NIOSOMAL DRUG DELIVERY SYSTEM-A REVIEW
Harini Chowdary Vadlamudi, 1 M. Sevukarajan 1

1Sree Vidyanikethan College of Pharmacy, A.Rangampet, Tirupati, 517102, Andhra Pradesh, India.

ARTICLE INFO

Article history
Received 15 Aug 2012
Available online 30 Sep 2012

Keywords
Niosomes, Surfactant, Amphiphilic, Vesicles

ABSTRACT
Niosomes are microscopic non-ionic surfactant vesicles formed by the self-assembly of non-ionic surfactant. Niosomal drug delivery poses a promising novel drug delivery approach. Niosomes and liposomes have similar physical properties but differ in the chemical nature. Niosomal vesicle is formed by non-ionic surfactants whereas liposomal vesicles of lipids. Niosomes are superior to liposomes because of higher chemical stability of surfactants than lipids. This review article focuses on the concept of niosomes, advantages and disadvantages, composition, method of preparation, factors influencing the niosomal formulation and characterization, application of niosomes. Niosomes can be utilized in the treatment of several diseases like Psoriasis, leishmaniasis, cancer, migraine, Parkinson etc. Niosomes can be used as diagnostic aid. Various methods of niosomal administration include intramuscular, intravenous, peroral and transdermal. Niosomal technology is widely used in cosmetics. Still researchers have to focus a lot on the commercial utility of niosomes in drug delivery.

Corresponding author

Harini Chowdary Vadlamudi, Dept. of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, A.Rangampet, Tirupati, 517102, Andhra Pradesh, India. Tel No: +91- 94945 98424
email: vadlamudi.harini@gmail.com

Please cite this article in press as: H C Vadlamudi, Niosomal Drug Delivery System-A Review. Indo American Journal of Pharm Research. 2012:2(9).
1. INTRODUCTION:

Niosomes are microscopic non-ionic surfactant vesicles attained by the hydration of synthetic non-ionic surfactant with or without inclusion of cholesterol. They are akin to liposomes. Both Niosomes liposomes act as active carriers of both amphiphilic and lipophilic drugs. Difference in the niosomal and liposomal system is that niosomal bilayer is formed by non-ionic surfactant where as liposomal bilayer made up of phospholipids. Niosomes are formed by the self assembly of non-ionic surfactants in aqueous media as spherical, unilamellar, bilayered, multilamellar system and polyhedral structures depending on the method used to prepare and the inverse structure in case of non-aqueous solvent. The orientation of the surfactant in niosome in hydrophilic ends exposed outwards while hydrophobic ends face each other forming bilayer of the surfactant. The size of the niosomes ranges between 10 to 1000nm. Addition of cholesterol and a small quantity of anionic surfactant for instance dicetyl phosphate stabilizes the niosomal vesicles formed by the non-ionic surfactant. Niosomes are suggested to be better than liposomes because of the higher chemical stability of surfactants than phospholipids which are easily hydrolyzed due to the ester bond and cost effective. Niosomes illustrate a promising drug delivery. Various methods of administration of niosomal formulation include intramuscular, intravenous, peroral and transdermal.

A. Advantages of Niosomes:

1. The vesicle suspension being water-based vehicle offers high patient compliance when compared to oily dosage forms.
2. Drug molecules of wide range of solubilities can be accommodated in the niosomes provided by the infrastructure consisting of hydrophilic, lipophilic and amphiphilic moieties.
3. Vesicle characteristics can be controlled by altering the composition of vesicle, size lamellarity, surface charge, tapped volume and concentration.
4. They can release the drug in sustained/controlled manner.
5. Storage and handling of surfactants oblige no special conditions like low temperature and inert atmosphere.
6. They can act as a depot formulation, thus allowing the drug release in a controlled manner.
7. They enhance the oral bioavailability of poorly soluble drugs.
8. They possess stable structure even in emulsion form.
9. Surfactants are biodegradable, biocompatible, non-toxic and non-immunogenic.
10. They are economical for large scale production.
11. They can protect the drug from enzyme metabolism.
12. They are not only osmotically stable and active but also improve the stability of entrapped drug.
13. They can enhance the permeation of drugs through skin.
14. Therapeutic concert of the drug molecules can be improved by tardy clearance from circulation.
15. They can protect the active moiety from biological circulation.
16. They can restrict the drug delivery rate as aqueous phase niosomal dispersion can be emulsified in the non-aqueous phase and thus normal vesicle can be administered in an external non-aqueous phase.

B. Disadvantages of Niosomes:

Limited shelf life of the aqueous suspensions of niosomes due to fusion, aggregation, leakage of entrapped drugs and hydrolysis of encapsulated drugs.

1. Preparation of multilamellar vesicles by extrusion, sonication method is time consuming and requires specialized equipments for processing.

2. FORMULATION OF NIOSOMES:

A. Composition:

The two main components utilized for the formulation of niosomes are:
1. Cholesterol
2. Non ionic surfactant
   1) Cholesterol: Cholesterol is used in the niosomal formulation to provide rigidity, proper shape and conformation to the niosomes. It provides stability to the vesicles.

2) Non ionic surfactant: the commonly used non ionic surfactants in the formulation of niosomes are
   - Spans - Span 20, 40, 60, 80 and 85
   - Tweens - Tween 20, 40, 60 and 80
   - Brij - Brij 30, 35, 52, 58, 72 and 76

They possess hydrophilic head and hydrophobic tail.

B. Different Classes of Surfactants Utilized in the Niosomal Formulation:

1) Ether linked:-
   Hydrophilic and hydrophobic moieties are ether linked in these surfactants\(^{11}\).
   Eg: polyoxy ethylene alkyl ethers (C\(_n\)E\(_m\)O\(_m\))

Where n- number of carbon atoms varies from 12 to 18
m- Number of polyethylene units Varies from 3 to 7

2) Dialkyl chain surfactant:-
   It has the molecular weight of 972. The molecular formula is
   \[
   \text{C}_{16}\text{H}_{33}\text{CH-O-[CH}_2\text{-CH-O]}_7\text{-H}
   \]
   \[
   \| \\
   \text{CH}_2\text{CH}_2\text{OH} \\
   | \\
   \text{C}_{12}\text{H}_{25}\text{-O}
   \]
   It is used in the sodium stibogluconate niosomal formulation\(^{12}\).

3) Ester linked surfactant:
   Hydrophilic and hydrophobic moieties are ester linked in these surfactants.

Eg: C\(_{15}\)H\(_{31}\)CO[O-CH2-CH-CH2]2-OH

| 
| OH
Molecular weight- 393
4) Sorbitan esters:

They are H-C-OH mixtures of the partial esters of sorbitol. Molecular formula is as follows

\[
\begin{align*}
\text{CH}_2 \\
\mid \\
\text{H-C-CH} \\
\mid \\
\text{R-COO-CH} \\
\mid \\
\text{H-C-OH} \\
\mid \\
\text{H-C-OOC-R} \\
\mid \\
\text{CH}_2\text{OOC-R}
\end{align*}
\]

Where R is H or an alkyl chain

5) poly-sorbates:

The structural formula of poly-sorbates is

\[
\begin{align*}
\text{CH}_2 \\
\mid \\
\text{H-C-O(CH}_2\text{-CH}_2\text{-O)}_x\text{H} \\
\mid \\
\text{(OCH-CH}_2\text{-O-C-H)} \\
\mid \\
\text{H-C-O(CH}_2\text{-CH}_2\text{-O)}_y\text{H} \\
\mid \\
\text{CH}_2\text{-O(CH}_2\text{-CH}_2\text{-O)}_z\text{OCR}
\end{align*}
\]

\[n = x + y + z + 2\]

R- alkyl chain

Polysorbates are used in the niosomal entrapped methotrexate pharmacokinetics studies.

C. Methods of Preparation:

The method of preparation influences the size, size distribution and number of bilayers, entrapment efficiency of the aqueous phase and the membrane permeability of the vesicles.

a) Ether injection method
b) Hand shaking method/thin film hydration method

c) Micro fluidization

d) Multiple membrane extrusion method

e) Reverse phase evaporation technique

f) Sonication

g) Transmembrane \( p_H \) gradient drug uptake

h) The bubble method

i) Formation from pro-niosomes

a) Ether injection method:-

This method involves the introduction of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The ether solution with surfactant is injected into an aqueous solution of material through the 14-guage needle. Single layered needles are formed due to the vaporization of ether\(^{13}\). The diameter of the vesicle varies from 50-1000nm depending upon the conditions used.

b) Hand shaking method/thin film hydration method:-

Surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl ether or chloroform or menthol. Using the rotary flash evaporator, the organic solvent is removed at room temperature of 20ºc which leaves a thin layer of solid mixture on the wall of the flask. The dried surfactant film is then rehydrated with aqueous solution of drug at the temperature of surfactants used for specified period of time (time of hydration) with gentle agitation. Multilamellar niosomes are formed by this method\(^{14}\). Thermo sensitive niosomes are prepared by evaporating organic solvent at 60ºC leaving a thin film on the wall of rotary flask evaporator and then the aqueous solution with drug is added slowly by shaking at room temperature followed by sonication.

c) Micro fluidization:-

Micro fluidization is the technique which forms unilamellar niosomes of defined size distribution, uniformity and better reproducibility. The principle involved in this technique is submerged jet principle in which two fluidized streams interact with each other at ultra high velocities, in the micro channels within the interaction chamber. The impingements of thin liquid sheet along with common front are arranged such that the energy supplied remains same within the area of niosomes formation. It results in the formation of niosomal vesicles of greater uniformity, smaller size and better reproducibility\(^{15}\).

d) Multiple membrane extrusion method:-

Desired size of the vesicles can be prepared by this method. It can be achieved by placing polycarbonate membranes in series up to 8 passages. Thin film of the surfactant, cholesterol and dicetyl phosphate mixture is made by evaporation. The film is then rehydrated with the aqueous solution containing drug\(^{16}\). The resultant solution is extruded through poly carbonate membrane (0.1\(\mu\)m nucleophore) by using C\(_{16}\)G\(_{12}\).

e) Reverse phase evaporation technique:-

Cholesterol and surfactant in the ratio of 1:1 are dissolved in the mixture of ether and chloroform. Aqueous drug solution is added to this. The two phases are sonicated at 4-5ºc. Small amounts of phosphate buffered saline (PBS) are added to the clear gel and sonicate it again. The organic phase is removed at 40ºc and lower pressure.
The viscous niosomal suspension is further diluted with PBS and heated on a water bath at 60ºc for 10min to yield niosomes 17.

f) Sonication:-

The production of vesicles by the sonication of solution is described by cable. An aliquot of buffer solution containing drug is added to the mixture of surfactant/cholesterol mixture in a 10ml glass vial. Then the mixture is subjected to sonication at 60ºc for 3min in a sonicator with titanium probe to produce niosomes 18.

g) Transmembrane P^H gradient drug uptake:

Surfactant and cholesterol are dissolved in chloroform in a round bottomed flask. The solvent evaporation is done under reduced pressure to get the thin film on the wall of the flak. The film is then hydrated with 300mm citric acid (P^H 4.0) by vortex mixing. It results in the formation of multilamellar vesicles. Then they are frozen and thawed 3 times and later sonicated to get niosomes. To this niosomal suspension, aqueous drug solution is added and vortexed. To maintain the P^H between 7.0-7.2, phosphate buffer is used. Then the mixture is heated at 60ºc for 10 minutes to yield niosomes 19.

h) The bubble method:-

It is the novel technique used for the one step preparation of niosomes without the use of organic solvents. The bubbling unit has round-bottomed flask with three necks positioned in water bath to control the temperature. In the first neck, water cooled reflux; thermometer in the second and nitrogen supply through the third neck is provided. Cholesterol and surfactant are dispersed in P^H 7.4buffer at 70ºc. The dispersion is mixed for 15 seconds using high shear homogenizer. Then nitrogen gas is bubbled at 70ºc immediately 20.

I) Formation of niosomes from pro-niosomes:-

Water or saline at 80ºc is added in a screw capped vial and proniosomal powder is filled in it. Then it is mixed by vortexing followed by agitation for 2min. It results in the formation of niosomal suspension 21. The niosomes are formed by the addition of aqueous phase at T >> T_m and brief agitation.

T= temperature

T_m=mean phase transition temperature

D. Sizing of Niosomes:

The size ranges of niosomes have a great effect on their in-vitro and in-vivo fate. Thus, after the hydration stage of niosomes, sizes reduction stage is important.

Methods Implemented for Niosomal Size Reduction:

a) Probe sonication

b) Nucleophore filters extrusion

c) Laser diffraction

a) Probe Sonication:

Reverse phase evaporation and hand shaking method generally produces the niosomes of micron size ranging between 1.15 and 2.75 mm. by using probe sonication their size can be reduced to 100-140nm.
b) Nucleopore Filter Extrusion:

By the extrusion of niosomes through the nucleopore filters of pore size 100nm, niosomal size can be reduced to nano range.

Table no 1: Applications of Niosomes

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CATEGORY</th>
<th>YEAR OF WORK</th>
<th>REFERENCE NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Psoriasis</td>
<td>Azmin et al -1985</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chandraprakash et al-1992,1993</td>
<td>41, 42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Udupa et al- 1993</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lakshmi et al-2007</td>
<td>44</td>
</tr>
<tr>
<td>5,6- carboxy fluorescence</td>
<td>Diagnostic agent</td>
<td>Baillie et al -1985</td>
<td>18</td>
</tr>
<tr>
<td>Sodium stibogluconate</td>
<td>Anti-leishmaniasis</td>
<td>Baillie et al -1986</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carter et al -1989</td>
<td>45</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>Anti-cancer</td>
<td>Rogerson et al- 1987</td>
<td>46</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Anti-cancer</td>
<td>Rogerson et al- 1988</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cable et al -1989</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uchegbu et al -1995</td>
<td>05</td>
</tr>
<tr>
<td>Antimony</td>
<td>Anti-leishmaniasis</td>
<td>Hunter et al -1988</td>
<td>39</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Oxygen carrier</td>
<td>Moser et al -1989</td>
<td>48</td>
</tr>
<tr>
<td>9-desglycinamide,</td>
<td>Peptides</td>
<td>Yoshida et al -1992</td>
<td>27</td>
</tr>
<tr>
<td>8-arginine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine serum albumin</td>
<td>Protein</td>
<td>Brewer and Alexander-1992</td>
<td>49</td>
</tr>
<tr>
<td>Flurbiprofen, Piroxicam</td>
<td>Anti-inflammatory</td>
<td>Reddy et al -1993</td>
<td>50</td>
</tr>
<tr>
<td>Vincristine sulphate</td>
<td>Anti-cancer</td>
<td>Parthasarthi et al -1994</td>
<td>51</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Anti-inflammatory</td>
<td>Raja naresh et al -1994</td>
<td>52</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Hormone</td>
<td>Hofland et al -1994</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Don et al-1997</td>
<td>54</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Anti-tubercular</td>
<td>Jain et al-1995,2006</td>
<td>55, 56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mullaicharam et al- 2004</td>
<td>57</td>
</tr>
<tr>
<td>Drug</td>
<td>Category</td>
<td>Reference</td>
<td>Page</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------</td>
<td>-------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Anti-bacterial</td>
<td>Jayraman et al-1996</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vyas jig er et al -2011</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perini et al -1996</td>
<td>60</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Anti-cancer</td>
<td>Naresh et al -1996</td>
<td>61</td>
</tr>
<tr>
<td>Ciprofloxacin, norfloxacin</td>
<td>Anti-bacterial</td>
<td>Souza DS et al -1997</td>
<td>62</td>
</tr>
<tr>
<td>Withaferin A</td>
<td>Anti-tumour</td>
<td>Sheena et al -1998</td>
<td>63</td>
</tr>
<tr>
<td>Timolol maleate</td>
<td>Anti-hypertensive</td>
<td>Vyas SP et al -1998</td>
<td>64</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Anti-inflammatory</td>
<td>Namdeo et al-1999</td>
<td>65</td>
</tr>
<tr>
<td>Luteinizing hormone</td>
<td>Hormone</td>
<td>Arunothayanam et al-1999</td>
<td>4</td>
</tr>
<tr>
<td>Sumatriptan succinate</td>
<td>Treat migraine</td>
<td>Gayatri DS et al -2000</td>
<td>26</td>
</tr>
<tr>
<td>Cytarabine hydrochloride</td>
<td>Anti-cancer</td>
<td>Ruckmani et al- 2000</td>
<td>66</td>
</tr>
<tr>
<td>Pentoxyfylline</td>
<td>Anti-parkinson</td>
<td>Japtap And Inamdar-2001</td>
<td>67</td>
</tr>
<tr>
<td>Dithranol</td>
<td>Anti-psoriatic</td>
<td>Agarwal et al -2001</td>
<td>68</td>
</tr>
<tr>
<td>Enoxacin</td>
<td>Anti-bacterial</td>
<td>Fang et al -2001</td>
<td>69</td>
</tr>
<tr>
<td>Tretoin</td>
<td>Anti-acne</td>
<td>Manconi et al -2002</td>
<td>70</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Mutagen</td>
<td>Hao et al -2002</td>
<td>23</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Anesthetic</td>
<td>Carafa et al -2002</td>
<td>71</td>
</tr>
<tr>
<td>Trans retinoic acid</td>
<td>Anti-acne</td>
<td>Desai et al -2002</td>
<td>72</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>Anti-inflammatory</td>
<td>Shahiwala et al -2002</td>
<td>36</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Anti-fungal</td>
<td>Satturwar et al -2002</td>
<td>73</td>
</tr>
<tr>
<td>Daunorubicin hydrochloride</td>
<td>Anti-cancer</td>
<td>Balasubramanian et al -2002</td>
<td>75</td>
</tr>
<tr>
<td>Tretoin II</td>
<td>Anti-acne</td>
<td>Manconi et al -2003</td>
<td>76</td>
</tr>
<tr>
<td>PEGylated paramagnet</td>
<td>Diagnostic agent</td>
<td>Luciana et al -2004</td>
<td>77</td>
</tr>
<tr>
<td>Vaso active peptide</td>
<td>Peptide</td>
<td>Dufes et al -2004</td>
<td>78</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>Diuretic</td>
<td>Aggarwal et al -2004</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guinedi et al -2005</td>
<td>80</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Medical Use</td>
<td>Author(s)</td>
<td>Year</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------------</td>
<td>----------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Anti-malarial</td>
<td>Varghese et al. 2004</td>
<td>83</td>
</tr>
<tr>
<td>Bolaform</td>
<td>Anti- mydriatic</td>
<td>Muzzalupo et al. 2005</td>
<td>24</td>
</tr>
<tr>
<td>Timolol maleate</td>
<td>Treatment of male pattern</td>
<td>Tabbakhian et al. 2006</td>
<td>86</td>
</tr>
<tr>
<td>β-carotene</td>
<td>Vitamin</td>
<td>Palozza et al. 2006</td>
<td>85</td>
</tr>
<tr>
<td>Finesteride</td>
<td>Treatment of male pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Anti-inflammatory</td>
<td>Nidhi et al. 2006</td>
<td>87</td>
</tr>
<tr>
<td>Insulin</td>
<td>Hormone, anti-diabetic</td>
<td>Abbas et al. 2007</td>
<td>88</td>
</tr>
<tr>
<td>Tretoion III</td>
<td>Anti-acne</td>
<td>Manconi et al. 2006</td>
<td>89</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Anti-anginal</td>
<td>Varshney et al. 2007</td>
<td>90</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Anti-inflammatory</td>
<td>Mokhtar et al. 2008</td>
<td>91</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Anti-tubercular</td>
<td>Roopa et al. 2008</td>
<td>92</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>Anti-asthmatic</td>
<td>Elbary et al. 2008</td>
<td>93</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Treat alopecia</td>
<td>Prabagar et al. 2009</td>
<td>29</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Anti-fungal</td>
<td>Sandeep et al. 2009</td>
<td>94</td>
</tr>
<tr>
<td>Glicazide</td>
<td>Anti-diabetic</td>
<td>Tamizharsi et al. 2009</td>
<td>95</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Anti-fungal</td>
<td>Pratap et al. 2009</td>
<td>96</td>
</tr>
<tr>
<td>Salbutamol sulphate</td>
<td>Anti-asthmatic</td>
<td>Shyamala et al. 2010</td>
<td>97</td>
</tr>
<tr>
<td>Terbinafine hydrochloride</td>
<td>Anti-fungal</td>
<td>Abdul et al. 2010</td>
<td>98</td>
</tr>
<tr>
<td>Gatifloxacin, rifampicin</td>
<td>Anti-biotic</td>
<td>Pavala rani et al. 2010</td>
<td>99</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>Anti-inflammatory</td>
<td>Srinivas et al. 2010</td>
<td>13</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Anti-bacterial</td>
<td>Gupta et al. 2010</td>
<td>101</td>
</tr>
<tr>
<td>Brimonidine tartrate</td>
<td>Anti-glaucomatic</td>
<td>Prabhu et al. 2010</td>
<td>102</td>
</tr>
<tr>
<td>Salmeterol xinafoate</td>
<td>Anti-asthmatic</td>
<td>Ismail et al. 2011</td>
<td>103</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>Anti-inflammatory</td>
<td>Malay et al. 2011</td>
<td>104</td>
</tr>
</tbody>
</table>
Venlafexine Anti-depressant Purnima et al -2011 7
Miconazole Anti-fungal Mohamed et al -2011 105
Cefpodoxime proxetil Antibiotic Sambath kumar et al -2011 106
Acyclovir Anti-viral Anupriya et al -2011 107
Urea Anti-psoriatic Lakshmi et al -2011 108
Cefuroxime axetil Antibiotic Sambhakar et al -2011 109

c) Laser Diffraction:

It is used to reduce the size of niosomes up to nano range.

Apart from these methods, micro fluidization and high pressure homogenization are also used for the sizing of niosomes.

E. Separation of Unentrapped Drug:

The removal of unentrapped drug from the niosomal vesicles can be accomplished by various techniques such as

i. Dialysis

ii. Gel filtration

iii. Centrifugation

i. Dialysis:-

Dialysis of the aqueous niosomal dispersion is carried out in dialysis cellophane tubing against normal saline or phosphate buffer or glucose solution\textsuperscript{23, 24}.

ii. Gel Filtration:-

The unentrapped drug from the niosomal dispersion is removed by passing through sephadex G50 column and elution with phosphate buffered saline or normal saline. The vesicles percolate down the column whereas the free drug gets retained on column\textsuperscript{25, 26}.

iii. Centrifugation:-

The niosomal dispersion is centrifuged in water or saline. Niosomes get sedimented down as pellet which is washed and resuspended to obtain a niosomal suspended free from unentrapped drug. The supernatant containing the unentrapped drug is separated\textsuperscript{27}.

F. Characteristics of Niosomes:

i. Vesicle diameter and morphology

ii. Vesicle charge

iii. Bilayer formation
iv. Number of lamella

v. Membrane rigidity and homogeneity

vi. Drug loading and encapsulation efficiency

vii. In-vitro drug release

viii. Stability studies

i. Vesicle diameter:

Niosomes are spherical in shape and the size range from 20nm to 50μm. Techniques used to determine the vesicle size and size distribution include light microscopy, coulter counter, and photon correlation microscopy and freeze fracture electron microscopy. Scanning electron microscopy, atomic force microscopy and cyto transmission electron microscopy are used to determine the shape and surface characteristics of the niosomes. 28

ii. Vesicle charge:

The vesicle surface charge plays a major role in the stability and behaviour of niosomes. Charged niosomes are found to be more stable than uncharged niosomes against aggregation and fusion. Surface potential of niosomes can be estimated by the zeta potential measured by micro electrophoresis or dynamic light scattering 29. PH sensitive fluorophores can be used as an alternative method.

iii. Bilayer formation:

Bilayer vesicle formation can be characterized by x-cross formation due to the assembly of non-ionic surfactants under light polarization microscopy 30.

iv. Number of lamellae:

Number of lamellae in vesicles is characterized by NMR spectroscopy, electron microscopy and small angle X-ray scattering 31.

v. Membrane rigidity and homogeneity:

Membrane rigidity influences the bio distribution and bio degradation of niosomes. The bilayer rigidity of vesicles can be determined by the mobility of fluorescence probe as function of temperature. Membrane homogeneity can be identified by P-NMR, differential scanning calorimetry(DSC), fourier transform-infra red spectroscopy(FT-IR) and fluorescence resonance energy transfer(FRET). 24

vi. Drug loading and encapsulation efficiency:

Drug loading and encapsulation efficiency of niosomal dispersion is determined after the separation of unentrapped drug. The unentrapped drug is separated by dialysis or centrifugation or gel filtration. Niosomal recoveries can be calculated as

\[
\text{recovery (\%)} = \frac{\text{Amount of niosomes Niosomal recovered} \times 100}{\text{Amount of polymer} + \text{unentrapped drug}}
\]
The drug entrapped in the niosomes is determined by complete vesicular disruption using 0.1% triton x-100 or 10% n-propanol. The resultant solution can be assayed by appropriate method.\textsuperscript{28} Entrapment efficiency can be calculated by using the formula

\[
\text{Entrapment efficiency (\%) } = \left(\frac{\text{Amount of drug in niosomes}}{\text{Amount of drug used}}\right) \times 100
\]

Drug loading percentage can be calculated as

\[
\text{Drug loading (\%) } = \left(\frac{\text{Amount of drug in niosomes}}{\text{Amount of niosomes recovered}}\right) \times 100
\]

The entrapment efficiency can also be determined by using carboxyfluorescein as marker.\textsuperscript{32}

\textbf{vii. In-vitro drug release:-}

\textit{In-vitro} drug release of niosomes can be characterized by the following methods:\textsuperscript{33}

1. Dialysis
2. Reverse dialysis
3. Franz diffusion cell

1) Dialysis:

It is the simplest method used to determine the invitro release kinetics of the niosomal loaded drug. Dialysis tubing is used. Niosomal suspension is placed in the dialysis sack which is hermetically sealed. Dialysis is carried out by placing the sack in 200ml of buffer solution with constant stirring at 25\textdegree{}C or 27 \textdegree{}C. Samples are withdrawn at regular intervals and drug content analysis is carried out by suitable method.

2) Reverse dialysis:

1 ml of dissolution medium is taken in a number of small dialysis tubes into which niosomes are added. Then the niosomes are displaced from the dissolution medium.

3) Franz diffusion:-

Niosomes are dialyzed against suitable dissolution media through a cellophane membrane at room temperature in Franz diffusion cell. The samples are withdrawn at regular intervals of time and analysis is carried out to determine the drug content. Now-a-days FRET is used to monitor the release of encapsulated matter in niosomes.
viii. Stability of niosomes:

Stability of niosomes is indicated by the constant particle size and constant concentration of entrapped drug. Stability of niosomes depends upon the concentration and type of surfactant, cholesterol.  

E.g.: Sonicated spherical niosomes are stable at room temperature. Sonicated polyhedral niosomes are instable at room temperature but stable at the temperature above the phase transition temperature.

C. Factors Influencing Niosomal Formulation:

i. Nature of surfactant

ii. Structure of surfactant

iii. Composition of membrane

iv. Nature of encapsulated drug

v. Hydration temperature

vi. Cholesterol content

vii. Charge

viii. Resistance to osmotic stress

i. Nature of surfactant:

Ether type surfactant with single alkyl hydrophobic tail is more toxic than the dialkyl ether chain. The ester based surfactants are chemically less stable than ether type surfactant as ester linkage is more prone for degradation by esterases to fatty acids and tri-glycerides. Ether type surfactants are more toxic than ester based surfactants.

Increase in the HLB value of surfactants leads to the increase in the mean size of niosomes due to the decrease in surface free energy with an increase in the surfactant hydrophobicity. The bilayers of the niosomes can exist either as a liquid state or in gel state. It depends upon the temperature, type of surfactant and cholesterol. Alkyl chains are well ordered in gel state whereas disordered in the liquid state. Entrapment efficiency is affected by the gel liquid phase transition temperature (TC) of the surfactant.  

Eg: span 60 with higher TC exhibits better entrapment.

HLB value of surfactants ranging between 14 and 17 are not suitable for niosomal preparations. Decrease in the HLB value of surfactants from 8.6 to 1.7 decreases the entrapment efficiency and highest entrapment efficiency is found with the HLB value of 8.6.  

For the preparation of niosomes, the surfactants of alkyl chain length ranging C_{12}-C_{18} are suitable.

ii. Structure of surfactant:

Critical packing parameter of the surfactant structure affects the geometry of the vesicle. The geometry of the vesicle can be predicted by the critical packing parameters (CPP).  

If \( CPP < \frac{1}{2} \) => spherical micelles

\( \frac{1}{2} < CPP < 1 \) => bilayer micelles
CPP > 1  => inverted micelles

Critical packing parameter (CPP) can be obtained by using the following equation

\[ \text{CPP} = \frac{v}{l_c \cdot a_o} \]

Where CPP = critical packing parameters

- \( V \) = hydrophobic group volume
- \( l_c \) = critical hydrophobic group length
- \( a_o \) = area of hydrophilic head group

**iii. Composition of membrane:**

Addition of different additives to the surfactant and drug is done to stabilize the niosomes. Addition of cholesterol provides better rigidity to the membrane and reduces the leakage of drug. Addition of low amount of solulan C_{24} (cholesteryl poly-24-oxy ethylene ether) to the polyhedral niosomes formed from C_{16}G_{2} prevents the aggregation due to the development of steric hindrance.

**iv. Nature of encapsulated drug:** The charge and the rigidity of the niosomal bilayer are greatly influenced by physico-chemical properties of the encapsulated drug. Entrapment of drug occurs by interacting with the surfactant head groups leading to the increasing charge and creates mutual repulsion of the surfactant bilayer and thus increases vesicle size. The HLB of drug influences the degree of entrapment.

**v. Hydration temperature:**

The size and shape of the niosome is affected by the temperature of hydration. Hydration temperature should be above the gel liquid phase transition temperature. Change in temperature affects the assembly of surfactants into vesicles and vesicle shape modification. Hydration time and volume of hydration medium also accounts for the modification. Improper selection of the hydration temperature, time and hydration medium volume produces fragile niosomes / drug leakage problems may arise.

**vi. Cholesterol content:-**

Incorporation of cholesterol increases the entrapment efficiency and hydro-dynamic diameter of niosomes. Cholesterol acts in two ways:

- Increases the chain order of liquid state bilayers.
- Decreases the chain order of gel state bilayers.

Increase in the cholesterol concentration causes increase in the rigidity of the bilayers and decrease in the release rate of encapsulated material.

**vii. Charge:-**

Presences of charge leads to an increase in inter lamellar distance between successive bilayers in multi lamellar vesicle structure and greater overall entrapped volume.

**viii. Resistance to osmotic stress:**

Addition of hypertonic solution causes reduction in vesicle diameter. In hypotonic solution, inhibition of eluting fluid from vesicles results in the slow release initially followed by the faster release due to the mechanical loosening of vesicle structure under osmotic stress.
3. Applications of Niosomes:

Niosomal cosmetics are already in market. Examples of niosomal cosmetic preparations include Estee Lauder - Beyond Paradise After Shave Lotion, White Shoulders Eau De Cologne Spray, Orlane Lip Gloss, Le Classique Eau De Toilette Spray, Love In Paris- Deodorant Spray, Liz Claiborne - Realities Shower Gel, Givenchy - Blanc Parfait - Day Care, Lancome- Foundation & Complexion, Britney Spears- Curious Coffret, Elene - Eye Care, Guinot - Night Care, Gatinneau - Moderactive – Cleanser, Shiseido - Bio Performance - Night Care, Boss Soul After Shave, Amarige Eau De Toilette Spray, Chrome Eau De Toilette Spray, Golden Beauty After Sun Soothing Moisturiser, Guinot – Cleanser Gentle Face Exfoliating Cream. Apart from these other application of niosomes are tabulated in table no 1

4. Conclusion:

From the past few decades, there is a great revolution in development of novel drug delivery system. The technology of utilizing niosomes as promising drug delivery system is still in its infancy. Niosomes have shown a profound influence in targeting the particular organ and tissue. Niosomes can serve as better diagnostic agents, vaccine delivery system, tumour targeting agents, ophthalmic, nasal and transdermal delivery systems. Research has to be carried out extensively to have commercially available niosomal formulations.

References:


