International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1794-1809 www.ijprajournal.com ISSN: 2249-7781

Niosomes A Potental Vesicular Carrier in Novel Drug Delivery System

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Submitted: 15-05-2023 Accepted: 30-05-2023

ATBSTRACT

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic non-ionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilicdrugs niosomes are poromising vehicle for drug delivery and being non-ionic, biodegaradable, biocompatible, and exhibit flexibitity is their structural characterization. It can entrap both hydrophilic and lipophilic drugs and can prolong the circuladion of entrapped drug in body. Drug encapsulated in the vesicular structure of proniosomes prolong the existence of drug in the systemic circulation and enhances the penetration into target tissue & reduce toxicity.

The technology utilized in niosomes is still greatly in its infancy,and already it is promise in the fields of cancer and infectious disease treatments.

KEY WORDS: Vesicular drug delivery, Targeted drug delivery, Proniosomes, Niosomes, Non-ionic surfactants.

INTRODUCTION

In recent years, vesicles have become the vehicle of choice in drug delivery. Controlled release drug products are often formulated to permit the establishment and maintenance of any concentration at target site for longer intervals of time. Therefore vesicles can be viewed as drug carriers and they change the rate and extent of absorption as well as the disposition of the drug. Vesicular drug delivery systems used in ophthalmic broadly include liposomes and niosomes.[8]

NIOSOMES [1,2]

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. The niosomes are very small and microscopic in size. Although structurally similar to liposome, they offer several advantages over them.

TRANFEROSOMES [3]

Liposomal as well as niosomal systems are not suitable for transdermal delivery because of the poor skin permeability, breaking of vesicles, leakage of drug, aggregation and fusion of vesicles. To overcome these problems, a new type of carrier system called tranferosomes has recently being introduced which is capable of transdermal delivery of low as well as high molecular weight drugs.

PHARMACOSOMES

The limitations of tranferosomes as that of liposomes can be overcome by the pharmacosomes approach. These are defined as colloidal dispersions of drug covalently bound to lipids and may exist as ultra fine vesicular, micellar (or) hexagonal aggregates, depending on the chemical structure of drug – lipid complex.

STRUCTURE OF NIOSOMES [4, 5]

Niosomes are microscopic lamellar structures, which are formed on the admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. 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

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Volume 8, Issue 3 May-June 2023, pp: 1794-1809 www.ijprajournal.com ISSN: 2249-7781

phospholipids as seen in the case of liposomes. Most surface active agents when immersed in water yield micellar structures; however some surfactants can yield bilayer vesicles which are niosomes. Niosomes may be unilamellar or multilamellar depending on the 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.

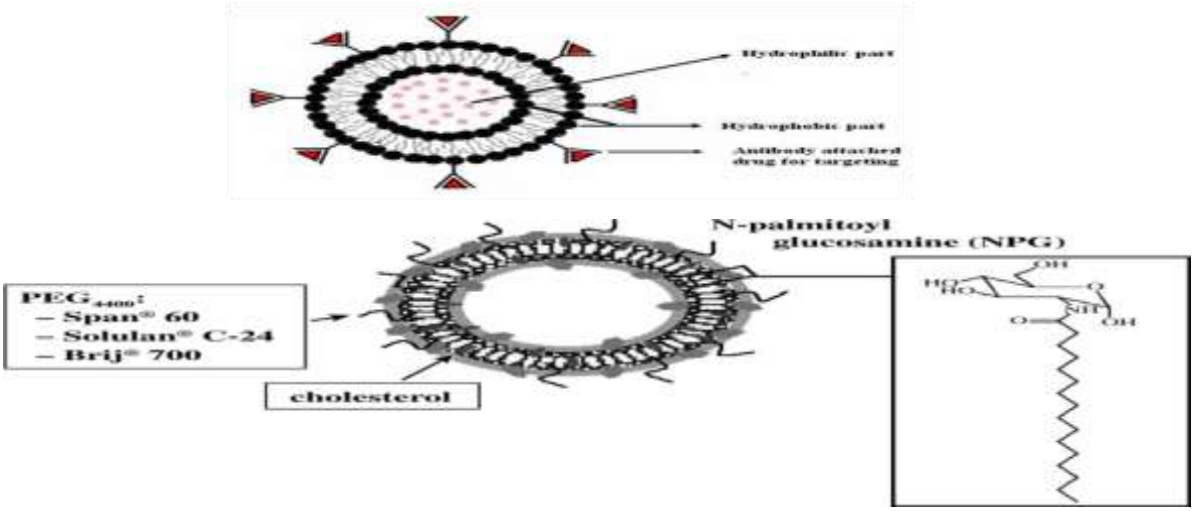

Figure1. Structure of niosome representing hydrophilic and hydrophobic regions

Hence, the vesicle holds hydrophilic drugs within the space enclosed in the vesicle, while hydrophobic drugs are embedded within the bilayer itself.

Salient Features of Niosomes [6, 7]

- Niosomes can entrap solutes in a manner analogous to liposomes.
- Niosomes are osmotically active and stable.
- Niosome possess an infra structure consisting of hydrophobic and hydrophilic mostly together and so also accommodate the drug molecules with a wide range of solubility.
- Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
- No special conditions are required for handling and storage of niosomes.
- Niosomes are bio degradable, biocompatible and non-immunogenic.
- Niosomes can improve the performance of the drug molecules by:

1) Delayed clearance from the circulation.
2) Better availability to the particular site, just by protecting the drug from biological environment.
3) Controlled delivery of drug at a particular site.

COMPARISON OF NIOSOMES AND LIPOSOMES[8]

Niosomes are now widely studied as an alternative to liposomes as niosomes are promising vehicle for drug delivery and being non ionic, less toxic improves the therapeutic index of drug by restricting its action to target cells.	Liposomes exhibit certain disadvantages such as they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids are variable.

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Niosomes are prepared from uncharged single -chain surfactant and cholesterol.	Liposomes are prepared from double- chain phospholipids (neutral or charged).
Niosomes behave in vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability.	As with liposomes, the properties of niosomes depends both on the composition of the bilayer and on the method of their production.

However niosomes are similar to liposomes in functionality. Niosomes also increase the bioavailability of the drug and reduce the clearance like liposomes. Niosomes can also be used for targeted drug delivery, similar to liposomes. As with liposomes, the properties of the niosomes depend both on the composition of the bilayer and the method of production used.

Advantages of Niosomes for Ocular Drug Delivery Systems [9]

1. Targeted drug delivery can be achieved using niosomes the drug is delivered directly to the body part where the therapeutic effect is required.
2. Reduced dose is required to achieve the desired effect.
3. Subsequent decrease in the side effects.
4. The therapeutic efficacy of the drugs is improved by reducing the clearance rate, targeting to the specific site and by protecting the encapsulated drug.
5. Niosomes are amphiphillic i.e. both hydrophilic and lipophilic in nature and can accommodate a large number of drugs with a wide range of solubilities.
6. Improve the oral bioavailability of poorly soluble drugs.
7. Enhance the skin permeability of drugs when applied topically.
8. Provide adventage of usage through various routes viz. oral, parentral,topical,ocular etc.
9. The bilayers of the niosomes protect the enclosed active pharmaceutical ingredient from various factors present both inside and outside the body.
10. The surfactants used and also the prepared niosomes are biodegradable,biocompatible and non-immunogenic.
11. They are osmotically active and stable.

Method of Preparation of Niosomes[10]

Small unilamellar vesicles: SUV are commonly produced by sonication and French Press procedures. Ultrasonic electrocapillary emulsification or solvent dilution techniques can be used to prepare SUVs4

Multilamellar vesicles: MLV exhibit increased-trapped volume and equilibrium solute distribution and require hand-shaking method for formulation. They show variations in lipid compositions1, 4.

Large unilamellar vesicles: The injections of lipids solubilised in an organic solvent into an aqueous buffer, can result in spontaneous formation of LUV. But the better methods of preparation of LUV are Reverse phase evaporation and Detergent solubilization method.1, 4, 5

LABORATORY METHODS OF NIOSOME PREPARATION[11]

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.

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 thin layer 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. Thermo sensitive 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 containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.

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C. Sonication

A typical method of production of the vesicles is by sonication of solution. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10ml glass vial. The mixture is probe sonicated at 60°C for 3 min. using a sonicator with a titanium probe to yield niosomes.

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 result is a greater uniformity, smaller size and better reproducibility of niosomes formed.

E. Multiple membrane extrusion method

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

F. Reverse Phase Evaporation Technique (REV)

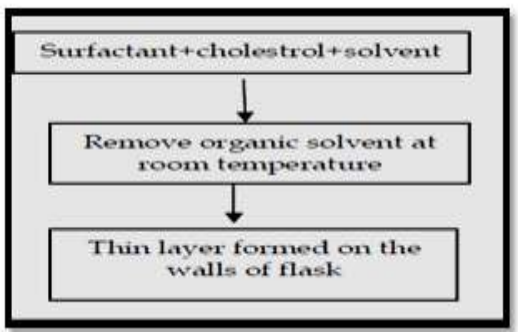
Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). 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.

G. Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading) [32]

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 hydrated with 300ml citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. 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 1M disodium phosphate. This mixture is later heated at 60°C for 10 min. to give niosomes.

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 water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through 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.



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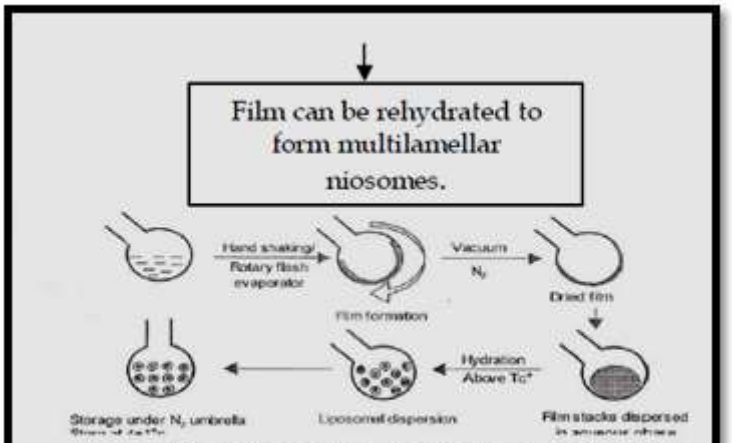
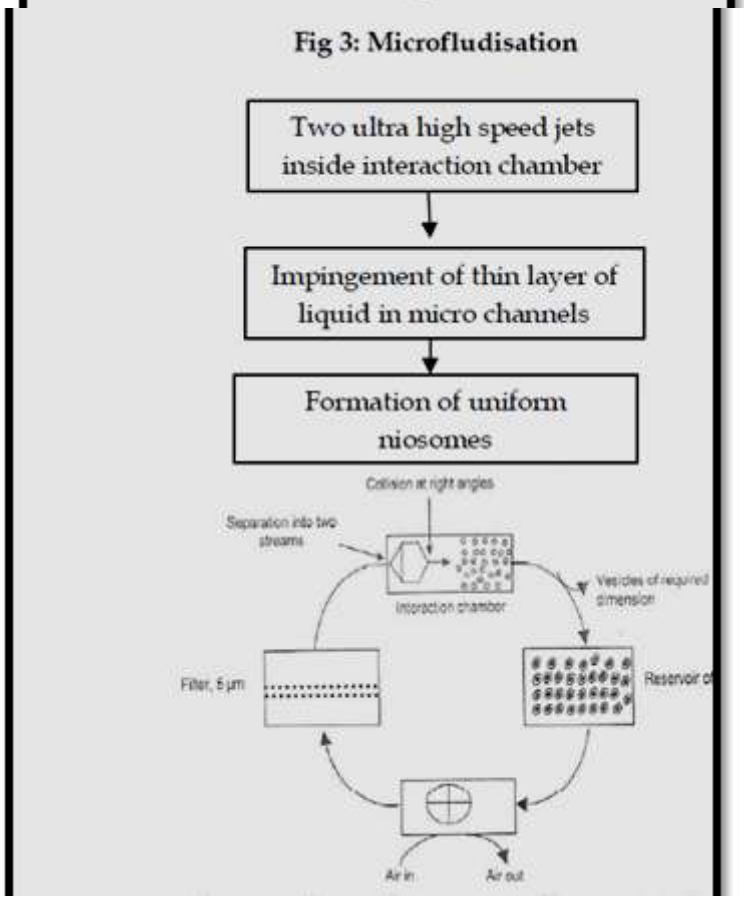


Fig 2: Hand Shaking Method of Niosomes Preparation

Fig 3: Microfludisation



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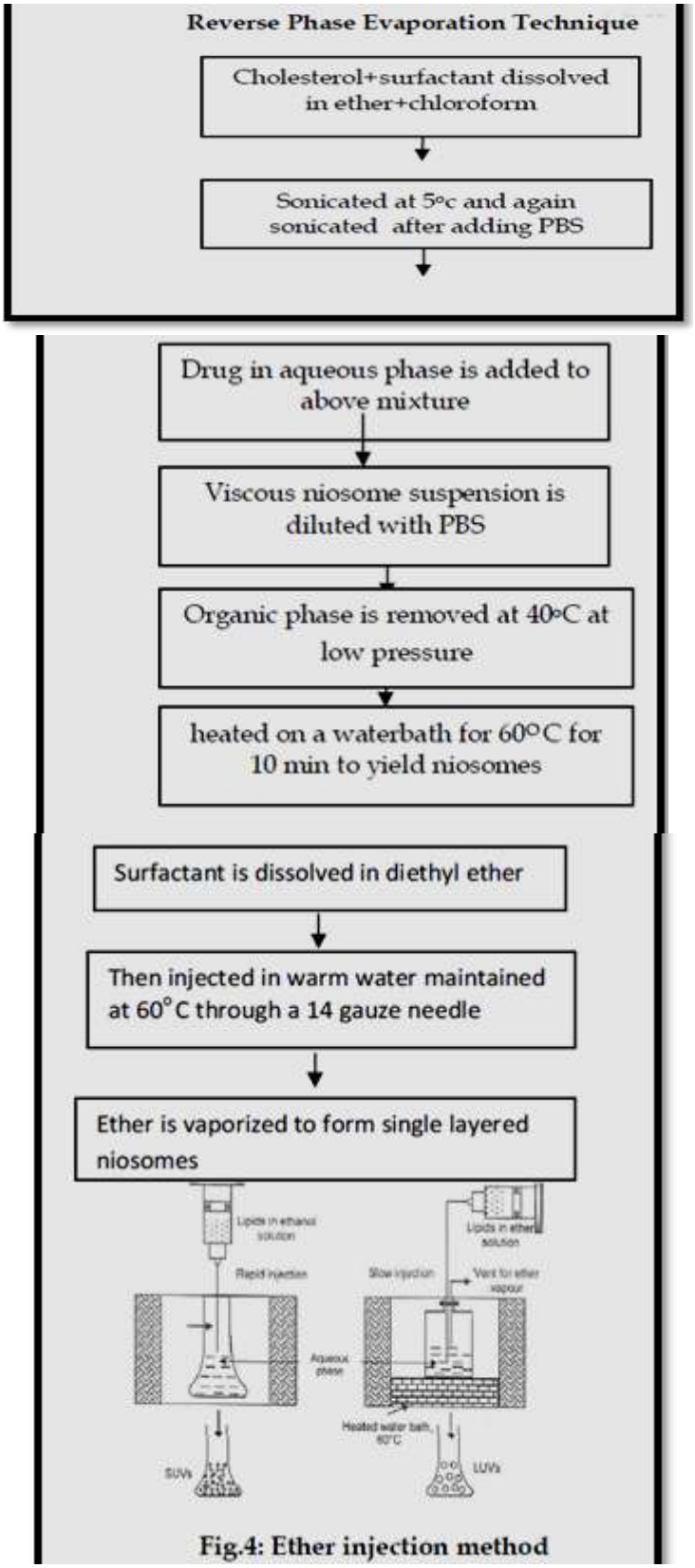

Fig.4: Ether injection method

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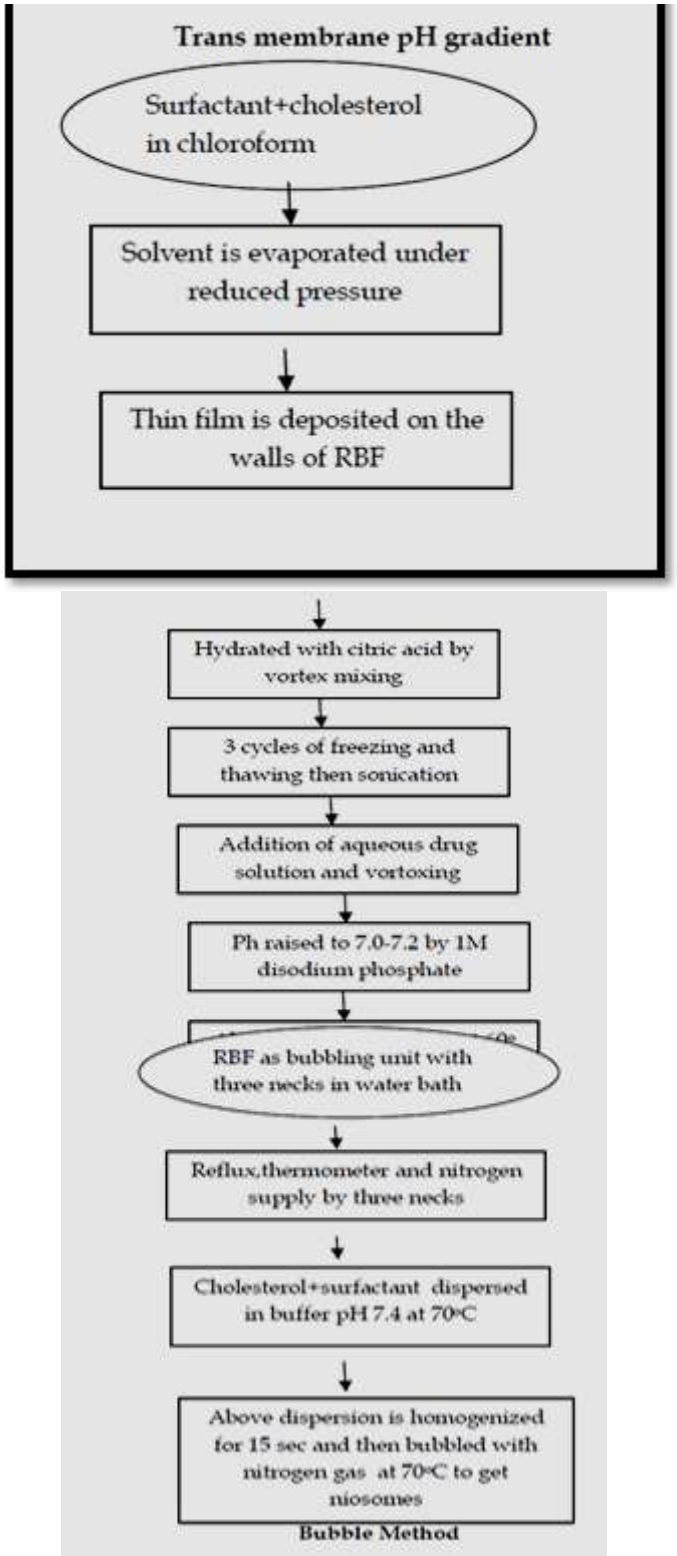

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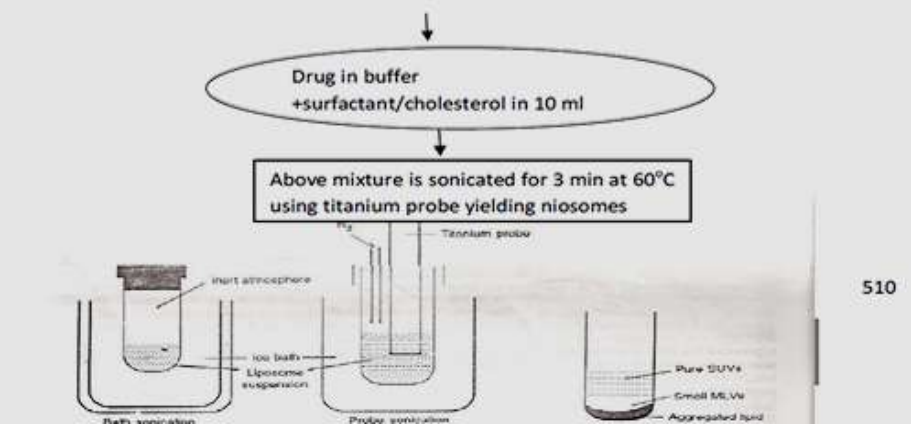
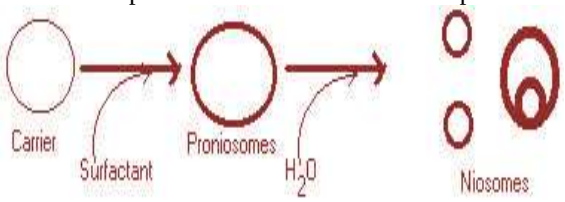


FORMATION OF NIOSOMES FROM PRONIOSOMES [10, 12]

In this method, niosomes can be produced to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes". The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation.

T=Temperature.

Tm = mean phase transition temperature [13].



Method of Preparation	Drug Incorporated
Ether Injection	Sodium stibogluconate,Doxorubicin
Hand Shaking	Methotrexate, Doxorubicin
Sonication	9-desglycinamide, 8-arginine, Vasopressin, Oestradiol

CHARACTERIZATION OF NIOSOMES [12,13]

Entrapment efficiency

After preparing niosomal dispersion, unentrapped drug is separated by dialysis [7] centrifugation or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzing the resultant solution by appropriate assay method for the drug.

Size

Shape of niosome vesicles assumed to be spherical, their mean diameter can be determined by using laser light scattering method. Also, diameter can be determined by using electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy and optical microscopy.

In-vitro release

A method of in-vitro release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle

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suspension is pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method

Bilayer formation

Assembly of non-ionic surfactants to form bilayer vesicle is characterized by X-cross formation under light polarization microscopy.

Number of lamellae

It is determined by using NMR spectroscopy, small angle X-ray scattering and electron microscopy .

Membrane rigidity

Membrane rigidity can be measured by means of mobility of fluorescence probe as function of temperature .

Surfactants

The chain length and hydrophilic head of non-ionic surfactants affect entrapment efficiency, such as stearyl chain C18 non-ionic surfactant vesicles show higher entrapment efficiency than lauryl chain C12 non-ionic surfactant vesicles. The tween series surfactants bearing a long alkyl chain and a large hydrophilic moiety in the combination with cholesterol at 1:1 ratio have highest entrapment efficiency for water soluble drugs. 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. The entrapment efficiency is affected by phase transition temperature of surfactants, i.e. span 60 exhibits highest entrapment efficiency in series having highest transition temperature (Tc)

Cholesterol contents [14]

The incorporation of cholesterol into bilayer composition of niosome induces membrane-stabilizing activity and decreases the leakiness of membrane. Hence, incorporation of cholesterol into bilayer increases entrapment efficiency. The permeability of vesicle bilayer to 5, 6-carboxy flourescein (CF) is reduced by 10 times due to incorporation of cholesterol. [32]

S. No.	Parameter	Instrument / Method Employed
1	Vesicle size Determination and size distribution	1.Malvern Mastersizer 2.Photon correlation spectroscopy(PCS) 3.Optical microscopy 4.Scanning electron microscopy(SEM) 5.Salad-1100 laser diffraction particle size analyzer 6.Coulter submicron particle size analyzer 7.Klotz® particle sizer 8.Anderson cascade impactor
2	Shape and morphological characterization	1.Optical microscopy 2.Polarized light microscopy 3.Transmission electron microscopy 4.Freez fracture microscopy(FF-TEM) 5.Multiple tau digital correlator 6.Small angle X-ray diffraction (SA-XRD) 7.Phase Contrast microscopy 8.Quasi elastic light scattering
3	Zetapotential / Surface charge	1.Microelectrophoresismeter 2.High performance capillary electrophoresis 3.Malvern Zetasizer (zetameter)

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4	Lamellarity	1.Optical microscopy 2.Transmission electron microscopy
5	Membrane microstructure	Negative staining TEM
6	Bilayer fluidity	Differential polarized phase flourometry
7	Bilayer spacing and thickness	X-ray scattering
8	Thermal behavior and shape transition	1.Differential thermal analysis (DTA) 2.Differential scanning calorimetry (DSC) 3.Hot stage microscopy
9	Rheological properties	1.Oswalt-U-tube 2.Low shear rheoanalyser
10	Conductivity	Conductometer

SEPARATION OF UNENTRAPPED DRUG

The removal of unentrapped solute from the vesicles can be accomplished by various techniques, which include:

1. Dialysis

The aqueous niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or normal saline or glucose solution.

2. Gel Filtration

The unentrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline.

3. Centrifugation

The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from unentrapped drug.

SURFACTANTS USED IN THE PREPARATION OF NIOSOMES

Niosomes are unilamellar or multilamellar vesicles formed from synthetic non-ionic surfactants. The surfactants that are reported to form niosomes are as follows:

Ether linked surfactant:

In which the hydrophilic hydrophobic moieties are ether linked, polyoxyethylene alkyl ethers with the general formula (CnEOm),

Where n; i.e. number of carbon atoms varies between 12 and 18 and m; i.e. number of oxyethylene unit varies between 3 and 7.

The surfactants used were C12EO3, C12EO7, C18EO3, and C3EO7.

Single alkyl chain surfactant C16 mono alkyl glycerol ether with an average of three glycerol units [surfactant 1]. C16H33O [CH2-CH-O]3-H CH2OH Mol. Weight =473 Surfactant 1 was used for the preparation of niosomes **.** The effect of surfactant 1 based niosomes on absorption, metabolism and excretion of Methotrexate in the mice was studied ·The drug entrapment, stability and release of drug from adrimycin loaded niosomes based on surfactant 1 was studied. Effect on the absorption and distribution of Methotrexate entrapped in niosomes was studied. Surfactant 1 based stibogluconate bearing niosomes were prepared and evaluated for various parameters for their effect on the in vivo absorption, distribution and elimination of the contained drug.

Di-alkyl chain surfactant:

Surfactant was used as a principal component of niosomal preparation of stibogluconate and its

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potential in delivering sodium stibogluconate in experimental marine visceral leishmaniasis has been explored.

C16H33CH-O[-CH2-CH-O]7-H
| |
CH2 CH2OH
|
C12H25-O Surfactant11, mol. Wt. 972

Ester linked:

Surfactants in which hydrophilic and hydrophobic moieties are ester linked. Ester linked surfactant,

C15H31CO [O-CH2-CH-CH2]2-OH
|
OH Surfactant 11 mol. Wt. 393

Surfactant 11was also studied for its use in the preparation of stibogluconate bearing niosomes and in delivery of sodium stibogluconate to the experimental marine visceral leishmaniasis following administration of niosomal system**.**

Sorbitan Esters

CH2 where, R is H or an alkyl chain. |
H-C-OH
|
RCOO- C-H
| - The commercial sorbitan esters are

H-C-OH mixtures of the partial esters of
| sorbital and its mono and di-an-
H-C-OOC-R hydrides with oleic acid.
|
CH2OOC-R

The formula of a representative component is shown above.

Sorbitan esters based niosomes bearing methotrexate were
prepared and evaluated for pharmacokinetics of the entrapped methotrexate
in tumor bearing mice.

Poly sorbates:

The typical structural formula of polysorbates is -

CH2
|
H-C-O(CH2-CH2-O) H
|
(OCH-CH2)-O-C-H
|
H-C-O-(CH2-CH2-O)y H
|
CH2-O(CH2-CH2-O)z OCR

When n=X+Y+Z+2 and R is an alkyl chain this series of surfactants
has been used to study the pharmacokinetics of niosomal entrapped
methotrexate.

TABLE NO 1: DIFFERENT TYPES OF NON-IONIC SURFACTANT

Type of Non-ionic surfactant	**Examples**
Fatty alcohol	Cetyl alcohol, Steryl alcohol, Cetosteryl alcohol, oleyl alcohol
Ethers	Brij, Decyl glucoside, Lauryl glucoside, Octyl glucoside, Triton X-100, Nonoxynol-9
Esters	Glyceryl laurate, Polysorbates, Spans
Block copolymers	Poloxamers

FACTORS AFFECTING FORMATION OF NIOSOMES

Nature of surfactants

A surfactant used for preparation of niosomes must have a hydrophilic head and hydrophobic tail. The hydrophobic tail may consist of one or two alkyl or perfluoroalkyl groups or in some cases a single steroidal group**.** The ether type surfactants with single chain alkyl as hydrophobic tail is more toxic than corresponding dialkylether chain **.** The ester type surfactants are chemically less stable than ether type surfactants and the former is less toxic than the latter due to ester-linked surfactant degraded by esterases to triglycerides and fatty acid in vivo**.** The surfactants with alkyl chain length from C12-C18 are suitable for preparation of niosome [23-24]**.** Surfactants such as C16EO5 (poly-oxyethylene cetyl ether) or C18EO5
(polyoxyethylene steryl ether) are used for preparation of polyhedral vesicles**.** Span series surfactants having HLB number of between 4 and 8 can form vesicles**.**

Structure of surfactants

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 can predicate geometry of

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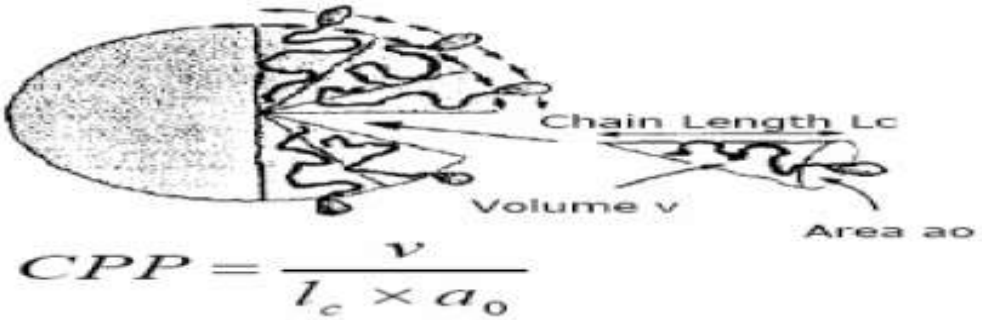
vesicle to be formed. Critical packing parameters can be defined using following equation,



$$CPP = \frac{v}{l_c \times a_o}$$

Where v = hydrophobic group volume,, lc = the critical hydrophobic group length,, a0= the area of hydrophilic head group.

From the critical packing parameter value type of miceller structure formed can be ascertained as given below,
If CPP < ½ then formation of spherical micelles, If ½ < CPP < 1 formation of bilayer micelles,
If CPP > 1 formation inverted micelles.

Membrane composition

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 characteristics by different additives. In case of polyhedral niosomes formed from C16G2, the shape of these polyhedral niosome remains unaffected by adding low amount of solulan C24 (cholesteryl poly-24-oxyethylene ether), which prevents aggregation due to development of steric hindrance[26]**.**

In contrast spherical Niosomes are formed by C16G2: cholesterol: solulan (49:49:2) [26]**.**The mean size of niosomes is influenced by membrane composition such as Polyhedral niosomes formed by C16G2: solulan C24 in ratio (91:9) having bigger size (8.0 ± 0.03mm) than spherical/tubular niosomes formed by C16G2: cholesterol:solulan C24 in ratio (49:49:2) (6.6±0.2mm) [26]. Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and reduces the leakage of drug from noisome.

Nature of encapsulated drug

The physico-chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The drug interacts with surfactant head groups and develops the charge that creates mutual repulsion between surfactant bilayers and hence increases vesicle size [28].The aggregation of vesicles is prevented due to the charge development on bilayer.

TABLE NO 2: EFFECT OF THE NATURE OF THE DRUG ON THE FORMATION OF NIOSOMES

Nature of the drug	Leakage from the vesicles	Stability	Other properties
Hydrophobic drug	Decreased	Increased	Improved transdermal delivery
Hydrophobic drug	Increased	Decreased	-
Amphiphilic drug	Decreased	-	Increased encapsulation, Altered elecrophoretic mobility

Temperature of hydration

Hydration temperature influences the shape and size of the noisome. For ideal condition it should be above the gel to liquid phase transition temperature of system. Temperature change of niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation**.** It has been reported that a polyhedral vesicle formed by 16G2: solulan C24 (91:9) at 25°C which on heating transformed into spherical vesicle at 48°C, but on cooling from 55°C, the vesicle produced a cluster of smaller spherical niosomes at 49°C before changing to the polyhedral structures at 35°C**.** In contrast vesicle formed by C16G2: cholesterol: solulanC24 (49:49:2) shows no shape transformation on

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heating or cooling. Along with the above mentioned factors, volume of hydration medium and time of hydration of niosomes are also critical factors. Improper selection of these factors may result in formation of fragile niosomes or creation of drug leakage problems.

Physical stability study

Physical stability study is required to investigate the leaching of drug from niosomes during storage. Seal the prepared niosomes in 20ml glass vials and store at a temperature of 2 - 8ºC for a period spread over 60 – 90 days. Withdraw samples from each batch at definite time intervals and determine the residual amount of the drug in the vesicles after separation from un-entrapped drug by ultracentrifugation or dialysis method.

Zeta potential analysis

The presence of surface charge in vesicular dispersions is critical. Aggregation is attributed to the shielding of the vesicle surface charge by ions in solution and thereby reducing the electrostatic repulsion. Vesicle surface charge can be estimated by measurement of particle electrophoretic mobility and is expressed as the zeta potential which can be calculated using the Henry equation.

□ □ = □ E4□ □ / □

Where, □ = zeta potential, □ E = electrophoretic mobility, □ = viscosity of the medium, □ = dielectric constant.

STABILITY OF NIOSOMES

Stable niosome suspension must exhibit a constant particle size and constant concentration of entrapped drug. Stability of niosome is influenced by entrapped drug, its concentration and type of surfactant used along with cholesterol content. Sonicated niosomes exhibit different stability at room temperature on basis of formulation ingredients. Cholesterol- rich spherical/tabular C16 G2 niosomes are at room temperature, where as sonicated polyhedral niosomes are stable above phase transition temperature but not at room temperature.

THERAPEUTIC APPLICATIONS

There are very less marketed niosomal formulations found in market. But some experimentally evaluated application of niosomal formulation identified in literature listed below.

Anti-cancer drug

Daunorubicin HCl

Niosomal daunorubicin hydrochloride exhibited an enhanced anti-tumor efficacy when compared to free drug. The niosomal formulation was able to destroy the Dalton's ascitic lymphoma cells in the peritoneum within the third day of treatment, while free drug took around six days and the process was incomplete. The hematological studies also prove that the niosomal formulation was superior to free drug treatment. An enhanced mean survival time was achieved by the niosomal formulation that finally substantiates the overall efficacy of the niosomal formulation .

Doxorubicin

Rogerson et al., studied distribution of niosomal doxorubicin prepared from C16 monoalkyl glycerol ether with or without cholesterol. Niosomal formulation exhibited an increased level of doxorubicin in tumor cells, serum and lungs, but not in liver and spleen. Doxorubicin loaded cholesterol-free niosomes decreased the rate of proliferation of tumor and increased life span of tumorbearing mice. The cardio toxicity effect of doxorubicin was reduced by niosomal formulation. Niosomal formulation changes the general metabolic pathway of doxorubicin

Methotrexate

Azmin et al., quoted in their research article that niosomal formulation of methotrexate exhibits higher AUC as compared to methotrexate solution, administered either intravenously or orally. Tumoricidal activity of niosomally-formulated methotreaxate is higher as compared to plain drug solution

Bleomycin

Niosomal formulation of bleomycin containing 47.5% cholesterol exhibits higher level drug in the lever, spleen and tumour as compared to plan drug solution in tumorbearing mice. There is no significant difference in drug concentration with niosomal formulation in lung as compared to plan drug solution.10Also, there is less accumulation of drug in gut and kidney in case of niosomal formulation.

Vincristine

Niosomal formulation of vincristine exhibits higher tumoricidal efficacy as compared to

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1794-1809 www.ijprajournal.com ISSN: 2249-7781

plain drug formulation . Also, niosomal formulation of carboplatin exhibits higher tumoricidal efficacy in S-180 lung carcinoma-bearing mice as compared to plan drug solution and also less bone marrow toxic effect.

Anti-infective agents

Sodium stibogluconate is a choice drug for treatment of visceral leshmaniasis is a protozoan infection of reticuloendothelial system. Niosomal or liposomal formulation of sodium stibogluconate exhibits higher levels of antimony as compared to free drug solution in liver . Antimony level is same in both formation i.e. niosome and liposome. Niosomal formulation of rifampicin exhibits better antitubercular activity as compared to plain drug.

Anti-inflammatory agents

Niosomal formulation of diclofenac sodium with 70% cholesterol exhibits greater anti-inflammation activity as compared to free drug. Niosomal formulation of nimesulide and flurbiprofen also exhibits greater anti-inflammation activity as compared to free drug.

Diagnostic imaging with niosomes

Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglcemine with [N-palmitoyl-glucosamine (NPG)], PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging.

Ophthalmic drug delivery

It is difficult to achieve excellent bioavailability of drug from ocular dosage form like ophthalmic solution, suspension and ointment due to the tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time. But to achieve good bioavailability of drug various vesicular systems are proposed to be use, in experimental level, like niosomes, liposomes. Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate exhibits more tendency for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide) (Aggardwal D et al., 2004). The chitosan-coated niosomal formulation timolol maleate (0.25%) exhibits more effect for reduction intraocular pressure as compared to a marketed formulation with less chance of cardiovascular side effects.

Transdermal drug delivery[15]

Administration of drugs by the transdermal route has advantages such as avoiding the first pass effect, but it has one important drawback, the slow penetration rate of drugs through the skin. Various approaches are made to overcome slow penetration rate, one approach for it is niosomal formulation. Alsarra et al., studied transdermal delivery pro-niosomal formulation of ketorolac prepared from span 60 exhibits a higher ketorolac flux across the skin than those proniosome prepared from tween20. It is also identified in literature that the bioavailability and therapeutic efficacy of drug like diclofenac , flurbiprofen and nimesulide are increased with niosomal formulation .

Niosomes in oral drug delivery

An oral administration of niosomal formulation of methotrexate exhibits higher concentration of drug in serum with more uptakes by the liver as compared to plain drug in mice (Azmin MN et al., 1985). So it concludes that gastrointestinal tract absorption of drug increases in niosomal formulation. Niosomal formulation of insulin prepared from span 20, 40, 60, 80 shows lower in-vitro release of insulin in simulated intestinal fluid from span 40 and 60 than span 20 and 80.

Niosomes prepared from span 60 exhibits highest protection of insulin against proteolytic enzymes and good stability in presence of sodium deoxycholate and storage temperature.

Niosome formulation as a brain targeted delivery system for the vasoactive intestinal peptide (VIP)

Radio labelled (I125) VIP-loaded glucose-bearing niosomes were injected intravenously to mice. Encapsulated VIP within glucose-bearing niosomes exhibits higher VIP brain uptake as compared to control.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1794-1809 www.ijprajournal.com ISSN: 2249-7781

S.No	Purpose / Application	Drugs studied
1	Cancer chemothraphy and targeted drug delivery	Doxorubicin, Danorubicin Hcl Methotrexate, 5-flurouracil, Adriamycin, Vincristine, Cytarabine Hcl.
2	Transdermal drug delivery	Nimesulide, Lidocaine, Cyclosporin, Estradiol, Erythromycin, Alpha-Interferon, Indomethacin, Plasmid DNA for the human Interleukin1 receptor, Finasteride, Enoxacin, Trentinoin, Dithranol.
3	Enhancement of bioavailabity	Diclofenac, Flurbiprofen, Bleomycin, Vincristin, Acetazolamide, Doxorubicin.
4	Ocular drug delivery	Timolol maleate, Acetazolamide, Cyclopentolate.
5	Pulmonary drug delivery	All trans retinoic acid (ATRA).
6	Brain targeted drug delivery	Vasoactive intestinal peptide loaded glucose bearing NSVs.
7	Protein/Peptide and Harmone delivery	LHRH, Insulin (oral), 9-desglycinamide-8-arginine vasopressin(DGAVP).
8	Local/ Intra articular drug delivery	Radiolabelled Diclofenac sodium niosomal vesicles.
9	Enhancement of stability	9-desglycinamide-8-arginine vasopressin(DGAVP). Heamoglobin, Dithranol, Beta Carotene.
10	Improved photostability	Beta Carotene.
11	Improved thermal and oxidative	Propranolol hydrochloride, Doxorubicin.
12	stability Prolonged release	Sodium stibogluconate, Rifampicin, Bacopasaponin-C.
13	For improved anti infective therapy	Haemagglutinin,Ovalbumin,Hepatitis B DNA vaccine NSVs, Plasmid DNA encoding proteins of Hepatitis B virus, Influenza DNA vaccine NSVs, Tetanus toxoid NSVs.
14	Immunostimulatory NSVs(antigenic)	Urokinase
15	Diagnosis Radiopharmaceutical carrier and Imaging study	Iobitridol (X ray imaging studies) Iopromide (kidney imaging studies)

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