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Nanoparticle vesicular systems: A versatile tool for drug delivery

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Abstract

The recent scientific and patented literature concluded that an increased interest in nanoparticle vesicular systems like liposomes, niosomes etc. has been shown in last few decades. A nanomaterial is a material with one or more external dimensions, or an internal structure, on the nano scale which could exhibit novel characteristics compared to the same material without nano scale features. Role of self assembeled structure as a vehicle is significant over the years. Their applications have been found for all routes of delivery. These micron and nano structures are containers loaded with drugs which are ideal for sustained and targeted release of the drug. Drug efficacy depends on the drug loaded into the vehicle, temperature, drug solubility, pH, release characteristics, additives and most significantly, the vehicle morphology. In this review we specially focused on nano-particles (liposomes and niosomes) which can be successfully used as a drug carrier in drug delivery systems.

Key words: Nano-particles, Liposomes, Niosomes.

Introduction

Drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bio-conjugate chemistry and molecular biology to minimize drug degradation, to prevent harmful side-effects. To increase drug bioavailability and fraction of the drug accumulated in the required zone various drug delivery and drug targeting systems are currently under development. Among drug carriers one can name soluble polymers, micro

particles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Colloid is a system in which finely divided particles, which are approximately 10 to 10,000 angstroms in size, are dispersed within a continuous medium in a manner that prevents them from being filtered easily or settled rapidly. Thomas Graham (1805-69), Scottish chemist, is best known for research in diffusion in both gases and liquids that led to his formulation of Graham's law. His discovery in 1960 that certain substances (e.g., glue, gelatin, starch) pass through a semi-permeable membrane more slowly than others (inorganic salts, e.g., common salt, or sodium chloride) led him to draw a distinction between the two groups, calling the former (the slower) colloids and the later crystalloids [1]. Although there are no precise boundaries of size between the particles in mixtures, colloids or solutions, colloidal particles are usually in the range of 10^{-7}-10^{-5} cm in size [2]. The shape adopted by colloidal particles in dispersion may also influence pharmacological action [3]. This article basically emphesize on the increasing interest of various inventors and researchers in nano size colloidal systems, specially highlighting the liposomal and niosomal drug delivery.

1. Types of colloids:[2-3]

Colloid can be classified based on their affinity for solvent such as:-

1.1 Lyophilic

The particles in a lyophilic system are readily solvated, with the solvent and dispersed, even at high concentrations. In this colloid system, the disperse phase is relatively liquid, usually comprising highly complex organic substances such as starch, which readily absorb solvent, swell, and distribute uniformly through the medium.

1.2 Lyophobic

The particles resist solvation and dispersion in the solvent, and the concentration of particles is usually relatively low.

1.3 Amphiphilic

When present in liquid at low concentration, the amphiphiles exist separately and of such a size as to be subcolloidal. As concentration is increased, aggregation occurs over a narrow concentration range. The micelles lie within the size range of colloids. The number of monomers aggregates to form the micelle is known as the aggregation number.

Table 1 Types of colloids with examples

Type	**Compound**	**Amphiphile**
Anionic	Sodium lauryl sulphate	$CH_3\ (CH_2)_{11}\ OSO^-_3$
Cationic	Cetyl trimethyl ammonium bromide	$CH_3\ \ (CH_2)_{15}N^+\ (CH_3)_3$
Nonionic	Polyoxyethylene lauryl ether	$CH_3(CH_2)_{10}CH_2O(CH_2OCH_2)_{23}H$
Ampholytic	Dimethyl dodecyl ammonio	$CH_3\ \ (CH_2)_{11}N^+\ \ (CH_3)_2\ \ (CH_2)_3\ OSO^-_2$

2.1 Various Carrier Based Dosage Forms: [4]

2.1.1Nanoparticles

- Solid Lipid Nanoparticles
- Polymeric Nanoparticles
- Hydrogel Nanoparticles
- Ceramic Nanoparticles

2.1.2 Functionalized Nanocarriers
2.1.3 Liposomes & Proliposomes
2.1.4 Lipid Emulsions & Lipospheres
2.1.5 Ethosomes
2.1.6 Aquasomes
2.1.7 Niosomes & Proniosomes
2.1.8 Micro-emulsions & Microspheres.
2.1.9 Enzymosomes
2.1.10 Virosomes

3.1 Liposomes:

Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments with a diameter ranging from 25 nm to 1000 nm. According to their size, liposomes are known as Small Uni-lamellar Vesicles (SUV) (10-100 nm) or Large Uni-lamellar Vesicles (LUV) (100-3000 nm). If more than one bilayers are present, then they are referred as Multi-lamellar Vesicles (MUV). Liposomes are formed when thin lipid films or lipid cakes are hydrated and stacks of liquid crystalline bilayers become fluid and swell. During agitation hydrated lipid sheets detach and self associate to form vesicles, which prevent interaction of water with the hydrocarbon core of the bilayer at the edges.

3.2 Niosomes:

Niosomes are non-ionic surfactant vesicles and, as liposomes, are bi-layered structures. Niosomes present low production cost, greater stability, and resultant ease of storage. Niosomes are chemically stable, can entrap both lipophilic and hydrophilic drugs either in aqueous layer or in vesicular membrane and present low toxicity because of their non-ionic nature. Other advantages include flexibility in their structural constitution, improvement of drug availability and controlled delivery at a particular site, and, at last, niosomes are biocompatible, biodegradable and non-immunogenic. Niosomes are present with a range in size of 10 to 1000 nm. The colloidal drug-loaded particles consist of macromolecular materials in which drugs are dissolved, entrapped, encapsulated, and/or to which the drugs are adsorbed or attached.

4.1 Liposomes: [5-7]

Liposomes were discovered in the early 1960's by Bangham and his coworkers. They have since gained recognition in the field of drug delivery. The particle size of liposomes ranges from 20 nm to 10 μm in diameter. Liposomes vary in charge and in size depending on their manufacturing protocol and type of (phospho) lipid bilayer used. The small uni-lamellar vesicle (SUV) size range is 0.02 -0.05 μm, the large uni-lamellar vesicles (LUV) size range is greater than 0.06 μm and the multi-lamellar vesicle (MLV) size range is 0.1 – 0.5 μm. The physicochemical characteristics of the liposomes, like particle size, lamellarity, surface charge, sensitivity of pH changes and bilayer rigidity can be manipulated. Liposomes showed promising

result in the drug delivery but their applicability is limited primarily to specific use because of short half-life in blood circulation. The circulation time of liposomes in the blood stream is dramatically increased by attaching polyethylene glycol (PEG) – units to the bilayer, known as long circulating (Stealth) liposomes [12].

Liposomes are potential carrier for controlled drug release of tumours therapeutic agents and antibiotic, for gene and antisense therapy through nucleic acid sequence delivery, immunization through antigen delivery and for anti-Parkinson's. In last one decade, pharmaceutical researchers use the tools of biophysics in evaluating liposomal dosage forms. Liposomes have covered predominantly medical, albeit some non-medical areas like bioreactors, catalysts, cosmetics and ecology [6-11].

4.1.1 Types of Liposomes:

4.1.1.1 **Multilamellar vesicles** (MLV's) consist of several (up to 14) lipid layers (in an onion-like arrangement) separated from one another by a layer of aqueous solution. These vesicles are over several hundred nanometers in diameter.

4.1.1.2 **Small unilamellar vesicles** (SUV's) are surrounded by a single lipid layer and are 25-50 nm (according to some authors up to 100 nm) in diameter.

4.1.1.3 **Large unilamellar vesicles** (LUV's) are, in fact, a very heterogenous group of vesicles that, like the suvs, are surrounded by a single lipid layer. The diameter of these liposomes is very broad, from 100 nm up to cell size (giant vesicles).

4.1.2 Advantages of Liposomes:

- Liposomes are biocompatible, completely biodegradable, non-toxic, flexible and nonimmunogenic for systemic and non-systemic administrations.
- Liposomes increased efficacy and therapeutic index of drug (eg. Actinomycin-D).
- Liposomes have the ability to protect their encapsulated drug from the external environment and to act as sustained release depots (eg. Propranolol, Cyclosporin).
- Liposomes can be formulated as a suspension, as an aerosol, or in a semisolid form such as gel, cream and lotion, as a dry vesicular powder (proliposome) for reconstitution
- They can be administered through ocular, pulmonary, nasal, oral, intramuscular, subcutaneous, topical and intravenous routes.
- Liposomes supply both a lipophilic environment and aqueous "milieu interne" in one system and are therefore suitable for delivery of hydrophobic, amphipathic and hydrophilic drugs and agents.
- Liposomes could encapsulate not only small molecules but also macromolecules like superoxide dismutase, haemoglobin, erythropoietin, interleukin-2 and interferon-g.
- Liposomes reduced toxicity and increased stability of entrapped drug via encapsulation (eg. Amphotericin B, Taxol).
- Liposomes help to reduce exposure of sensitive tissues to toxic drugs.
- Alter the pharmacokinetic and pharmacodynamic property of drugs (reduced elimination, increased circulation life time).

- Flexibility to couple with site-specific ligands to achieve active targeting (Anticancer and Antimicrobial drugs).

4.1.3 Disadvantages of liposomes: [13]

- High production cost
- Leakage and fusion of encapsulated drug / molecules.
- Sometimes phospholipid undergoes oxidation and hydrolysis
- Short half-life
- Low solubility
- Less stability

Table- 2: Therapeutic applications of liposomes: [21]

Drug	**Route of administration**	**Application**	**Targeted Diseases**
Amphotericin-B	Oral delivery	Ergosterol membrane	Mycotic infection
Insulin	Oral, Ocular, Pulmonary and Transdermal delivery	Decreaase glucose level	Diabetic mellitus
Ketoprofen	Ocular delivery	Cyclo-oxygenase enzyme inhibitor	Pain muscle condition
Pentoxyfylline	Pulmonary delivery	Phosphodiesterase	Asthma
Tobramycin	Pulmonary delivery	Protein synthesis inhibitor	Pseudomonas infection, aeruginosa
Salbutamol	Pulmonary delivery	β_2- adrenoceptor antagonist	Asthma
Ketoconazole	Transdermal	Inhibit ergosterol membrane	Candida-albican's
Levonogesterol	Transdermal	Rhamnose receptor	Skin disorder
Ibuprofen	Oral delivery	Chemoreceptor, free nerve ending	Rheumatoid arthritis
Idoxiuridine	Ocular delivery	DNA-synthesis, Protein synthesis	Herpex-simplex, Keratitis
Adrenaline	Ocular delivery	Decreases intra-ocular pressure	Glucoma, Conjectivitis
Triamcinolone	Ocular delivery Transdermal	Inhibition of prostaglandin	Anti-inflammatory

5.1 Niosomes:

Niosomes are non-ionic surfactant based liposomes. They are mostly formed by cholesterol incorporation as an excipient. Niosomes have more penetrating capability than

various preparations of emulsions. They are structurally similar to liposomes in having a bilayer, however, the materials used to prepare niosomes makes them more stable and thus niosomes offer many more advantages over liposomes. Liposomes which may be used as carriers for administering both lipophllic and amphiphilic drugs have certain limitations. Liposomes are phospholipid vesicles which are very much prone to oxidation and in turn are susceptible to destabilization and degradation. Thus, liposomes require special handling and storage. Any change in surface charge of liposomes results in altered physical properties which in turn may render them toxic [14]. Niosomes are a better alternative to liposomes; these are vesicles containing non-phospholipid constituents. Niosomes are lamellar structures that are microscopic in size. They constitute of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media [15]. The surfactant molecules tend to orient themselves in such a way that the hydrophilic ends of the non-ionic surfactant point outwards, while the hydrophobic ends face each other to form the bilayer. These contain non-ionic surfactants which may or may not be incorporated with cholesterol and various other lipids. The studies have shown that niosomes *in-vivo* behaves like liposomes but increases the circulation of entrapped drug and modifying organ distribution and metabolic stability [16]. Niosomes were first reported in the seventies as a feature of cosmetic industry but have since been studied as drug targeting agents. Niosomes are chemically stable, biodegradable, biocompatible and can encapsulate large amount of active drug in approximately less volume of vesicles [15] and also are cost efficient. Thus, making them an appropriate choice as a drug carrier over liposomes. Niosomes prepared by thin layer evaporation method and physico-chemically characterized [17] are less toxic and provide precise control over the active availability of active drug at the stratum corneum as compared to other classical formulations of stratum corneum [18]. Niosomes are prepared to decrease the release of active drug which results into sustained release profile, less toxicity and drug targeting [19]. The size of niosomes increases on the incorporation of entrapped drug which is a result of interaction of solute with surfactant head groups, increasing charge and mutual repulsion of the surfactant bilayer and thus increasing the size of vesicles [20].

The ultimate identity of any niosomal system and hence its properties are determined by factors listed below:

- choice of main surfactant
- nature of membrane additives
- size reduction techniques
- addition of kinetic energy
- nature of drug
- hydration temperature

All these variables must be carefully controlled in the design of a niosomal drug delivery system.

5.1.1 **Niosomes: Salient Features [9]**

- Niosomes entrap solute in manner analogues to liposomes
- Niosomes are osmotically active and stable as well as they increase the stability of entrapped drug.
- Handling and storage of surfactants require no special conditions.
- Niosome possesses an infrastructure consisting of hydrophobic and hydrophilic moieties together, and as a result can accommodate drug molecules with wide range of solubility.

- Niosomes exhibit flexibility in their structural characteristics (composition, fluidity, size) and can be designed to desired situation.
- Niosomes improved the oral bioavailability of poorly soluble drugs and enhance skin penetration of drugs.
- They can be made to reach the site of action by oral, parental as well as topical routes.
- They allow their surface for attachment of hydrophilic group and can incorporate hydrophobic moiety in bilayer to bring about change in the in vivo behaviour of niosomes.
- Niosomes dispersion in aqueous phase can be emulsified in non-aqueous phase to regulate delivery rate of drug and administer niosomal vesicles in external non-aqueous phase.
- Niosomes surfactants are biodegrable, biocompatible and non-immunogenic.

Niosomes improve the therapeutic performance of the drug molecules by delayed clearance from the circulation; protect the drug from biological environment and restricting effects to target cells.

5.1.2 **Method of preparation:**

a) Ether injection method [22]

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, the diameter of the vesicle ranges from 50 to 1000 nm.

b) Hand shaking method (Thin film hydration technique) [23]

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.

c) Sonication [23]

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

d) Micro fluidization [24]

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 [24]

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

f) Reverse phase evaporation technique (REV) [25]

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)

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 300 mM 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 minutes to give niosomes.

h) The "bubble" method [25]

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 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.

5.1.3 Advantages of Niosomes:

- The vesicle suspension is water–based vehicle. This offers high patient compliance in comparison with oily dosage forms.
- They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.
- The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
- The vesicles may act as a depot, releasing the drug in a controlled manner.
- They are osmotically active and stable, as well as they increase the stability of entrapped drug.
- The surfactants are biodegradable, biocompatible and non-immunogenic.
- They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.

- They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.
- Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase

5.1.4 Limitation of niosomes:

- The chemical stability of niosomes and relatively low cost of materials, that forms them, makes niosomes more attractive than liposomes for industrial manufacturing.
- Like liposomes, aqueous suspensions of niosomes may exhibit aggregation, fusion, leaking of entrapped drugs, or hydrolysis of encapsulated drugs, thus limiting the shelf life of the dispersion.
- The traditional method for producing niosomes or liposomes involves drying the lipid to a thin film from organic solvent, and then hydrating this film with the aqueous solvent of choice. The resulting multilamellar vesicles can be further processed by sonication, extrusion, or other treatments to optimize drug entrapment. All of these methods are time consuming and may involve specialized equipment. The thin film approach allows only for a predetermined lot size so material is often wasted if smaller quantities are required for a particular application or dose.

Table- 3 Comparison of various aspects of particulate carriers and their applications

Sr. No.	Carrier System	Size Range	Features	Method of Preparation	Application
1	Liposomes	25nm-100μm	microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments	.Mechanical dispersion .solvent dispersion .detergent removal etc.	-In cancer, malaria, AIDS, lung therapies. -As radiodiagnostic carrier -As an immunological adjuvant
2	Niosomes	10 to 1000 nm	non-ionic surfactant vesicles are bilayered structures	Ether injection, Sonication, REV, microfuidization etc.	-Targeting of bioactive agents -Delivery of peptide drug -In diseases like neoplasia, leishmaniasis

6.1 Characterization of liposomes and niosomes: [9]

a) Vesicle diameter

Niosomes are spherical in shape and their diameter can be determined by using light microscope, photon correlation spectroscopy, freeze-fracture electron microscopy, SEM and TEM.

b) Entrapment efficiency

After preparation of niosomes, the entrapped drug is separated by dialysis, centrifugation, gel chromatography or filtration. The drug encapsulated in niosomes is determined by complete destruction of vesicles using 50% propane or 0.1% triton x 100 or unentrapped drug can be subtracted from total amount of drug. The entrapment efficiency is expressed by the following formula.

$$\text{Entrapment efficiency} = \frac{\text{Amount entrapped}}{\text{Total amount of drug}} \times 100$$

Although dialysis and gel chromatography are the common procedures, the former is rather time consuming and gel chromatography causes' dilution of the dispersion.

c) In vitro release

In vitro release can be determined by dialysing the niosomal suspension against buffer at definite temperature and determining the content of dialysate.

d) Stability studies

Stability of a formulated product on shelf is an important factor in successful development of a dosage form. Very few reports are available on shelf storage of niosomal preparations. The stability studies of prepared niosomes are performed at accelerated conditions of humidity and temperature and drug content is noted.

6.1.1 In vivo behavior: [9]

In vivo niosomes have been found equiactive to liposomes in improving the therapeutic performance of drugs and their distribution in body follows the pattern of other colloidal drug delivery systems. Although tissues of extravasations: liver, lung, spleen and bone marrow are responsible for disposition of major part of niosome. Yet their level in liver is always significantly higher due to the natural vectoring powers. Variation in size also influences the pattern of niosomes residence in lung due to alveolar retention and effect of alveolar phagocytic cells, while small sized vesicles, which can pass through, penetrate in liver sinusoidal epithelium, and have better access to spleen.

It appears that, like liposomes, niosomes are also taken up intact by liver, and break down substantially to release the free drug, which eventually renders the circulation, and maintain the plasma drug level. The effect of two doses of niosomal sodium stibogluconate given on successive days was additive, indicating that liver might act as depot of drugs.Parthasarthi et al. found niosomes to be stable in plasma. However, non-ionic surfactants in higher concentration delipidize the low density lipoproteins.

7.1 Recent developments:

Hunter and Dollan et al., 1988, on the basis of study done by Baillie et al. in 1986 experimented the animal model of vesicular systems (Niosomes and Liposomes) for delivery of anti-leishamnial drug sodium stibogluconate in experimental murine visceral leishmaniasis. [26]

A patent no. US 4,830,857 entitled "Cosmetic and pharmaceutical composition containing niosomes and a water-soluble polyamide, and a process for preparing these compositions" was

obtained by Handjani *et al.* in 1989 [27]. In which they described composition consisting of dispersion in an aqueous medium D of noisome and/or liposome spherules.

Katare et al., 1991, prepared and evaluated proliposome of indomethacin for oral administration. They concluded that homogenous size distribution and higher entrapment efficiency were derived from effervescent granule based proliposomes. It was also observed that the effervescent granule based liposomal products exhibited improved *in vivo* performace with reference to their cytoprotective and anti-inflammatory activities [28].

The interaction of vesicles based on phospholipids and non-ionic surfactants with hairless mouse skin was observed and studied by Guenin and Zatz in 1995. They observed that phospholipid vesicles increased water permeation rate (WPR) at pH 2 but no significant difference in WPR was at pH 5. While the effect of non-ionic surfactants vesicles were of much smaller magnitude at pH-2 [29].

Dufes et al., 2000, prepared niosomes and polymeric chitosan based vesicle bearing transferrin and ligands for drug targeting. They reported that glucose bearing vesicles bound Con A gold (concavavalin A Gold) to their surface and chitosan based vesicles were taken up by A431 cells, and transferrein enhanced that uptake [30].

The suitable liposome and niosome encapsulated drug delivery system for rifampicin was designed and evaluated for in vitro and in vivo behavior by Kamath et al. in 2000. They concluded that encapsulation retarded the removal of the drug from circulation compared to free drug due to slow drug release into systemic circulation. A five-fold increase in the area under plasma rifampicin concentration time curve for niosomal rifampicin as compared to free drug indicated better bioavailability of encapsulated drug [31].

Fang et al., 2001, studied the effect of liposomes and niosomes on skin permeation of enoxacin. They observed that delivery of enoxacin across skin was increased when encapsulated in vesicles. They also observed that inclusion of cholesterol improved the stability of enoxacin but addition of negative charge reduced the stability of niosomes [32].

Ribier et al., 2001, obtained a patent no. US 6,319,508 entitled “Anhydrous cosmetic composition containing a fatty phase and pro-liposomes”. They prepared an anhydrous cosmetic makeup composition contained in addition to a fatty phase formed from oils, fatty bodies and surfactants, and optionally waxes, a vesicular lipidic phase that contained at least one ionic or non-ionic amphiphilic lipid and optionally additives [33].

Dhoot and Wheatley prepared microencapsulated liposomes for controlled delivery to modulate drug release and eliminate the burst effect in 2002. They observed there was no burst from liposomes encapsulated in Ba^{2+} - Alginate which indicated that cross linking ions could affect release of entrapped protein. They concluded that release from microencapsulated liposomes was much faster than that of free liposomes [34].

The study based on the effect of cholesterol content and surfactant HLB on vesicle properties of niosomes encapsulated Primaquine phosphate was carried out by Agarwal, et al. in 2003. They

concluded that the lower the HLB, the smaller the initial size of the vesicles. Entrapment efficiency was found to be increased with increasing cholesterol content in the bilayers. Mean size was found to be increased in a regular manner with increasing surfactant HLB [35].

Vyas et al., 2005, developed, non-ionic surfactant based vesicles (niosomes) for topical DNA delivery. DNA encoding hepatitis B surface antigen (HBsAg) was encapsulated in niosomes. It was observed that topical niosomes elicited a comparable serum antibody titer and endogenous cytokines levels as compared to intramuscular recombinant HBsAg and topical liposomes. The study signifies the potential of niosomes as DNA vaccine carriers for effective topical immunization. The proposed system is simple, stable and cost effective compared to liposomes [36].

Girigoswami et al., 2006, prepared niosomes from Span20, Span80, Tween20 and Tween80. Fluorescence resonance energy transfer studies have been performed in these systems to determine donor–acceptor distances. It has been found that the fluorescence resonance energy transfer efficiency is better in niosomes compared to micelles. The formation of niosomes is guided by the hydrophile–lipophile balance value of the nonionic surfactant [37].

Wei Hua et al., 2007, prepared highly stable innocuous niosome composed of only three components Span 80/PEG 400/H_2O system.. The obtained results indicate that the niosome can be stable for over one year. The niosome diameter is between 100 and 180 nm. The compositions of the system affect the preparation and properties of the niosome. But the temperature and ionic intensity do not distinctly change the stability radius [38].

Paolino et al., 2008, prepared innovative niosomal system made up of α,ω-hexadecyl-bis-(1-aza-18-crown-6) (Bola), Span 80® and cholesterol (2:5:2 molar ratio) was proposed as a topical delivery system for 5-fluorouracil (5-FU), largely used in the treatment of different forms of skin cancers. Bola-niosomes provided an increase of the drug penetration of 8- and 4-folds with respect to a drug aqueous solution and to a mixture of empty bola-niosomes with a drug aqueous solution [39].

Manosroi et al., 2008, prepared niosomes by a novel supercritical carbon dioxide fluid ($scCO_2$) technique. Niosomes by the $scCO_2$ method with 10 % (w/w) ethanol gave higher trapping efficiency (12.22 ± 0.26%) than those by the conventional chloroform film method with sonication (10.85 ± 0.24%) and the $scCO_2$ method without ethanol (8.40 ± 1.60%).. This present study has demonstrated the trapping efficiency enhancement of water-soluble compounds in niosomes by the $scCO_2$ method with 10 % (w/w) of ethanol [40].

Patel et al., 2009, prepared and evaluated the topical carbopol gel formulation containing ketoconazole encapsulated liposomes by thin film hydration technique. The prepared liposomes were incorporated into 1% carbopol gel, and the systems were evaluated for in-vitro drug release, drug retention into skin and in-vitro antifungal activity. The in-vitro permeation of ketoconazole was compared with that of plain drug gel and also with plain drug cream containing 2% w/w of ketoconazole. The release of ketoconazole from liposomal gel was much slower than from non liposomal formulations. Gel containing liposomal ketoconazole showed maximum antifungal activity after 30 hours over plain ketoconazole gel and cream formulations [41].

Bhaskaran et al., 2009, prepared niosomes of salbutamol sulphate using Span 60 as the surfactant, by different techniques as, thin film hydration, hand shaking, ether injection, lipid layer hydration and transmembrane pH gradient method. The drug encapsulation efficiency varied from 62 % to 87 %. In vitro drug release studies was carried out and formulation exhibited retarded release for 24 h. Transmembrane pH gradient method was found to be most satisfactory which released 78.4 % of drug in 24 h. This formulation was lyophilized and characterized by infrared spectroscopy. Tissue distribution studies in albino rats and bio- availability studies in rabbits were carried out [42].

Srinivas et al., 2010, In their study developed and optimized niosomal formulation of aceclofenac in order to improve its bioavailability. In their evaluation study the effects of the varying composition of non ionic surfactant and cholesterol on the encapsulation efficiency, particle size and drug release was studied. Further, release of the drug from the most satisfactory formulation was evaluated through dialysis membrane to get the idea of drug release. The mechanism of dug release was governed by Peppas model [43].

Conclusion

Vesicular systems have been gaining a lot of interest of various researchers and scholars these days. It is because of their advantages of controlled and sustained release action, stability and versatility as a drug carrier. These carrier systems have immense scope in future, especially in the area of dermatitis, periodontitis, cosmetics etc. The other future area which can be focused for research might be some other types of new nanoparticles systems like proniosomes, proliposomes, ethosomes, enzymosomes, virosomes etc.

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