A Nano Drug Carrier System: NIOSOMES.

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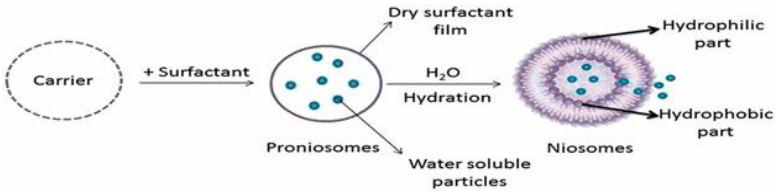
ABSTRACT:
Niosomes are a unique drug delivery system, within which the medication is encapsulated in a vesicle. Controlled drug release products are extremely used for the formation and maintenance of whichever concentration required at target site for extended length of time and this drug targeting methodology named as 'Niosomes'. Niosomes are nonionic surface-active agent vesicles created by hydrating artificial nonionic surfactants, either with or without cholesterol or its lipid, that are biodegradable, biocompatible, non-immunogenic, and structurally flexible. The low value of ingredients and manufacture, risk of large-scale production, stability and the resultant easy storage of niosomes have crystal rectifiers to the exploitation of those nano-carriers as alternatives to different small and nano-encapsulation technologies. The most object of this review, is the appliance of niosome technology, is employed to treat variety of diseases. Niosome smart chance in analysis and helpful for scientists and pharmaceutical industries.
Keywords: **Niosomes, Vesicles, Surfactant, Novel Drug Delivery.**

INTRODUCTION:

Paul Ehrlich bacteriologist initiated targeted delivery development in 1909 once he envisaged a mechanism for the delivery of medicine that may directly target pathological cell[1]. The biological origin of those vesicles was initially known by Bingham in 1965, and that they are referred to as Bingham bodies[2]. Niosomes are novel drug indefinite quantity kind for drug molecules having a good vary of solubility as their infrastructure consists of deliquescent and hydrophobic part[3]. By increasing oral bioavailability of poorly absorbed drugs, by delaying clearance from the circulation and by protecting the drug from biological surroundings, they improve the therapeutic performance of the drug molecules[4,5,6]. They are osmotically active, stable, and increase the stability of entrapped drugs. Targeted drug delivery may be a methodology of delivering a therapeutic agent to the tissue of interest, while lowering the relative concentration of the therapeutic agent in different tissues, raising therapeutic effectual ness and lowering aspect effects[7].

STRCTURE OF NIOSOME:



In niosomes, the vesicles forming amphiphiles a non-ionic chemical agent admire Span-60 that is typically stabilized by addition of sterol and little quantity of anionic surfactant such as dicetyl phosphate[8,9]. Niosomes are microscopic lamellar structures of the scale varying between 10-1000 nm[10].
The formation of this structure necessitates some type of energy input, comparable to physical agitation (e.g., the handclasp method), or heat (e.g., victimization, of the heating method). The hydrophobic parts of the molecule are oriented off from the binary compound solvent during this closed bilayer form, while the deliquescent head is in touch with the aqueous solvent[11]. Due to their distinctive structure as sac systems, niosomes will encapsulate each hydrophilic and lipophilic molecule[12]. Niosomes are the bi-layered structure of non-ionic active agents. These thermodynamically stable bilayered structures are shaped, only surfactants and cholesterol are mixed in an exceedingly correct proportion, and the temperature is on top of the gel liquid transition temperature[13,14,15]. This bi-layered structure contains a hollow house within the center[16]. A typical niosome cyst would contains a vesicle-forming amphiphilic i.e., a non-ionic wetter comparable to span-60, that is typically stabilized by the addition of cholesterol and a little quantity of anionic surfactant such as diacetyl phosphate, which additionally helps in helpful the vesicle[17].

Silent Features of Niosomes:

- Niosomes can entrap solutes in manner analogous to liposomes.
- Niosomes exhibit flexibility in their structural characteristics (composition, fluidity, and size) and may be designed according to the specified situation.
- Niosomes can enhance the overall performance of drug molecules. Higher availability to the particulate site, simply by protective the drug from biological environment[18].
- They'll be created to achieve the positioning of action by oral, epithelial duct additionally as topical routes[19].

The superiorities and benefits of niosomes, compared to alternative small and nano-encapsulation technologies may be summarized as follows:

- Compared to phospholipid molecules utilized in cyst formulations, the surfactants used in the formation of niosomes are additional stable;
- Simple strategies are needed for producing large- scale production of niosomes. Because the excipients and equipment used for production aren't expensive, niosome manufacturing methods are cost-effective;
- Niosomes possess a longer shelf-life than liposomes and most other nanocarrier systems;
- Not like liposomes, they are stable at space temperature and fewer vulnerable to light[20],[21].

TYPES OF NIOSOMES:

The different types of niosomes can be classified as follows:
1] Multilamellar vesicles (MLV)
2] Large unilamellar vesicles (LUV)
3] Small unilamellar vesicles (SUV)[22],[23],[24]

Parameters	Vesicle size	Method of Preparation
Multi Lamellar Vesicles	Greater than 0.05	Hand Shaking Method
Large Unilamellar Vesicles	Greater than 0.10	Reverse Phase Evaporation Method
Small unilamellar Vesicles	0.025-0.05	Sonication Extrusion Method Solvent Dilution Method

NIOSOMES VERSUS LIPOSOMES:

Structurally, niosmes are kind of like liposomes and are equiactive in drug delivery potential; however, high chemical stability and economy makes niosomes superior to those liposomes[25]. Liposomes embrace phospholipids that are unstable in nature, whereas niosomes contain non-ionic surfactants. Liposomes are made of double chain phospholipids, whereas niosomes are created up of unaltered single chain non-ionic surfactants. Niosomes are 10-100nm in size, whereas liposomes are 10-300nm. Whereas it involves pricing, niosomes are less costly than niosomes[26]. Within the body, niosomes behave like liposomes, similar to it, which prolongs the entrapped drug circulation and alters its organ distribution and stability metabolically. This sort of drug carrier sac systems changes the dynamics of plasma clearance, distribution of tissues, cellular interaction of medicine and its metabolism. So become the most effective alternative for controlled unharness and targeted drug delivery system[27],[28].

FORMULATION AND EVALUATION OF NIOSOMES:

A. Passive Trapping Techniques - This class includes most of the strategies utilized in the noisome preparation within which the drug is else throughout the noisome preparation, i.e., during its development.

1. Sonication:

Mixture of drug solution in buffer, surfactant and cholesterol.

↓

sonicated for 3 minutes at 60°C with a titanium sonicater to produce niosomes[29].

2. Ether Injection Method:

The niosomes are gradually dissolved in diethyl ether in a surfactant solution to keep the hot water at 60°C.

↓

The ether mixture is introduced into an aqueous solution of the substance through a 14-gauge needle.

↓

The ether evaporating in monolayer vesicles.

↓

The diameter of the vesicles between 501000 nm depends on the conditions used[30],[31].

3. Reverse Phase Evaporation Technique:
In this method, cholesterol and surfactant (1:1) are added to a mixture of ether and chloroform. An aqueous phase containing the drug is added and the two resulting phases are sonicated at 45°C. A small amount of phosphate-buffered saline is then added to the previously formed transparent gel and sonicated. The organic phase is eliminated at low pressure and 40 °C. Phosphate-buffered saline is added to dilute the resulting viscous niosome suspension and heated in a 60°C water bath for 10 minutes to produce niosome[32].

4. The Bubble Method:
The bubbler machine contains a three-column round-bottomed flask in a water bath to regulate the temperature.

↓

Cold reflux water is added to the first neck and the thermometer is inserted through the third neck into the second neck and the nitrogen source.

↓

Cholesterol and surfactant are spread in the buffer at 70°C (pH 7.4). Mix in dispersion with a high shear homogenizer for 15 seconds.

↓

"Bubble" with nitrogen gas at 70°C[33].

5. Hand Shaking Method (Thin Film Hydration Technique/Rotary Evaporator) –
The combined products cholesterol and surfactant and charge inducer.

↓

Dissolved in a round bottom flask in a volatile organic solvent at 20°C room temperature.

↓

A Thin layer of solid mixture forms.

↓

With gentle stirring, the dry surfactant film can be rehydrated with an aqueous phase at 0-60°C.

↓

Forming Niosomes[34].

6. Multiple Membrane Extrusion Method –
Surfactant, cholesterol and diacetyl phosphate are combined in chloroform during this process. The chloroform mixture then evaporates, creating a thin film. An aqueous drug-polycarbonate membrane is used to hydrate the thin film (consists of 8 passages). This approach also produces the desired size of niosomes[35].

7. Ethanol Injection Method –
A fine needle is used to easily administer an ethanol-surfactant solution.

↓

In excess of saline or another aqueous medium

↓

Ethanol Evaporation

↓

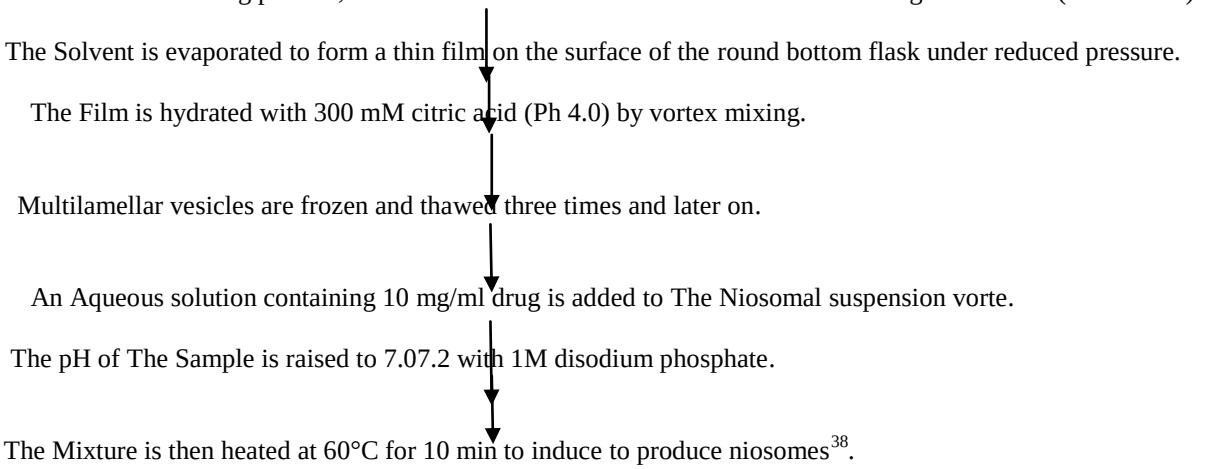
Vesicle Formation[36]

8. Micro-fluidization –
It is a method for making unilamellar vesicles with a preset size distribution. It works on the premise of the submerged jet principle, during which 2 fluidized streams act in exactly outlined small channels among the interaction chamber at ultra-high velocities (100 ml/min). The impingement of a thin layer of liquid sheet on a common front is organized in such the simplest way that the energy given to the system stays in the region of niosome formation area. This approach generates niosomes with a lot of uniformity, smaller size, and improved reproducibility[37].

B. Active Trapping Techniques –
It involves drug loading during niosome development. The niosomes are prepared and then the drug is filled with a pH gradient or an ion gradient to promote drug penetration into the niosomes. The various advantages of the niosome form include 100% containment, high drug lipid levels, zero leakage, cost effectiveness and suitability for labile drugs.

1. Trans Membrane Ph Gradient Drug Uptake Process-

In The Remote loading process, the surfactants and cholesterol are dissolved in an organic solvent (chloroform).



C. Miscellaneous Methods –

1. Emulsion Method:
   This is an easy methodology to create niosomes during which oil in water (o/w) emulsion is ready from organic solution of surfactant, steroid alcohol and a solution of the drug. Finally, the organic solvent is a gaseous effort of niosomes distributed within the liquid phase[39].

2. Heating Method:
   This process is scalable in one-step and non-toxic and additionally is based on, the patent procedure. An appropriate liquid medium like buffer, distilled water, and so on within which mixtures of non-ionic surfactants, sterol and charge causing molecules are accesso rial within the presence of the polyol like glycerol. The mixture is heated (at low shear forces) until the vesicles form[40].

3. Formation of Niosomes from Proniosomes:
   The Proniosome may be a dry formulation within which every soluble particle is coated with a thin film of dry surfactant. The niosomes are detected by the adding liquid part at T> Tm with temporary stirring. T is the temperature and Tm is the mean phase transition temperature[41].

   Carrier + Surfactant = Proniosomes
   Proniosomes + Water = Niosomes

4. Lipid Injection Method:
   This process does not require an expensive organic phase. The lipid-surfactant mixture is first melted and then injected into a heated, vigorously agitated aqueous phase containing the dissolved drug. The drug is dissolved in melted lipids and the mixture is injected into an aqueous surfactant phase[42],[43],[44],[45],[46].

SEPARATION OF UNTRAPPED DRUG:

- Dialysis: Phosphate buffer, glucose solution, or normal saline are used to dialyze the liquid niosomal suspension in qualitative analysis tubing.

- Gel filtration: The unentrapped drug within the niosomal suspension is extracted using a Sephadex-G-50 column with phosphate buffered saline or normal saline[47],[48].

- Centrifugation: The Niosome suspension is centrifuged and the supernatant is removed. The pellet is washed and then resuspended to induce an unentrapped drug-free niosome suspension[49],[50],[51].

ADVANTAGES:

1. The Niosome can accommodate a variety of drug fractions, such as hydrophilic, lipophilic, and amphiphilic drugs.
2. Vesicle Properties can be controlled by changing vesicle composition, lamina size, surface charge, extracted volume, and concentration.
3. The Drug may have delayed/controlled release.
4. Surfactants do not require any special handling or storage conditions.
5. Due to the depot formulation, it enables the controlled release of the active ingredient.
6. Poorly soluble drugs increase oral bioavailability. Surfactants possess the following biodegradable, biocompatible, non-toxic, and non-immunogenic response.
7. They can protect the active part of the biological cycle.
8. Pharmacological protection of enzymatic metabolism.

9. They improve the stability of the encapsulated drug.
10. They can improve the penetration of drugs through the skin.
11. They improve the therapeutic profile of drug molecules due to delayed clearance from the circulation[52],[53].
12. They are osmotically active and stable.
13. Oral, parenteral and topical applications are possible.
14. In order to control the rate of drug release and deliver normal vesicles in an external non-aqueous phase, the niosome dispersion in an aqueous phase can be emulsified in a non-aqueous phase[54],[55],[56],[57].

DISADVATAGES:

1. Fusion
2. Aggregation
3. Leaking of entrapped drug
4. Instability of the body
5. Encapsulated medicines are hydrolysed, reducing the shelf life of the dispersion[58],[59].
6. Time consuming[60]

Characteristics of Niosomes:

1. Size and shape:
   The shape of niosomal vesicles is considered to be spherical and the mean diameter of these vesicles can be calculated using the laser light scattering method. Electron microscopy, molecular sieve chromatography ultracentrifugation, photon microscopy and optical microscopy, and freeze electron microscopy also can be used to evaluate the diameter of those vesicle. The vesicles dimension will increase once frozen niosomes are thawed, that might contribute to vesicle fusion throughout the cycle[61].

2. Bilayer formation, membrane stiffness, and number of lamellae:
   The biodistribution and biodegradation of niosomes are determined by the stiffness of the bilayer. When homogeneous, scattering can occur within niosome and between niosome scaffolds and can be defined by PNMR, differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy techniques[62],[63],[64]. Through the use of electron microscopy, NMR spectroscopy, or the use of X-ray scattering, they can be used to fluorescence is used to measure membrane discomfort[65].

3. Entrapped Efficiency:
   The amount of active chemicals loaded within the niosomal structure is the entrapment efficiency (EF) of vesicular systems. It may be determined following the partition of drug unentrapped, by total destruction of vesicle with the employment of either 1ml of 2.5% sodium lauryl sulfate or 50% n-propanol, that is later emulsified and centrifuged, after which the resultant supernatant obtained is evaluated for drug by using sufficient dilutions[66].

$$\text{Entrapment Efficiency} = \frac{\text{Amount of drug in niosomes}}{\text{Amount of drug}} * 100$$

4. Stability studies:
   During storage, the drug can leak out of niosomes due to aggregation and fusion[67],[68]. performed the stability studies of the niosomes by exposing the preparation to different temperature conditions (4°, room temperature, and 45°) for two months. Niosomes are also exposed to various humidity and light (UV) conditions. During stability studies, parameters such as size, shape, and capture efficiency are regularly evaluated. In the same way, the stability of green tea extract niosomes[69], lornoxicam niosomes[70], cefdinimniosomes[71] and ginkgo biloba niosomes[72] was performed. Bayindir and Yuskel[73] studied the effect of gastrointestinal enzymes on the stability of niosomes. This study was conducted by exposing the drug and drug-loaded niosomes to various gastrointestinal enzymes such as pepsin, trypsin, and chymotrypsin, and it was found that the niosomes protected the drug from degradation by gastrointestinal enzymes.

   Stability of Niosomes:
   Vesicles are stabilized based upon the formation of 4 different forces –
   A) Van der Waals forces among surfactant molecules;
   B) Repulsive forces emerging from the electrostatic interactions among charged groups of surfactant molecules;
   C) Entropic repulsive forces of the head groups of surfactants;
   D) Short-acting repulsive forces[74].

5. Scanning Electron Microscope:
   The particle size of niosomes is a very important feature. Surface morphology (roundness, smoothness, and aggregate formation) and size distribution of niosomes were studied by scanning electron microscopy (SEM).

The niosomes were sprinkled onto the double-sided tape that was stuck onto the aluminum pieces. The aluminum piece was placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, The Netherlands). The samples were examined for their morphology. Characterization using a gaseous secondary electron detector (working pressure: 0.8 Torr, accelerating voltage: 30.00 KV) XL 30, (Philips, The Netherlands).

6. In-vitro Release:

a. Dialysis Tubing - A dialysis bag is washed with distilled water. The prepared vesicle suspension is fed into a bag made of dialysis tubing and then sealed. The bag with the vesicles is then placed in 200 ml of buffer solution in a 250 ml beaker with constant stirring at 25°C. The buffer is an analysis of the drug content of a suitable assay system at different time intervals.

b. Reverse Dialysis - A number of small dialysates are placed in proniosomes containing 1 ml of dissolution medium. The proniosomes are then fed into the dissolution process. Direct dilution of the proniosome is possible with this approach, and rapid release cannot be quantified with this method.

c. Franz diffusion cell - Using the Franz diffusion cell, the in vitro diffusion study can be performed. Proniosomes are placed in a Franz diffusion cell donor chamber filled with cellophane membrane. The proniosomes are dialyzed against an acceptable dissolution medium at room temperature; samples are taken from the medium at appropriate intervals and the drug content is analyzed using special methods such as UV spectroscopy, HPLC, etc.

- The Niosomal recovery can be calculated as[75,76].

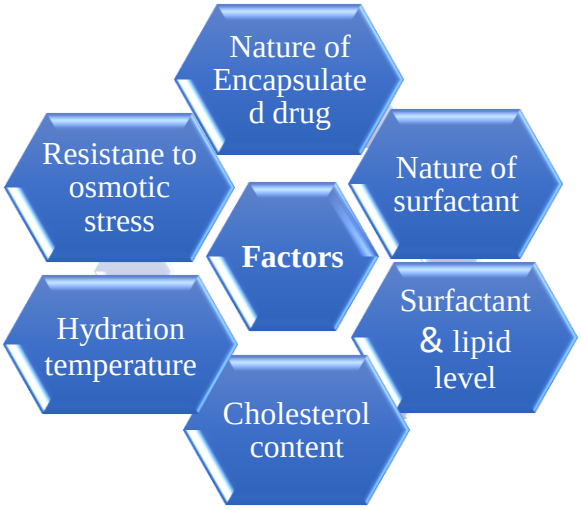
$$\% \text{ Recovery} = \frac{\text{Amount of noisome recovered}}{\text{Amount of polymer + drug + excipients}} * 100$$

- The Drug loading was calculated as:

$$\text{Drug Loading (\%)} = 1 + \frac{\text{Amount of drug in niosomes}}{\text{Amount of niosome}} *100$$

Sr. No.	Evaluation Parameter	Method/ Instrument
1.	Size Distribution, Polydispersity Index	SEM, Malvern Mastersizer, Anderson cascade impactor, Dynamic light scattering particle size analyser, Optical microscopy, Klotz particle size
2.	Morphology	SEM, TEM, Optical microscopy, freeze fracture technique, Phase contrast microscopy, Quasi elastic light scattering technique, small angle X-ray diffraction
3.	Thermal analysis	DSC, DTA, Hot stage microscopy
4.	Zeta potential	Malvern Zetasizer (zetameter) Micro-elecrtrophoresisimeter
5.	Lamellarity	Optical microscopy, TEM
6.	Membrane microstructure	Negative staining TEM
7.	Viscosity	Low shear rheoanalyser, Oswalt-U-tube
8.	Entrapment efficacy	Dialysis, gel chromatography, Centrifugation
9.	Conductivity	Conductometer
10.	In-vitro release study	Dialysis membrane
11.	Permeation study	Franz diffusion cell
12.	Turbidity	UV visible diode array spectrophotometer

FACTORS GOVERNING NIOSOME FORMATION:



Factors Influencing Niosomal Formulation

1. Composition of Niosome:
   - Cholesterol
   - Non-ionic surfactants
   - Charge inducer
   - Hydration medium

   i. Cholesterol: Cholesterol could be a waxy steroid matter found within the cell membrane[77]. The incorporation of cholesterol into the bilayer composition of niosome offers membrane stability and reduces membrane leakage. Therefore, incorporation of cholesterol into the bilayer will increase entrapment efficiency[78]. Steroid alcohol is another typically to the non-ionic surfactants to provide rigidity and orientational order to the niosomal bilayer[79]. Steroid alcohol is additionally referred to as get rid of gel-to-liquid activity of niosomal system leading to niosomes that are less leaky[80].

   ii. Non-ionic surfactants: The surfactant is the most important component in the niosome formulation. They have a polar head and a non-polar tail and are amphiphilic in nature. Compared to other surfactants such as anionic, cationic and amphoteric surfactants, these agents are more stable, tolerable and less harmful because they do not carry a charge. These compounds induce less hemolysis and cell surface irritation. They can be used as emulsifiers and wetting agents. Nonionic surfactants have the important property of inhibiting p-glycoprotein that inhibits the absorption and targeting of anti-cancer drugs (e.g., doxorubicin, daunorubicin, curcumin, morusin), steroids (e.g., hydrocortisone), inhibitors of HIV protease (e.g., ritonavir), cardiovascular drugs (e.g., digoxin, beta-blockers). Nonionic surfactants have high interfacial activity and are composed of polar and nonpolar segments and head groups.

   iii. Charge Inducer: To prevent coalescence, charge Inducers are added to the preparation to enhance the stability of the niosomes through electrostatic repulsion. Diacetyl phosphate and phosphatidic acid are the most commonly used negatively charged compounds. Stearyl amine and stearyl pyridinium chloride are positively charged inducers used in niosome preparations. Charged inducer concentrations of 25 mole percent are tolerable since higher concentrations can obstruct niosome formation[81,82]. The presence of charge leads to an increase in the interlamellar distance in the multilamellar vesicle structure between successive bilayers and a larger total trapped volume.

   iv. Hydration medium: Phosphate buffer is the most commonly used hydration medium in the production of niosomes. Phosphate buffers are used at a variety of pH values. The solubility of the encapsulated drugs determines the pH of the hydration medium[83].

2. Nature of encapsulated drugs:
   The physicochemical properties of encapsulated drugs directly have an effect on the rigidity and surface charge of the niosome bilayer. The drug interacts with the head groups of the surfactant and a charge is created that makes mutual repulsion between the surfactant Bilayers, increasing the size of the vesicles[84]. Vesicles aggregation is prevented because of charge development in the bilayer. In polyoxymethylene glycol-coated vesicles, some drug is entrapped within the long PEG chains, reducing the tendency to extend in the size. The hydrophilic lipotropic balance of drug affects the degree of entrapment[85].

Showing the Effect of Nature of 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 electrophoretic mobility
Macromolecules	Decreased	Increased	--

3. Nature of Surfactants:
A surfactant used to make niosomes must have a hydrophilic head and a hydrophobic tail. The hydrophobic tail can consist of one or two alkyl or perfluoroalkyl groups, or in some cases a single steroid group[86]. Ether type surfactant with a single chain alkyl as hydrophobic tail is more toxic than the corresponding dialkyl ether chain[87]. Ester-type surfactants are chemically less stable than ether-type surfactants, and the former are less toxic than the latter because the ester-linked surfactant is degraded to triglycerides and fatty acids by esterase in vivo. Surfactants with an alkyl chain length of C12C18 are suitable for the production of niosomes[88]. Surfactants such as C16E05 (polyoxyethylene cetyl ether) or C18E05 (polyoxyethylene stearyl ether) are used to produce polyhedral vesicles[89].

Showing different types of Non-ionic Surfactants

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

4. Surfactant And Lipid Level:
Other vital parameters are the extent of surfactant/lipid and therefore the surfactant/water magnitude relation. The surfactant/lipid ratio is mostly 10–30 millimeter (1–2.5% w/w). If the level of surfactant/lipid is just too high, increasing the surfactant/lipid level will increase the whole amount of drug encapsulated. A modification in the surfactant/water ratio throughout the association method might have an effect on the system's microstructure and thus, the system's properties.

5. Cholesterol Content:
Cholesterol incorporation improves the capture efficiency and hydrodynamic diameter of the niosomes. Cholesterol works in two ways:
   - It Increases the order of the double-layer chain in the liquid state.
   - It Reduces the order of the bilayer chain in the gel state.
     The rigidity of the bilayers and a decrease in the release rate of the encapsulated contents. Entrapment of cholesterol in the vesicle bilayer helps induce membrane stabilization.it reduces activity in niosomes and hence membrane leakage.

6. Hydration Temperature:
The hydration temperature affects the structural properties of niosomes. Temperature changes can also affect vesicle formation. For example, C16: solulan C24, they form polyhedral vesicles at 25°C, but when heated to 48°C they turn into spherical vesicles. Also, upon reverse cooling from 55 °C to 35 °C, a group of small spherical vesicles form at 49 °C and change to polyhedral vesicles at 35 °C. Considering that no changes in the structure of the vesicles with changing temperature were observed during the formation of the vesicles from C16: cholesterol: Solulan C24[90], Maryam[91] investigated this in her master's thesis in nanotechnology Influence of hydration time and temperature on the giant (discomes) niosome. He found that increasing temperature (from 55 to 800) and time (from 10 to 25 min) increases the number of oligolamellar, multilayered and multilamellar giant niosomes, and that the optimal time and temperature are 25 min and 70–75°C.

7. Charge:
   The presence of charge leads to an increase in interlamellar vesicle structure between successive bilayers and a larger total trapped volume.

8. Resistance to Osmotic Stress:
   When a hypertonic solution is added to a niosome suspension, the size of the niosome decreases. When stored in hypotonic saline, niosomes initially swell with slow drug release, although the swelling may be due to inhibition of fluid elution from vesicles and later to more rapid release. A phase was observed and this rapid release may be due to the change in the mechanical structure of the niosome due to mechanical stress[92], prepared and compared calcein niosomes and liposomes. They studied the influence of osmotic upshifting on niosomes by measuring calcein fluorescence (absorption). If the membrane was relatively permeable to the osmolyte (e.g., glycerol), the vesicle returns to its normal state in seconds or minutes, but if the osmolyte is comparatively impermeable (e.g., KCl) the vesicle remains within the contraction state for hours.

APPLICATION:

Targeting of Bioactive Agents

1. **Neoplasia-**
   The Anthracyclic antibiotic Doxorubicin, with broad spectrum anti-tum-r activity, shows a dose dependent irreversible cardio-toxic effect. The half-life of the drug increased by its niosomal entrapment of the drug and also prolonged its circulation and its metabolism altered. If mice bearing S-180 tumor is treated with niosomal delivery of this drug it was observed that their existence increased and the rate of proliferation of sarcoma decreased. Methotrexate entrapped in niosomes if administered intravenously to S-180 tumour bearing mice results in total regression of tumour and also higher plasma levels and slower elimination[93].

2. **To Reticulo-Endothelial System (RES)-**
   The vesicles preferentially occupy RES cells. It is known as 'Opsonin' due to circulating serum factors, which mark them for clearance. However, such a localized accumulation of drugs has been exploited in the treatment of animal tumours known to metastasize the liver and spleen and in parasitic infestation[94].

3. **To Organs Other Than Reticulo-Endothelial System (RES)-**
   Through the use of antibodies, the transport mechanism can be directed to specific locations in the body. Immunoglobulins tend to affect the lipid surface and thus provide a convenient means of attacking the drug carrier. Many cells have the intrinsic ability to recognize and bind to specific carbohydrate determinants and this property can be used to target the delivery system to specific cells[95].

Conclusion:

Niosomes are a drug delivery system which may be used for controlled, sustained and targeted delivery of drugs. They can be used to encapsulate drugs of natural origin, enzymes, peptides, genes, vaccines, anti-cancer and all varieties of drugs used as promising drugs carriers to attain higher bioavailability and targeting properties and for reducing the toxicity and side effects. While ionic drug carriers are relatively toxic and unsuitable, niosome carriers are safer and do not require special conditions for niosome handling and storage. Nonionic surfactant vesicles alter plasma clearance kinetics, tissue distribution, metabolism and cellular interactions of drugs. Niosomes play a very important and key role in various types of drug deliveries; like targeting, topical, ophthalmic and parenteral. Niosomes are useful in bright future for pharma industries. Niosomes play a very important and important role in various kinds of drug delivery. Targeted, topical, ophthalmic, parenteral, etc. Niosomes help the pharmaceutical industry have a bright future.

References:

1. [1] Khandare JN, Madhavi G, Tamhankar BM. Niosomes-Novel Drug Delivery System. Eastern Pharmacist. 1994;37:61-.
2. [2] Biju SS, Talegaonkar S, Mishra PR, Khar RK. Vesicular systems: an overview. Indian journal of pharmaceutical sciences. 2006;68(2).
3. [3] Chien YW, Lin S. Optimisation of treatment by applying programmable rate-controlled drug delivery technology. Clinical pharmacokinetics. 2002 Dec;41(15):1267-99.
4. [4] Biju SS, Talegaonkar S, Mishra PR, Khar RK. Vesicular systems: an overview. Indian journal of pharmaceutical sciences. 2006;68(2).
5. [5] Vyas SP, Khar RK. Controlled drug delivery concepts and advances. vallabh prakashan. 2002;1:411-47.
6. [6] Indhu PK, Garg A, Anil KS, Aggarwal D. Vesicular system in ocular drug delivery. Indian J Pharm Sci. 2004;269:1-4.
7. [7] Kamboj S, Saini V, Magon N, Bala S, Jhawat V. Vesicular drug delivery systems: a novel approach for drug targeting. International journal of drug delivery. 2013 Apr 1;5(2):121-30.

8. [8] Rogerson AC, Cummings J, Willmott N, Florence AT. The distribution of doxorubicin in mice following administration in niosomes. Journal of pharmacy and pharmacology. 1988 May;40(5):337-42.
9. [9] Keshav J. NIOSOMES AS APOTENTIAL CARRIER SYSTEM: A REVIEW. International Journal of Pharmaceutical, Chemical & Biological Sciences. 2015 Oct 1;5(4).
10. [10] Handjani-Vila RM, Ribier A, Rondot B, Vanlerberghie G. Dispersions of lamellar phases of non-ionic lipids in cosmetic products. International journal of cosmetic Science. 1979 Oct 1;1(5):303-14.
11. [11] Reddy BS, Padman JS, Santosh V. Niosomes as nanocarrier systems: a review. International Journal of Pharmaceutical Sciences and Research. 2012 Jun 1;3(6):1560.
12. [12] Muzzalupo R, Tavano L. Niosomal drug delivery for transdermal targeting: recent advances. Res. Rep. Transdermal Drug Deliv. 2015 Jul 29;4:23-33.
13. [13] Abdelkader H, Alani AW, Alany RG. Recent advances in non-ionic surfactant vesicles (niosomes): self-assembly, fabrication, characterization, drug delivery applications and limitations. Drug delivery. 2014 Mar 1;21(2):87-100.
14. [14] Azmin MN, Florence AT, Handjani-Vila RM, Stuart JF, Vanlerberghe G, Whittaker JS. The effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. Journal of pharmacy and pharmacology. 1985 Apr;37(4):237-42.
15. [15] Sahin NO. Niosomes as nanocarrier systems. Nanomaterials and nanosystems for biomedical applications. 2007:67-81.
16. [16] Moghassemi S, Hadjizadeh A. Nano-niosomes as nanoscale drug delivery systems: an illustrated review. Journal of controlled release. 2014 Jul 10;185:22-36.
17. [17] Devi SG, Udupa N. Niosomal sumartriptan succinate for nasal administration. Indian Journal of Pharmaceutical Sciences. 2000;62(6):479.
18. [18] Makeshwar KB, Wasankar SR. Niosome: a novel drug delivery system. Asian J. Pharm. Res. 2013 Jan;3(1):16-20.
19. [19] Nasir A, Harikumar SL, Amanpreet K. Niosomes: An excellent tool for drug delivery. international journal of research in pharmacy and chemistry. 2012;2(2):479-87.
20. [20] Alsarra IA, Bosela AA, Ahmed SM, Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. European journal of pharmaceutics and biopharmaceutics. 2005 Apr 1;59(3):485-90.
21. [21] Arunothayanun P, Uchegbu IF, Florence AT. Properties of polyhedral niosomes. Pharm. Res. 1996;13:159.
22. [22] Hu C, Rhodes DG. Proniosomes: a novel drug carrier preparation. International journal of pharmaceutics. 1999 Aug 5;185(1):23-35.
23. [23] Blazek-Welsh AI, Rhodes DG. Maltodextrin-based proniosomes. Aaps Pharmsci. 2001 Mar;3(1):1-8.
24. [24] Yoshioka T, Sternberg B, Florence AT. Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60 and 80) and a sorbitan triester (Span 85). International journal of pharmaceutics. 1994 Apr 25;105(1):1-6.
25. [25] Handjani-Vila RM, Ribier A, Rondot B, Vanlerberghie G. Dispersions of lamellar phases of non-ionic lipids in cosmetic products. International journal of cosmetic Science. 1979 Oct 1;1(5):303-14.
26. [26] Jothy MA, Shanmuganathan S. An overview on niosome as carrier in dermal drug delivery. Journal of pharmaceutical sciences and research. 2015 Nov 1;7(11):923.
27. [27] Baillie AJ, Coombs GH, Dolan TF, Laurie J. Non-ionic surfactant vesicles, niosomes, as a delivery system for the anti-leishmanial drug, sodium stibogluconate. Journal of pharmacy and pharmacology. 1986 Jul;38(7):502-5.
28. [28] Azmin MN, Florence AT, Handjani-Vila RM, Stuart JF, Vanlerberghe G, Whittaker JS. The effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. Journal of pharmacy and pharmacology. 1985 Apr;37(4):237-42.
29. [29] Sankhyan A, Pawar P. Recent Trends in Niosome as Vesicular DrugDelivery System. Journal of Applied Pharmaceutical Science. 2012 Jun 30(Issue):20-32.
30. [30] Rogerson AC, Cummings J, Willmott N, Florence AT. The distribution of doxorubicin in mice following administration in niosomes. Journal of pharmacy and pharmacology. 1988 May;40(5):337-42.
31. [31] Mayer LD, Bally MB, Hope MJ, Cullis PR. Uptake of antineoplastic agents into large unilamellar vesicles in response to a membrane potential. Biochimica et Biophysica Acta (BBA)-Biomembranes. 1985 Jun 27;816(2):294-302.
32. [32] Singh G, Dwivedi H, Saraf SK, Saraf SA. Niosomal delivery of isoniazid-development and characterization. Tropical journal of pharmaceutical research. 2011;10(2).
33. [33] Lohumi A. A novel drug delivery system: niosomes review. Journal of drug delivery and therapeutics. 2012 Sep 15;2(5).
34. [34] Madhav NV, Saini A. Niosomes: a novel drug delivery system. International journal of research in pharmacy and chemistry. 2011;1(3):498-511.
35. [35] Arunachalam A, Jeganath S, Yamini K, Tharangini K. Niosomes: a novel drug delivery system. International journal of novel trends in pharmaceutical sciences. 2012 Jan 10;2(1):25-31.
36. [36] Pravinagurjar N, Chouksey S. Niosome: a promising pharmaceutical drug delivery. Int J Pharm Drug Anal. 2014 May 12;2(5):425-31.
37. [37] Shakya V, Bansal BK. Niosomes: a novel trend in drug delivery. International journal of research and Development in Pharmacy and Life Sciences. 2014;3(4):1036-41.
38. [38] Kazi KM, Mandal AS, Biswas N, Guha A, Chatterjee S, Behera M, Kuotsu K. Niosome: a future of targeted drug delivery systems. Journal of advanced pharmaceutical technology & research. 2010 Oct;1(4):374.

39. [39] Keshav J. NIOSOMES AS APOTENTIAL CARRIER SYSTEM: A REVIEW. International Journal of Pharmaceutical, Chemical & Biological Sciences. 2015 Oct 1;5(4).
40. [40] Sarker A, Shimu IJ, Alam SA. Niosome: as dermal drug delivery tool. IOSR Journal of Pharmacy And Biological Sciences. 2015;10(2):73-9.
41. [41] Nasir A, Harikumar SL, Amanpreet K. Niosomes: An excellent tool for drug delivery. international journal of research in pharmacy and chemistry. 2012;2(2):479-87.
42. [42] Yoshida H, Lehr CM, Kok W, Junginger HE, Verhoef JC, Bouwstra JA. Niosomes for oral delivery of peptide drugs. Journal of controlled release. 1992 Jul 1;21(1-3):145-53.
43. [43] Dwivedi C, Sahu R, Tiwari SP, Satapathy T, Roy A. Role of liposome in novel drug delivery system. Journal of drug delivery and therapeutics. 2014 Mar 14;4(2):116-29.
44. [44] Biswal S, Murthy PN, Sahu J, Sahoo P, Amir F. Vesicles of non-ionic surfactants (niosomes) and drug delivery potential. International journal of pharmaceutical sciences and nanotechnology. 2008 May 31;1(1):1-8.
45. [45] Rastogi B, Nagaich U, Jain DA. Development and characterization of non-ionic surfactant vesicles for ophthalmic drug delivery of diclofenac potassium. Journal of Drug Delivery and Therapeutics. 2014 Jun 23:1-6.
46. [46] CA H. Dolan TF, Coombs GH, Baillie AJ. Vesicular system (niosomes and liposomes) for delivery of sodium stibogluconate in experimental murine visceral leishmaniasis. J Pharm Pharmacol. 1988;40:161-65.
47. [47] Gandhi M, Sanket P, Mahendra S. Niosomes: novel drug delivery system. International Journal of Pure & Applied Bioscience. 2014;2(2):267-74.
48. [48] Akhilesh D, Bini KB, Kamath JV. Review on span-60 based non-ionic surfactant vesicles (niosomes) as novel drug delivery. International journal of research in pharmaceutical and biomedical sciences. 2012 Mar;3(1):6-12.
49. [49] Arunachalam A, Jeganath S, Yamini K, Tharangini K. Niosomes: a novel drug delivery system. International journal of novel trends in pharmaceutical sciences. 2012 Jan 10;2(1):25-31.
50. [50] Tangri P, Khurana S. Niosomes: Formulation and evaluation. International Journal. 2011;2229:7499.
51. [51] Jaiswal PK, Kesharwani S, Kesharwani R, Patel DK. Ethosome: A new technology used as topical & transdermal delivery system. Journal of Drug Delivery and Therapeutics. 2016 May 15;6(3):7-17.
52. [52] Vadlamudi HC, Sevukarajan M. Niosomal drug delivery system-a review. Indo American Journal of Pharmaceutical Research. 2012;2(9).
53. [53] Muzzalupo R, Tavano L. Niosomal drug delivery for transdermal targeting: recent advances. Res. Rep. Transdermal Drug Deliv. 2015 Jul 29;4:23-33.
54. [54] Singh S. Niosomes: A role in targeted drug delivery system. International Journal of Pharmaceutical Sciences and Research. 2013 Feb 1;4(2):550.
55. [55] Shirsand SB, Keshavshetti GG. Recent advances in niosomal drug delivery—A review. Res. J. Life Sci. Bioinform. Pharm. Chem. Sci. 2019;3:514-31.
56. [56] Kalra N, Jeyabalan G. Niosomes: A versatile drug delivery system. Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences. 2016;2(4):44-54.
57. [57] Bhat MI, Ganesh NS, Majeed T, Chandy V. Niosomes a controlled and novel drug delivery system: A brief review. World journal of Pharmaceutical sciences. 2019;3(8):481-97.
58. [58] Sharma D, Ali AA, Aate JR. Niosomes as novel drug delivery system. PharmaTutor. 2018 Mar 1;6(3):58-65.
59. [59] Sudheer P, Kaushik K. Review on niosomes-a novel approach for drug targeting. Journal of Pharmaceutical Research. 2015 Mar 1;14(1):20-5.
60. [60] Usman MR, Ghuge PR, Jain BV. Niosomes: a novel trend of drug delivery. European Journal of Biomedical and Pharmaceutical Sciences. 2017;4(7):436-42.
61. [61] Kazi KM, Mandal AS, Biswas N, Guha A, Chatterjee S, Behera M, Kuotsu K. Niosome: a future of targeted drug delivery systems. Journal of advanced pharmaceutical technology & research. 2010 Oct;1(4):374.
62. [62] Keservani RK, Sharma AK, Ayaz MD, Kesharwani RK. Novel drug delivery system for the vesicular delivery of drug by the niosomes. International Journal of Research in Controlled Release. 2011;1(1):1-8.
63. [63] Shalin C, Nair SP, Shijila P. Effect of Surfactants And Cholesterol On Physical Properties of BCS Class 2 Drug Loaded Niosomes. International Journal of Applied Pharmaceutical And Biological Research. 2017;2(6):8-14.
64. [64] Malhotra M, Jain NK. Niosomes as drug carriers. Indian Drugs-Bombay-. 1994;31:81-.
65. [65] Manosroi A, Wongtrakul P, Manosroi J, Sakai H, Sugawara F, Yuasa M, Abe M. Characterization of vesicles prepared with various non-ionic surfactants mixed with cholesterol. Colloids and Surfaces B: Biointerfaces. 2003 Jul 1;30(1-2):129-38.
66. [66] Balasubramaniam A, Anil Kumar V, Sadasivan Pillai K. Formulation and in vivo evaluation of niosome-encapsulated daunorubicin hydrochloride. Drug development and industrial pharmacy. 2002 Jan 1;28(10):1181-93.
67. [67] Moghassemi S, Hadjizadeh A. Nano-niosomes as nanoscale drug delivery systems: an illustrated review. Journal of controlled release. 2014 Jul 10;185:22-36.
68. [68] Kopermsub P, Mayen V, Warin C. Potential use of niosomes for encapsulation of nisin and EDTA and their antibacterial activity enhancement. Food Research International. 2011 Mar 1;44(2):605-12.
69. [69] Isnan AP, Jufri M. Formulation of niosomal gel containing green tea extract (Camellia sinensis L. Kuntze) using thin-layer hydration. International Journal of Applied Pharmaceutics. 2017 Oct 1;9:38-43.
70. [70] Bini KB, Akhilesh D, Prabhakara P, Kamath JV. Development and characterization of non-ionic surfactant vesicles (niosomes) for oral delivery of lornoxicam. International Journal of Drug Development and Research. 2012;4(3):0-.

71. [71] Bansal S, Aggarwal G, Chandel P, Harikumar SL. Design and development of cefdinir niosomes for oral delivery. Journal of pharmacy & bioallied sciences. 2013 Oct;5(4):318.
72. [72] Jin Y, Wen J, Garg S, Liu D, Zhou Y, Teng L, Zhang W. Development of a novel niosomal system for oral delivery of Ginkgo biloba extract. International journal of nanomedicine. 2013;8:421.
73. [73] Bayindir ZS, Yuksel N. Characterization of niosomes prepared with various nonionic surfactants for paclitaxel oral delivery. Journal of pharmaceutical sciences. 2010 Apr 1;99(4):2049-60.
74. [74] Alsarra IA, Bosela AA, Ahmed SM, Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. European journal of pharmaceutics and biopharmaceutics. 2005 Apr 1;59(3):485-90.
75. [75] Keservani RK, Sharma AK, Ayaz MD, Kesharwani RK. Novel drug delivery system for the vesicular delivery of drug by the niosomes. International Journal of Research in Controlled Release. 2011;1(1):1-8.
76. [76] Shivahare R, Vishwakarma P, Parmar N, Yadav PK, Haq W, Srivastava M, Gupta S, Kar S. Combination of liposomal CpG oligodeoxynucleotide 2006 and miltefosine induces strong cell-mediated immunity during experimental visceral leishmaniasis. PLoS One. 2014 Apr 14;9(4):e94596.
77. [77] Nasir A, Harikumar SL, Amanpreet K. Niosomes: An excellent tool for drug delivery. international journal of research in pharmacy and chemistry. 2012;2(2):479-87.
78. [78] Girigoswami A, Das S, De S. Fluorescence and dynamic light scattering studies of niosomes-membrane mimetic systems. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2006 Jul 1;64(4):859-66.
79. [79] Rogerson A, Cummings J, Florence AT. Adriamycin-loaded niosomes: drug entrapment, stability and release. Journal of microencapsulation. 1987 Jan 1;4(4):321-8.
80. [80] Rogerson AC, Cummings J, Willmott N, Florence AT. The distribution of doxorubicin in mice following administration in niosomes. Journal of pharmacy and pharmacology. 1988 May;40(5):337-42.
81. [81] Louis D, Mahmoud K, Mohamed M, Ibrahim A. An overview on niosomes: a drug nanocarrier. Drug Des Intellect Prop Int J. 2018:143-51.
82. [82] Kauslya A, Borawake PD, Shinde JV, Chavan RS. Niosomes: A Novel Carrier Drug Delivery System. Journal of Drug Delivery and Therapeutics. 2021 Jan 15;11(1):162-70.
83. [83] Khan R, Irchhaiya R. Niosomes: a potential tool for novel drug delivery. Journal of pharmaceutical investigation. 2016 Jun;46(3):195-204.
84. [84] Stafford S, Ballie AJ, Florence AT. Drug effects on the size of chemically defined non-ionic surfactant vesicles. J. Pharm. Pharmacol. 1988;40:26.
85. [85] Hu C, Rhodes DG. Proniosomes: a novel drug carrier preparation. International journal of pharmaceutics. 1999 Aug 5;185(1):23-35.
86. [86] Uchegbu IF, Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. International journal of pharmaceutics. 1998 Oct 15;172(1-2):33-70.
87. [87] CA H. Dolan TF, Coombs GH, Baillie AJ. Vesicular system (niosomes and liposomes) for delivery of sodium stibogluconate in experimental murine visceral leishmaniasis. J Pharm Pharmacol. 1988;40:161-65.
88. [88] Nasseri B, Florence AT. Some properties of extruded non-ionic surfactant micro-tubes. International journal of pharmaceutics. 2003 Mar 18;254(1):11-6.
89. [89] OZER A, Hincal AA, Bouwstra JA. A novel drug delivery system-nonionic surfactant vesicles.
90. [90] Arunothayanun P, Bernard MS, Craig DQ, Uchegbu IF, Florence AT. The effect of processing variables on the physical characteristics of non-ionic surfactant vesicles (niosomes) formed from a hexadecyl diglycerol ether. International journal of pharmaceutics. 2000 May 15;201(1):7-14.
91. [91] Homaei M. *Preparation and characterization of giant niosomes* (Master's thesis).
92. [92] Kazi KM, Mandal AS, Biswas N, Guha A, Chatterjee S, Behera M, Kuotsu K. Niosome: a future of targeted drug delivery systems. Journal of advanced pharmaceutical technology & research. 2010 Oct;1(4):374.
93. [93] Chandraprakash KS, Udupa N, Umadevi P, Pillai GK. Formulation and evaluation of Methotrexate niosomes. Indian Journal of Pharmaceutical Sciences. 1992;54(5):197-200.
94. [94] Malhotra M, Jain NK. Niosomes as drug carriers. Indian Drugs-Bombay-. 1994;31:81-.
95. [95] Gregoriadis G. Targeting of drugs: implications in medicine. The Lancet. 1981 Aug 1;318(8240):241-7.