of Niosomes from Proniosomes

Another method of producing niosomes is to coat a watersoluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-solubleparticle is covered with a thin film of drysurfactant. This preparation is termed "Proniosomes". The niosomes are recognized by the addition of aqueous phase at T > Tm andbrief agitation.{3,4,}

T=Temperature

Tm= mean phase transition temperature

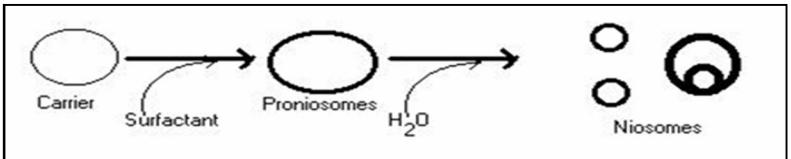


Figure 2: Formation of Niosomes from Proniosomes

IV. EVALUATION OF NIOSOMES

Sr.No	Evaluation Parameter	Method
1.	Morphology	SEM,TEM,Freeze fracture technique
2.	Size distribution	Dynamic light scattering particle,opticalmicroscopy
3.	Polydispersity index	Size analyzer
4.	Viscosity	Ostwald viscometer, brokfield viscometer
5.	Drug analysis	Uv diode array spectrophotometer,IR
6.	Entrapment efficiency	Centrifugation,dialysis,gel chromatography
7.	In-vitro release study	Dialysis membranes
8.	Permeation study	Franz diffusion cell
9.	Thermal analysis	DSC
10	Membrane thickness	x-ray scattering analysis

V. EXPERIMENTAL WORK

Pre-Formulation StudiesDrug Characterization

A. Glimepiride Drug Authentication

Preformulation studies were performed to determine the physiochemical properties of thedrug that affectthe development and efficacy of new drug formulation.

1) *Descriptions:* The sample of the drug was visually observed for color, odor, and appearance.
2) *Melting Point Determination:* The melting point of Glimepiride was determined by Thiele's tube method i.e., by taking a small amount of the drug in one end closed capillary tube placed in the melting point apparatus and taking the temperature at which, the drug melts was noted. The average of triplicate readings was noted and compared with standard values.
3) *Solubility Study:* The solubility of the drug was determined by adding an excess amount of the drug in 10 ml ofdistilled water in glass tubes sealed with aluminum foil. Resultant suspension shaking for 48 hr. on the mechanical shaker and filtered. The filtrate obtained was diluted with distilledwater and analyzed spectrophotometrically using a UV- spectrometer.

B. Spectroscopic Studies

1) *UV Spectroscopic*

a) *Preparation of Standard stock Solution:* Accurately weigh 10 mg of glimepiride dissolved in ethanol to make 50ml (100 up/ml. (stocksolution A) 1 ml ofsolutions separately diluted with methanol up to 10 ml to obtain the concentration of 10 up/ml (stock solution) and scanned in the wavelength range of 200-400 nm.

2) *Selection of Analytical Wavelength*

From the standard stock solution 'B', various dilution ranging between 2-10 up/ml was prepared and scanned in the wavelength range 400-200 nm using a UV spectrometer.

3) *Preparation of Calibration Curve for Glimepiride in Ethanol*

By using the standard stock solution, the concentration ranges from 2,4,6,8, and 10 up/ml. The absorption of theabove solution was measured at 301 nm and a calibration curve of absorbance against concentration was plotted.

4) *Fourier Transform Infrared Spectroscopy (FTIR)*

One of the most important advantages of IR over the usual methods of structural analysis is that it provides usefulinformation about the structure of the molecule quickly, withouttiresome evaluation methods. The technique is based on the fact that a chemical substance shows marked selective absorption in the IR region. The FT-IR spectrum of chlorpromazine HCl was recorded to confirm its purity on the FTIR spectrophotometer using the KBr powderpress technique. The baseline correction was done using dried potassium bromide. The instrument was operated under a dry air purge with a resolution of cm-1 over the region 4000-400 cm-1. The scans were evaluatedfor the presence of principal peaks of the drug. Theidentified peaks were compared with the principal peaks of thereported IR spectrum. The FTIR spectra of Glimepiride are depicted in FIG and observed peaks are reported in table.

C. Compatibility Studies of Drug and Excipients

1) Fourier Transform Infrared Spectroscopy (FTIR) Study: FTIR spectra of pure glimepiride and excipients were obtained on an FTIR spectrometer using KBr powder. The instrument was operated under dry air purge and the scans were collected at the scanning speed of 2mm/sec with a resolution of 4 cm-1 over the region of 4000-400 cm-1. The scans were evaluated for the presence of principal peaks of the drug, shifting and disappearance of drug peaks, and appearance of the new peak due to conformer interaction. The result is reported in Fig.

VI. PREPARATION OF NIOSOMES

Niosomes loaded with glimepiride were formulated by ether injection method based on 32 factorial design . 3^2 Factorial design is a three-level and two factorsbased factorial design as reported by Webb . In total, there are nineruns or combinations. In designing niosomes, cholesterol and span 60 were selected as two independent variables,both at three different levels (1, 0, +1). In the design, the lower concentration of cholesterol, i.e. 1.0%w/v, has been assigned at 1 level, whereas 2.0% w/v concentration was assigned the level 0. The concentration at highest level +1 was 3.0% w/v. In case of span 60, concentrations at three levels from lowest to highest (1, 0, +1) were 0.5, 1.0 and 3.0% w/v, respectively. Based on this factorial design, nine niosomal formulations were developed. Span 60, cholesterol and drug were dissolved in a mixture of diethyl ether and methanol as per the composition given in and was stirred continuously on a magnetic stirrer . Distilled water was heated to 55 ± 1C. Organic phase was then injected into an aqueous phase.

A. Purification of drug-loaded niosomes

Drug-loaded niosomes were purified by dialysis membrane technique to remove the free drug from niosomal suspension. For this, Hi-media dialysis membrane was kept in saline solution for 2 h before dialysis to ensure complete wetting of the membrane. Niosomal vesicles loaded with glimepiride were placed in a dialysis bag, which was transferred into 200 ml of phosphate buffer pH 7.4. The receiver medium was stirred with a magneticstirrerat 500 rpm. Five millilitres of sample was withdrawn at appropriate time intervals and replaced with an equal volume of fresh media and analyzed spectrophotometerically for the amount of free drug. Purification timewas optimized by applying statistical paired t test at5% level of significance.

Table 1 3^2 Factorial design of niosomal formulations of glimepiride

FORMULATION	DRUG (mg)	CHOLESTROL (mg)	SPAN60 (mg)	DIETHYL ETHER (ml)	METHANOL (ml)
F1	10	10	5	5	5
F2	10	10	10	5	5
F3	10	10	15	5	5
F4	10	20	5	5	5
F5	10	20	10	5	5
F6	10	20	15	5	5
F7	10	30	5	5	5
F8	10	30	10	5	5
F9	10	30	15	5	5

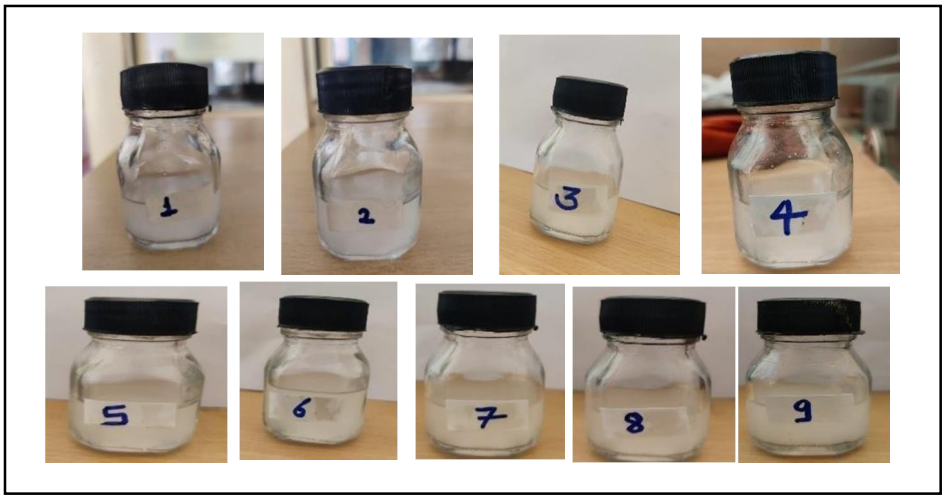


Fig 1 Formulation Of Niosomes

VII. RESULT AND DISCUSSION

A. Pre-Formulation Studies

1) Drug Characterization

a) Organoleptic Properties

The drug was studied for its organoleptic properties like color, odor, taste, and crystallinity observation was recorded in table

Table no. 1 Organoleptic properties of Glimepride

Parameters	Result
Color	White
Odor	Odorless
Appearance	Crystalline powder

b) Melting Point

The melting point of the drug was determined by the capillary method and was found to be 207℃ . The observedvalue was found to be between the reported value range i.e., 200 ℃ to 230℃. The observed melting point confirmed the drug as Glimepride.

Table no.2 Melting point of Glimepride

Drug	Observed	Reference
Glimepride	207 ℃	205 ℃ -210 ℃
Glimepride	210 ℃	
Glimeprid	207 ℃	

c) Solubility Analysis

The solubility of Chlorpromazine HCl in various mediums was studied and the results of the study were shown inTable

Table no.3 Solubility Determination in Solvents

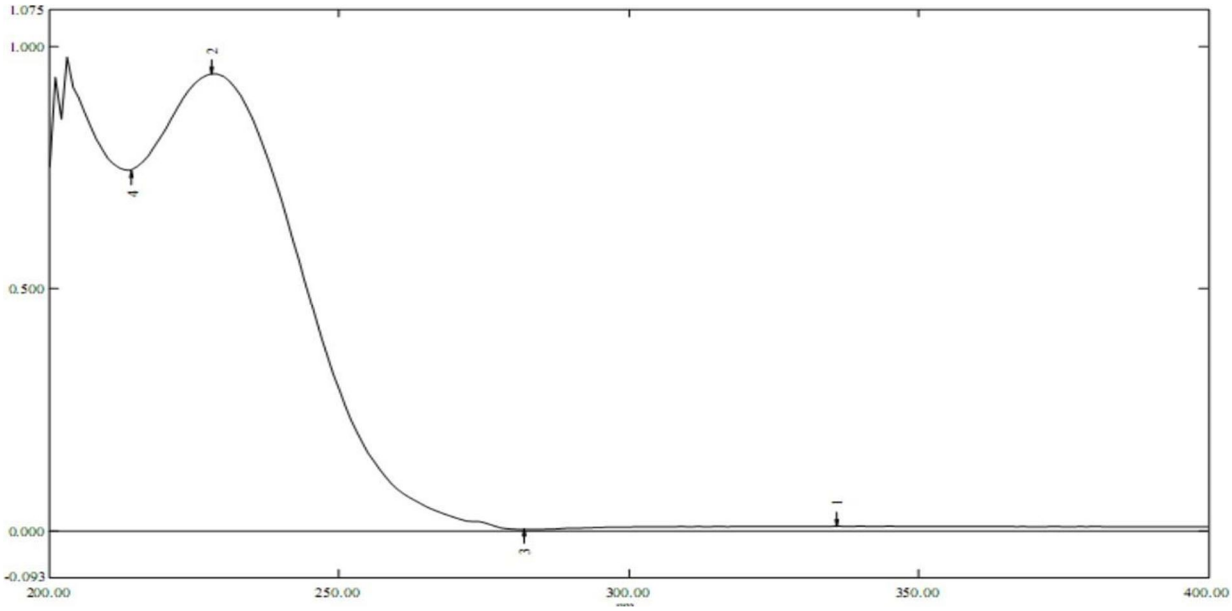
Solvents	**Solubility**
Water	Insoluble
Methanol	Soluble
Ethanol	Soluble
Cloroform	Soluble

2) Determination of λmax by UV

Identification of the drug was also carried out using UV Visible Spectrophotometer. Ethanol was used as the medium and observed absorption maxima were compared with the reported value. The wavelength of maximum absorbance acts as a characteristic value for a compound. The observed value for the obtained sample of pure Glimepride was 301.5nm found to be identical to the reported value that confirmed the obtained sample as Glimepride.

Media λ	λ max Observed
Ethanol	237nm

It shows λmax of Glimepiride

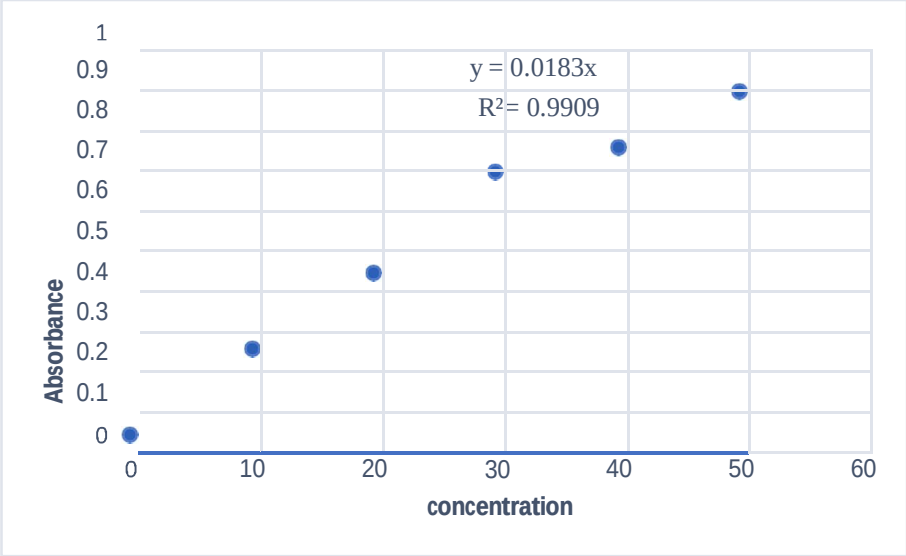


3) Calibration curve of Glimepiride

The wavelength of maximum absorbance, λ max for Glimepiride in ethanol was determined with the help of a UV Visible Spectrophotometer. The prepared solution of concentration 40µg/ml was scanned in the range of 200-400nm. The λmax observed was 237.5nm. Observed absorption maxima, λmax 237nm was used for further analysis of absorption for concentrations ranging from 10to 50µg/ml. The linear plot was obtained and the concentration range of 10 to 50µg/ml and correlation coefficient (r2) value were found to be 0.9954. The results were plotted in Fig

Table no.8.4 Absorbance data of Glimepiride for preparation of calibration curve at 237 nm.

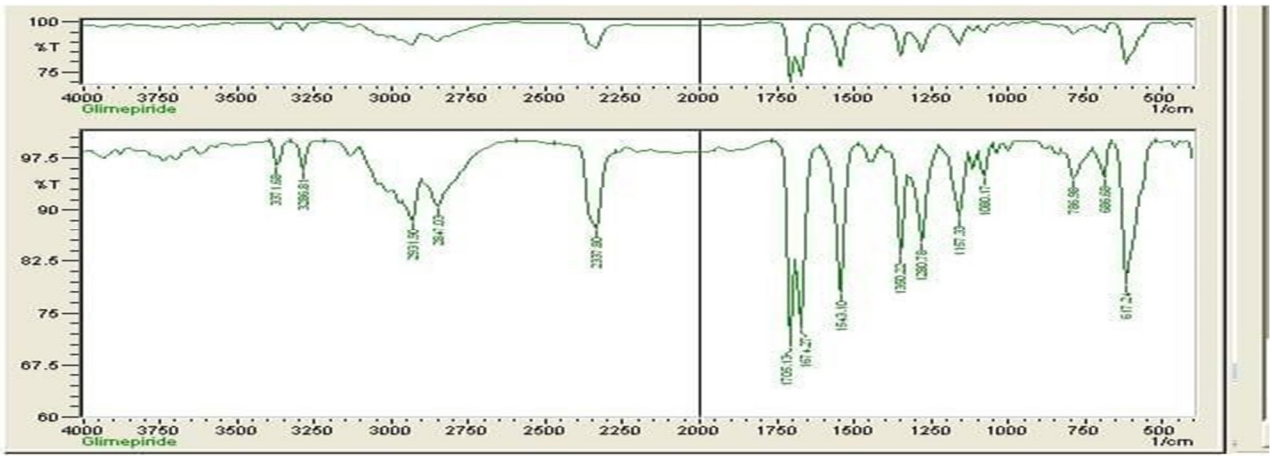
Sr.No	Concentration	Absorbance
1	10	0.21
2	20	0.43
3	30	0.65
4	40	0.71
5	50	0.85



4) FT-IR Spectroscopy

Calibration curve of Glimepiride

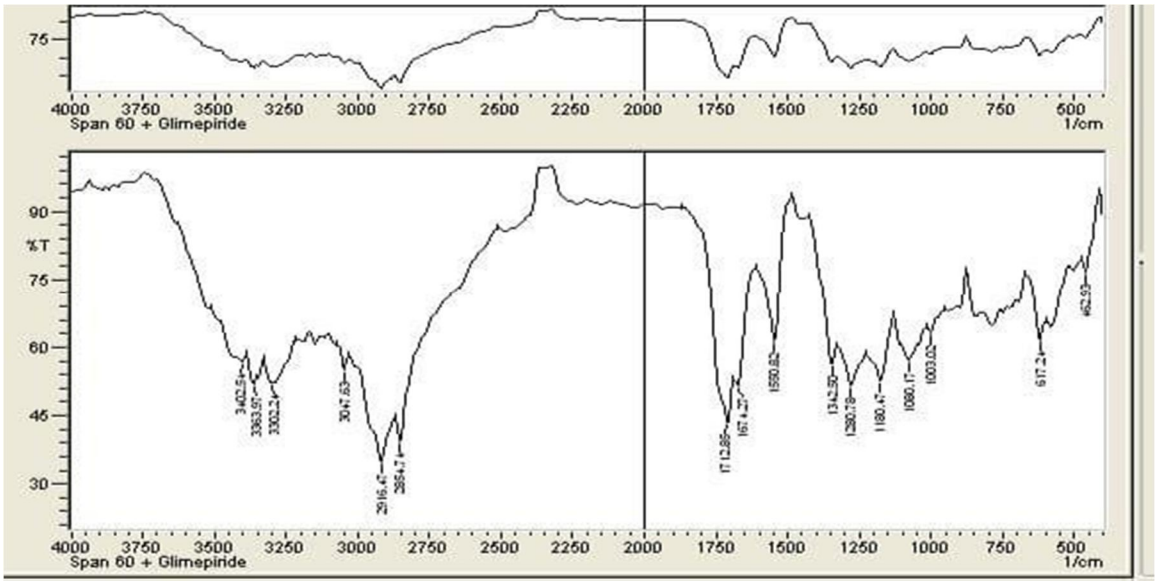
FTIR Spectrum of Glimepiride was obtained by scanning the drug in the 4000 to 400cm range. Observed FTIR spectra and standard values were as mentioned in Table The observed value was within the range or very close tothe characteristic peaks of the standard value confirming the drug is Glimepiride.



FTIR spectra of Glimepiride

SR.NO.	FUNCTIONAL GROUP	REPORTEDPEAK	OBSERVED PEAK
1	C-H alkanes	3000-2850	2931.90
2	C=O Keton	1725-1705	1705.13
3	C-N Amines	1350-1000	1280.76
4	C-X Chloride	785-540	696.68

5) Drug Excipients Compatibility Study

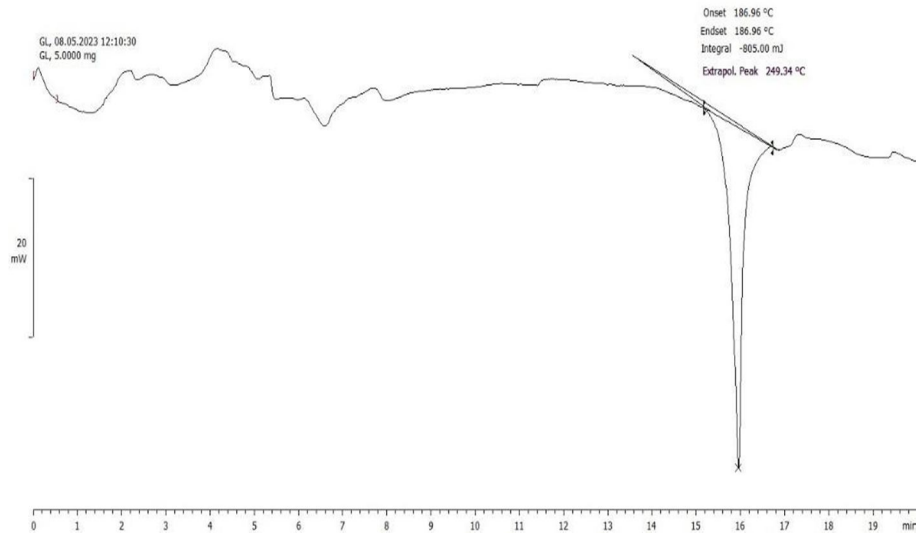


FTIR spectra of Glimepiride and span 60

With the help of FT-IR spectroscopy, the compatibility study of Glimepiride HCl and span 60was done. The observed peak of Glimepiride in peak in figure are retained in figure no chemical change and no reaction happenedbetween the Glimepiride and span 60.

6) Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) can be used to investigate and predict the changesin the crystalline form of the drug. Polymorphism is the capability of a substance to crystallize into two or more different crystalline forms. Any polymorphic changes in the drug may change its melting point, bioavailability, and release kinetics. The polymorphic change in the drug Glimepiride, was also studied using differential scanning calorimetry (DSC) by testing the melting characteristics of the drug.shows the DSC thermograms of Glimepiride l pure drug shows the DSC thermograms of Glimepiride Glimepiride showed a sharp characteristic endothermic peak at 237.53°C due to its phase transition.



DSC thermograms of Glimepiride pure drug

B. Preparation And Characterization Of Glimepiride Niosomes

1) Zeta Potential and Particle Size of the Glimepiride Noisomes

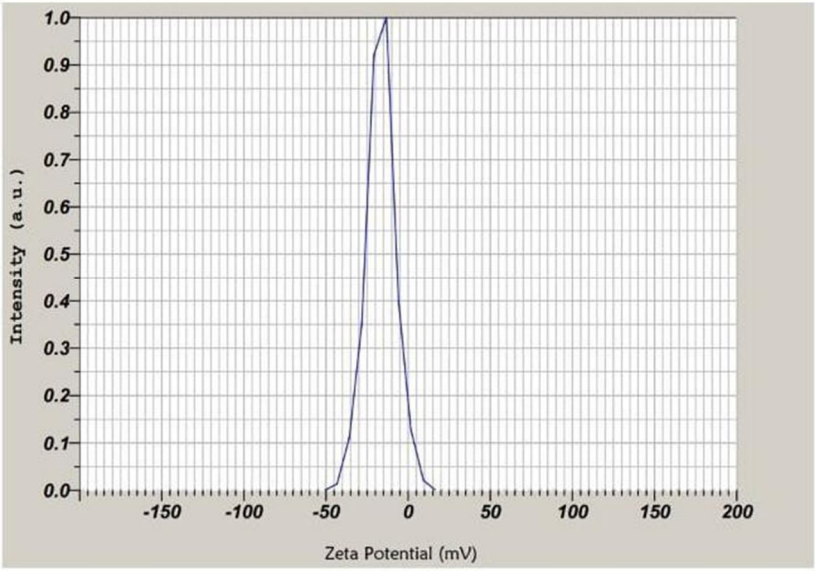
Niosomes formulations were evaluated for particle size, and zeta potential. It was observed that the niosomal vesicles of formulations (F1–F9) varied in size range of -9.9 mm to -16.6 mm. It was observed in niosomes that as the concentration of span 60 increased, vesicularsize of the particles also increased. Further it has also been evaluated that with enhanced concentration of cholesterol, vesicle size also increased. Availability of higher amount of raw materials probably led to the formation of larger-sized vesicles ., vesicle size was dependent primarily on the amount of cholesterol, as the concentration of cholesterol increases, the size of vesicles increased from formulation . where the authors reported an increase in niosomal vesicular size on increasing cholesterol concentration

Table no.5

FORMULATION CODE	Zeta Potential(mV)
F1	-9.9
F2	-10.5
F3	-11
F4	-11.9
F5	-12.1
F6	-12.8
F7	-13.4
F8	-15.3
F9	-16.6

Calculation Results

Peak No	S.P Aera Ration	Mean	S. D	Mode
1	1.00	421.1nm	95.8nm	382.3nm



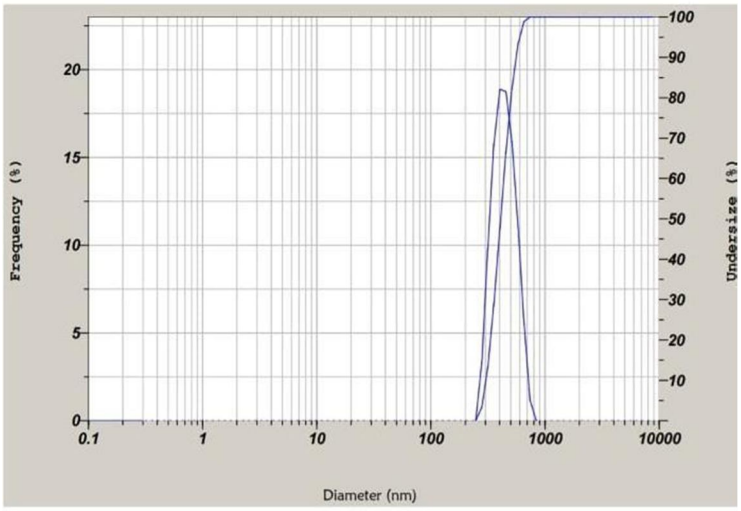
Optimized niosomes (F9) batch graph (Zeta Potential(nm))

2) Particle Size

Table no.6

FORMULATIONCODE	PARTICALSIZE (nm)
F1	298.1
F2	306.1
F3	320.4
F4	328.1
F5	336.6
F6	348.2
F7	352.8
F8	360.6
F9	372.9

Calculation Results



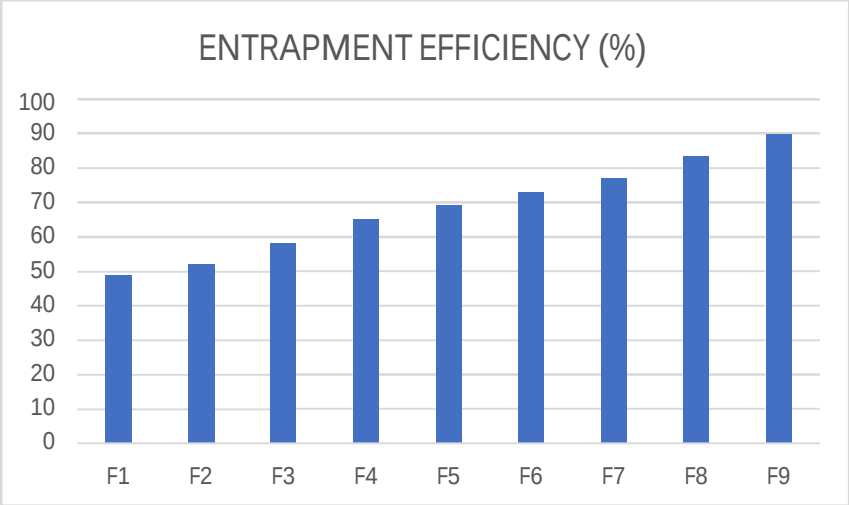
optimized niosomes (F9) batch graph (Particle size)

Peak No	S.P Aera Ration	Mean	S. D	Mode
1	1.00	421.1nm	95.8nm	382.3nm

3) . % Entrapment Efficiency

Among all the niosomal formulations, percent entrapment efficiency was found to be maximum in formulation F9 (90.04%), The presence of span 60 had a positive impact on percent drug entrapment of the vesicular carrier. The percentage entrapment efficiency was found to be increased by increasing concentration of cholesterol. At aratio of 1:1 of span 60:cholesterol, entrapment efficiency was found to be maximum.

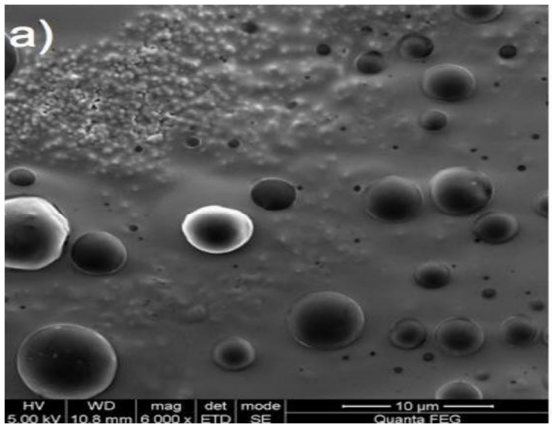
FORMULATION CODE	ENTRAPMENT EFFICIENCY (%)
F1	49.08
F2	52.11
F3	58.26
F4	65.24
F5	69.31
F6	73.08
F7	77.08
F8	83.44
F9	90.04

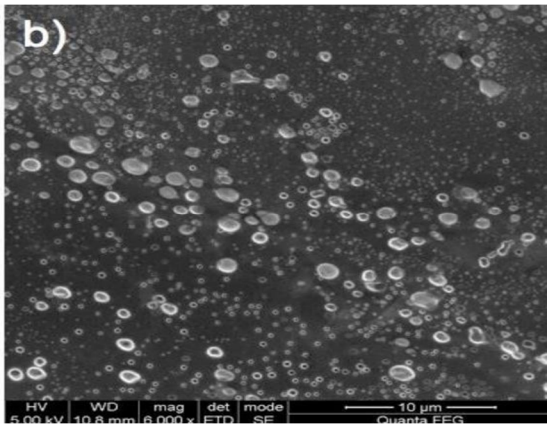


Entrapment Efficiency of Niosomes Formulation

4) Characterization of the Glimepiride Noisomes

Dynamic light scattering (DLS) was used to determine the particle size of the Glimepiride Noisomes. The mean particle size of the Glimepiride Noisomes was 372.2 nm suggesting thatthe system was homogenous with a narrowparticle size distribution. The mean zeta potential was −16.6 mV. The morphology of the Glimepiride Noisomes was studied by SEM . The Glimepiride Noisomes were generally spherical in shape with a mean diameter of around 108nm.





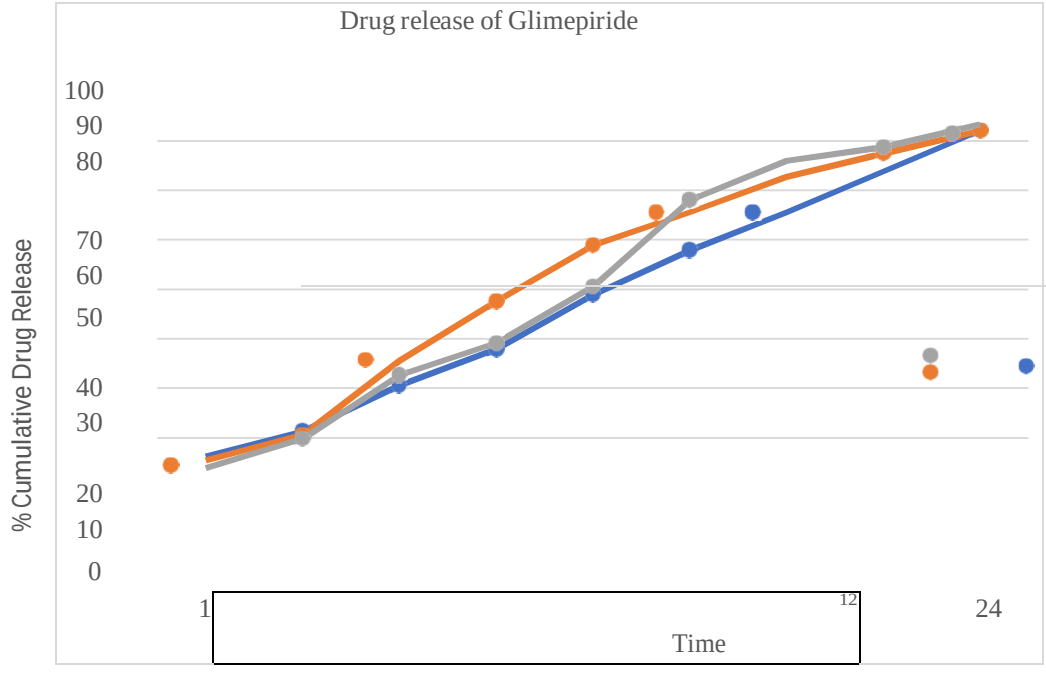
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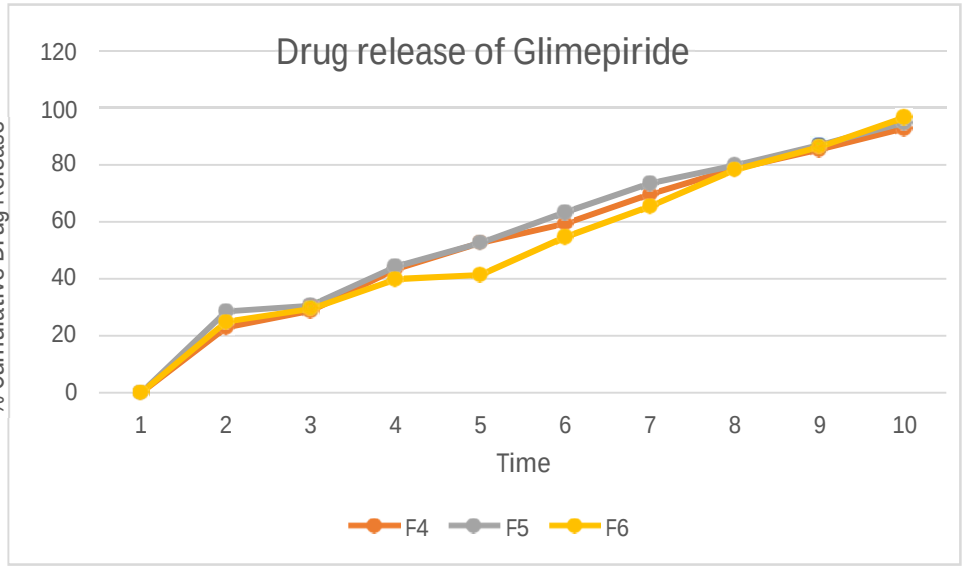
5) .E Drug release of Glimepiride Noisomes

Vitro release pattern of niosomes suspension was carried out by dialysis bag method . A dialysis sac was washed and soaked in distilled water. The vesicle suspension was pipetteinto a bag made up of tubing and sealed followed by placing the dialysis bag into a beaker containing 200 mL of PBS pH 7.4. The vessel was placed over magnetic stirrer (50 rpm) and the temperature was maintained at 37°C ± 0.5°C. Samples were withdrawn at predetermined time intervals and immediately replaced with the fresh medium to maintain the sink condition throughout experiment. Samples were diluted and analyzed for drug content by using UV/visible spectrophotometer at 265 nm.

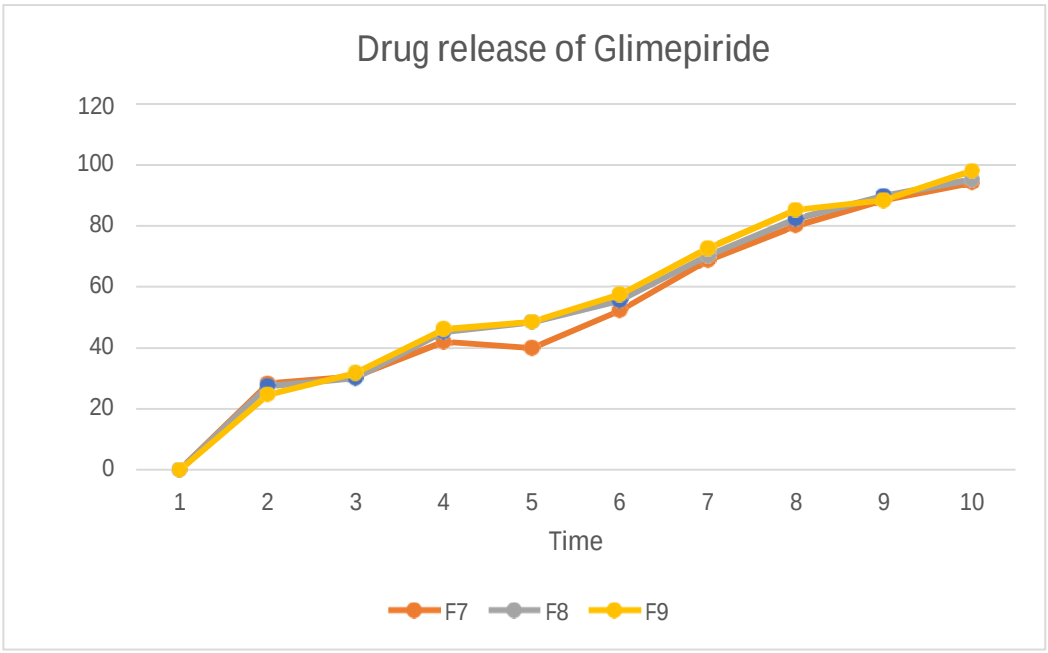
Table no In Vitro Release Profile Of Different Formulation F1- F9

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	26.2	25.4	23.8	22.9	28.4	24.87	28.24	27.45	24.61
2	31.2	30.5	29.8	28.7	30.6	29.45	30.67	30.1	31.75
3	40.5	45.5	42.6	43.2	44.16	39.79	42	45.26	46
4	47.9	57.6	49.1	52.6	52.6	41.22	40	48.44	48.44
6	58.9	68.8	60.5	59.21	63.2	54.6	52.1	55.46	57.49
8	67.8	75.5	78	69.5	73.3	65.4	68.7	70.27	72.59
10	75.5	82.7	85.91	78.5	79.6	78.2	80	82.2	85.12
12	83.8	87.4	88.72	85.2	86.8	86.2	88.4	89.78	88.29
24	92.1	92	93.37	92.68	94.64	96.4	94.1	95.23	98





Drug release profile of Glimepiride (F4to F6).



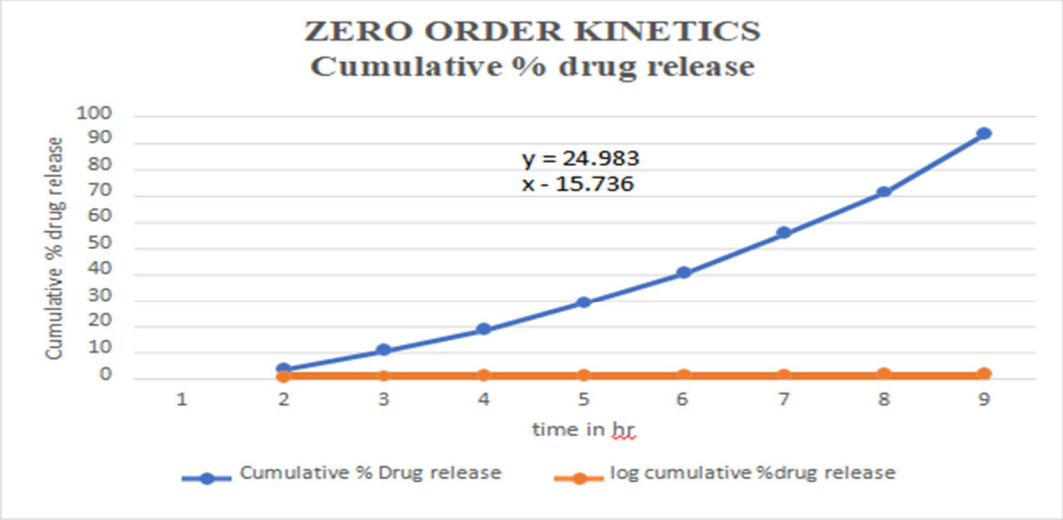
Drug release profile of Glimepiride (F7to F9).

6) Release Kinetics Modeling

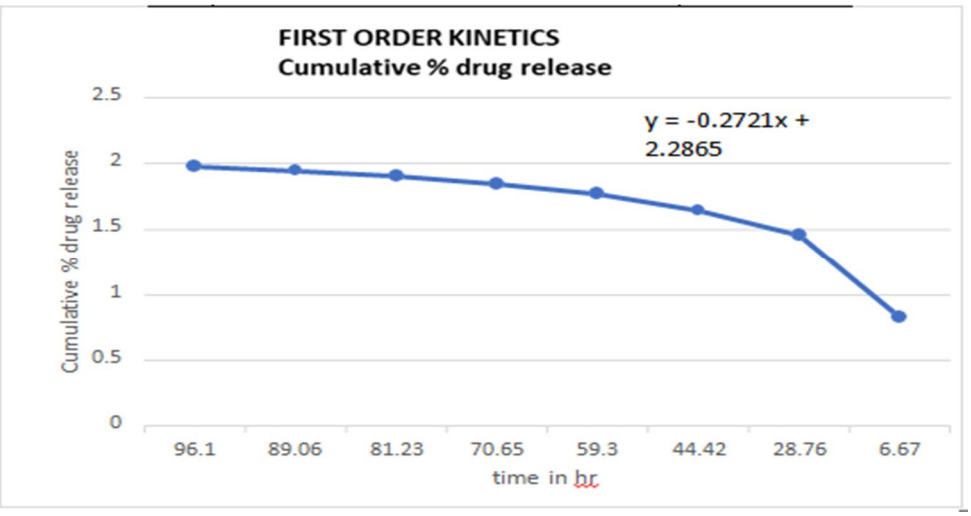
The dissolution data of batches F1 to F9 was fitted zero order,fitted to zero order, first order, higuchi, korsemayer-peppasand models. The coefficient of determination(R2)value was used as criteria to choose the best model to describe drug release from the beads. The R2 values of various models are in table 8.9. In case diffusion release kinetic all formulations the R2values were in higuchi models indicating that the drug release from the formulation followed Higuchi model.The R2 value of F9 (R>0.999) obtained for fitting the drug release data to the higuchi model indicating that the drug release mechanism from the niosomes was diffusion mechanism. The values of higuchi model also indicated that all the formulations followed diffusion controlled release mechanism this indicated that the drug release is controlled by diffusion.

Table no 8.9 Release Kinetics Modeling

Formulation code	Zero order	First order	HiguchI model	Korsemeyer-Peppasmodel
F1	0.869	0.815	0.991	0.986
F2	0.872	0.853	0.993	0.992
F3	0.901	0.777	0.992	0.965
F4	0.901	0.972	0.997	0.833
F6	0.936	0.823	0.995	0.806
F7	0.954	0.853	0.996	0.832
F8	0.966	0.795	0.998	0.815
F9	0.971	0.887	0.999	0.820



Graph of zero Order Kinetics



Graph of First Order Kinetics

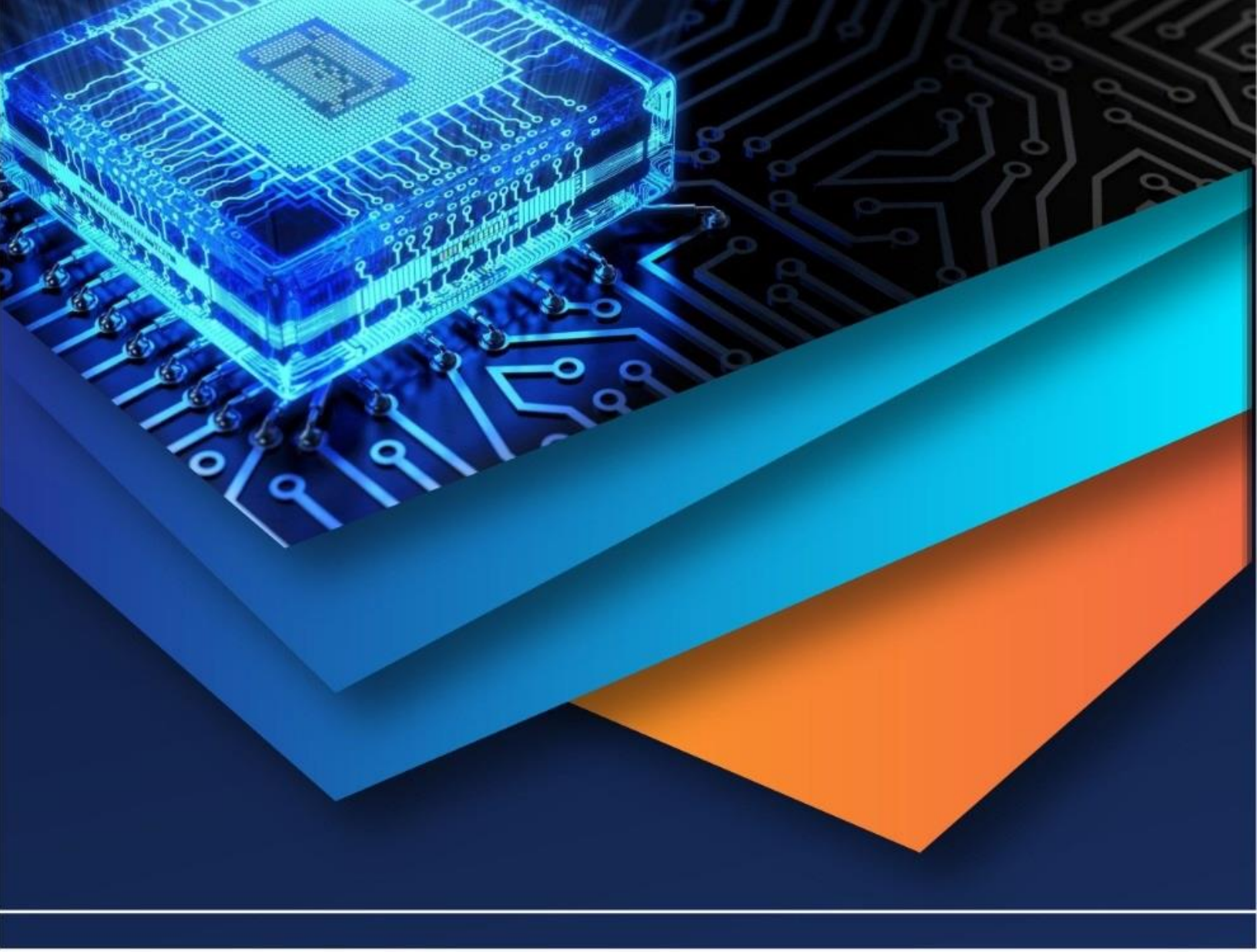
VIII. SUMMARY AND CONCLUSION

1) Oral formulation has been preferred and most common route of drug delivery.
2) In the begining of the work, drug authentication was performed. The authentication study showed that the obtained sample of Glimepiride was pure and complied with IP limit.
3) Niosomes are versatile in structure, morphology and size; they can entrap hydrophilic drugs in aqueous compartments to decrease the degradation of durg.
4) Glimepiride niosmes were prepared with an provide the drug prolonged period of timein the stomach. . Glimepiride was targeted to stomach because it has the absorption window in upper part of GIT so it hasbeen provided for prolonged period of time in stomach for better therapeutic activity by increasing its bioavailability.
5) Glimepiride is an Antidibetic drug of BCS class II having low solubility and high permeability. It has biological half life of 5 to 8 hours , log P value is 3.81, and molecular weight of 490.617 g/mol, these characteristics makes Glimepiride drug model for formulating it into niosomes.
6) Glimepiride niosomes were prepared using surfactants span 60 and Cholesterol in twodifferent ratios bythree methods.
7) Niosomes were prepared by ether injection method. Span 60 used as the Surfactant.The Cholestrol was used as carrier and diethyl ether and ethanol used asthe solvent.
8) The shape of Glimepiride niosomes are spherical in nature and the size ranges between 50 and 200 nm.
9) The niosomal formulations were characterized for their vesicle size, entrapment efficiency and invitro release study.
10) The formulated and optimized niosomes batch (F9) shows 90.04 % entrapment efficiency.
11) From factorial design study, it was concluded that Cholesterol concentration increase entrapment efficiency ani partical size alo increase.
12) The present study concluded that the aqueous solubility of poorly water soluble drug Glimepiride can be enhanced by the formulation by Cholestrol surfactant by using ether injection method.

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