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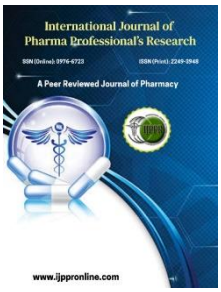

Recent Innovation in Niosomes-A Comprehensive review of advancements and Applications

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ABSTRACT:
The management of infectious diseases and immunization practices have experienced a revolutionary change in recent years. With the development of biotechnology and genetic engineering, not only have numerous biologicals targeted at certain diseases been created, but the focus has also been placed on the efficient delivery of these biologicals. As an alternative to liposomes, niosomes are vesicles made of non-ionic surfactants that are biodegradable, more harmless, more stable and less costly. This article summarizes various literature with the outcomes of the utilization of niosomes for different diseases.

1. Introduction:

A novel drug delivery system in which medication is encapsulated in a vesicle is called Niosomes. The vesicle is consisted of a non-ionic surfactant bilayer hence named Niosomes. The size of the niosomes lies on a nanometric scale. They offer various advantages over liposomes in spite of similar structural characteristics. Niosomes have shown great potential in the delivery of drugs by various routes and increased knowledge of such novel structures can open innovative ideas for any delivery.

2. Salient Features of Niosomes:

Solute particles can be entrapped in Niosomes in a manner similar to liposomes**.** They are osmotically active and stable. They can also load drug molecules having a wide range of solubility pertaining to the attachment of both polar and nonpolar compounds. Niosomes show formability in their structural characteristics that is composition, fluidity, size and thus can be designed according to the desired situation. The activity of the drug molecule can be improved by encapsulating them in niosomes. They provide protection to the drug from the biological environment and improve availability at a

particular site. They are biodegradable, biocompatible, and non-immunogenic.[1]

3. Advantages of Niosomes:

These lipid and non-ionic surfactant vesicles exhibit various advantages like vesicle suspension is water–based vehicle, which offers high patient compliance in comparison with oily dosage forms. They have the ability to accommodate drug molecules having a wide range of solubility due to the presence of hydrophilic, amphiphilic and lipophilic moieties in their infrastructure. Vesicle formation characterization can be controlled by altering their vesicle composition, size, lamellarity, tapped volume, surface charge and concentration. The drug is released in a controlled manner from the vesicle due to depot formation. They are osmotically active and stable, as well as they increase the stability of entrapped drugs. No special environmental conditions are required for their handling and storage. Oral bioavailability as well as skin permeation can be improved by delivering drugs as niosomes. They can be administered by several routes i.e. oral, parenteral as well as topical routes to reach their site of action.[2]

4. Applications:

Niosomes have various applications such as targeting bioactive agents (to the reticulo-endothelial system (RES) and to organs other than reticulo-endothelial system (RES)), neoplasia**,** peptide drugs delivery and as a carrier for haemoglobin**,** transdermal drug delivery, diagnostic imaging with niosomes, leishmaniasis therapy, niosome formulation as a brain targeted delivery, ophthalmic drug delivery.[3]

5. Types of Niosomes:

On the basis of vesicle size, they can be divided into three groups-

5.1 Small Unilamellar Vesicles (SUV, Size=0.025-0.05 μm)

5.2 Multilamellar Vesicles (MLV, Size=>0.05 μm)

5.3 Large Unilamellar Vesicles (LUV, Size=>0.10 μm).[4]

6. Methods of Preparation:

6.1 Ether injection method:

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

6.2 Hand shaking method (Thin film hydration technique):

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using a 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 a typical multilamellar niosomes film of lipid on the wall of rotary flash evaporator. The aqueous phase containing the drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.

6.3 Sonication:

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**.**

6.4 Micro fluidization:

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra-high velocities, in precisely defined micro channels within the interaction chamber. The impingement of a 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.[5]

6.5 Multiple membrane extrusion method:

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

6.6 Reverse phase evaporation technique (REV):

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes. Raja Naresh *et al*. has reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.[6]

7. Evaluation of Niosomes:

7.1 Morphology:

The morphological characteristics of prepared niosomes would be visualized under microscope after suitable dilution.

7.2 Vesicle size determination:

7.2.1 By optical microscopy:

For determination of size of vesicles, a drop of prepared niosomes (diluted with water if required) would be placed on a clean glass slide and observed under an optical microscope. The vesicle will be observed under low as well as high power and up to 100 vesicles would be counted.

7.2.2 Scanning electron microscopy (SEM)

Selected samples would also examine under scanning electron microscope.

7.3 Zeta potential- Zeta potential would be determined using Zetasizer (Malvern Instruments). It indicates the degree of repulsion between adjacent, similarly charged particles in dispersion system.[7]

7.4 Encapsulation efficiency- encapsulation efficiency would be determined by centrifuging the niosomal dispersion at 3500 for 2hr. the clear supernatant would be separated, filtered and sufficiently diluted with ethanol and absorbance would be recorded at respective wavelength by U.V visible spectrophotometer and % drug entrapment would be calculated.

7.5 *In-vitro* release: *In-vitro* diffusion study would be performed by franz diffusion cell using cellophane membrane previously soaked in mixture of phosphate buffer pH7.4 and ethanol. A section of membrane would be cut, measured and placed on receiver compartment. The donor compartment would be filled with niosomal formulation, mixture of ethanol and pH7.4 phosphate buffer (4:6 v/v) would be used as receptor medium, maintained at 37ºC and stirred at 300rpm. About 0.5 ml receptor medium would be withdrawn and replaced by an equal volume of fresh medium at appropriate time intervals up to 12 hr. The samples would be diluted appropriately and will be observed spectrophotometrically at the respective wavelengths.[8]

8. Evaluation of Niosomal Gel:

The formulated niosomes gels would be evaluated for various parameters such as pH, viscosity, spreadability, *In-vitro* drug release and rat skin permeation

8.1 pH Measurements: The pH measurements would be performed by using digital pH meter.

8.2 Viscosity Measurements- The viscosity of the gel formulations would be measured by a Brookfield viscometer (DV 1 prime). About 25g of the gel would be taken into a beaker and the spindle will be dipped into the gel formulation,

and viscosity of the gel formulation would be measured by rotating the spindle at 50rpm.

8.3 Spreadability: The spreadability of niosomal gel formulations would be calculated by using spreadability apparatus consisted of two glass slideon the lower slide. The gel sample would be placed (1g) and upper slidewill exert force(approx. 80g) to the sample on lower slide. The spreadability was calculated by the following equation.

$S = m \times L/t$ (2)

Where S: Spreadability, m: mass of the gel formulation, L: length travel by upper slide and t: time.

8.4 *In-vitro* drug release study: *In-vitro* drug release would be performed using franz diffusion cell.

8.5 Skin Permeation Studies- Skin from male albino rats weighing 180-200g was used in studies. Percutaneous absorption of drug would be studied using franz diffusion cell. The male albino rats (weighing 180 200mg) would be used in the study. Then the skin would be separated from the connective tissues and kept frozen at -20ºC. The skin would be mounted on the with dermis facing the receptor chamber.1g sample would be in donor compartment and the receptor chamber would be filled with 5ml of pH7.4 PBS, maintained at 37±0.5ºC. Appropriate samples would be out at the time interval of 1h, 2h, 3h, 4h, 6h, 8h, 10h, and 12h from receiver chamber and replaced with a same amount of pH 7.4 PBS. The sample would be then analyzed by U.V/visible spectrophotometer at respective wavelength.

8.6 Stability studies - The prepared niosomal gel would be kept at non-accelerated (2-8C) and accelerated condition (25±2°C) to carry out stability analysis for 12 weeks.[9]

9. Various Researchers have reported recent advances of Niosomes for pharmaceutical applications.

Some of these are summarized here:

Alla-Nasr M. *et al.* (2015) formulated niosomal gel of Baclofen using various ratios of surfactant (span 60,40) cholesterol and charge-inducing agent by thin film hydration method. The prepared niosomal formulations were evaluated on the basis of various physicochemical parameters viz; encapsulation efficiency, maximum entrapment efficiency (analyzed by transmission electron microscopy, DSC, particle size analysis, zeta potential, analysis). And *In-vitro* drug release (after 24 hr.) was also evaluated. The prepared niosomes were further formulated as niosomal gels using different gelling agents like Carbopol. In research, it was demonstrated that carbopol-based niosomal gel was more suitable for topical drug delivery of baclofen.[10]

Sidramappa B Shirsand *et al.* (2015) have developed and characterize niosomal gel formulation of clotrimazole to increase retention time in the dermis layer through controlled release of the drug. Clotrimazole niosomes were prepared by thin film hydration method using span 40 (as non-ionic surfactant) and cholesterol (as a stable vesicle forming agent). The niosomal dispersion was evaluated for vesicle size, surface morphology, percent entrapment efficiency and *in-vitro* drug release. Among the five formulations prepared, the formulation CN3 (containing 100 mg drug, 200 mg surfactant) was found to be promising. Selected niosomal suspension (CN3) containing clotrimazole equivalent to 2 % w/w was incorporated into gel base composed of carbopol (1%), triethanolamine 0.3% and distilled water quantity sufficient. The gel was studied for its different parameters such as pH, *in-vitro* drug release, anti-fungal activity and skin irritation effect. The studies suggest that encapsulating clotrimazole in non-ionic surfactant vesicles would provide better patient compliance by achieving prolonged release of the drug to the dermis with improved efficacy.[11]

Indira. S *et al.* (2015) determined the Loratadine allergic inflammation treatment property. Poor bioavailability of the drug from conventional dosage forms is especially attributable to mucociliary clearance and transient residence

time. These problems can be reduced by the employment of niosomal *in-situ* gelling system. *In-situ* gelling of niosomal drops was developed to maintain the drug localization for extended period of time. The niosomal *in-situ* gel formulation was transformed into gel once it is instilled into the nasal cavity. Niosomes were formulated using various surfactants (span 20, 40, 60 and 80) in different ratios using thin film hydration technique. Niosomes were evaluated for particle size, drug entrapment efficiency and *in-vitro* drug release. Niosomes prepared using cholesterol and span 60 in the ratio 1:1 (F3) showed higher entrapment efficiency (94.87%) and *in-vitro* drug release (59.90%) was optimized. The optimized niosomes were developed into *in-situ* gel (pH induced and thermoreversible). The gels were evaluated for gelling capability, pH, viscosity, drug content and *in-vitro* drug release. *Ex-vivo* permeation was performed for optimized *in-situ* gels (G2 and T5). The flux (Jss) and Permeability Coefficient (Kp) was found to be higher for G2. Hence niosomal *in-situ* gelling system may have its potential applications than the conventional nasal formulations and to improve the bioavailability of the drug through its longer residence time and ability to sustain drug release with minimal loss of drug.[12]

Ali Abdelhalem M. Ahmed. *et al.* (2014) have prepared a niosomal gel formulation which contains phenytoin sodium and enhances skin wound healing property. Solvent evaporation-film hydration methodology was adopted for noisome formation. Different compositions of phenytoin, surfactant and cholesterol were tested. The prepared niosomes were evaluated for size of vesicles, drug entrapment efficiency and release profiles. Niosome micrographs obtained by scanning electron microscopy indicated well-defined and spherically shaped vesicles. Niosomes's size and zeta potential indicated a smallest average size (74.4 nm), large polydispersity index (0.85) and optimum zeta potential (-58.9 mV) from niosomes containing Span 60 and Pluronic F127 at 1:1 ratio. Niosomes also enabled sustained release of phenytoin sodium from niosomal vesicles which depended on the type of surfactant used. Formulation containing Span 20 released more than 70 % and 100 % after 14 and 18 hours, respectively. Other formulations containing span 60 alone or mixed with other surfactants sustained the release for more than 24 hours. *In-vivo* evaluation performed on artificially injured guinea pig skin indicated significant differences ($P < 0.05$) between healing times for the treated group which completely healed within less than 9 days upon using phenytoin sodium niosomal gel formulations compared to placebo gel counterparts which lasted more than 17 days. These findings indicated that niosomes were considered highly effective carriers and skin penetration enhancers for phenytoin sodium. The effects were mainly due to their high content of surfactants and cholesterol combined with collagen proliferation benefits of phenytoin both led to successful and rapid wound healing when employed topically.[13]

Mishra Namrata *et al.* (2014) have formulated and evaluated the niosomes of aceclofenac using different concentrations of drug, cholesterol and surfactant (span 60) by Ether injection method. various methods i.e. vesicle shape, particle size, entrapment efficiency, drug content, compatibility studies and *in-vitro* drug release were used for the evaluation of niosomes and the result were found satisfactory.[14]

Srivastav Kumar Alok *et al.* (2014) prepared ofloxacin niosomes in various proportions using mixtures of non-ionic surfactant cholesterol and phosphate by lipid film hydration method. The prepared formulation was evaluated using various parameters such as morphological characterization, encapsulation efficiency and *in-vitro* drug release study. The vesicle size of the prepared Niosomes ranged between 100-300 nm and the entrapment efficiency was found to be 78.4% with a partition coefficient of 0.5.[15]

Apurva Saxena *et al.* (2014) have prepared roxithromycin niosomes for enhancement of skin penetration. Roxithromycin is a macrolide antibiotic, which is used commonly for the treatment of soft tissue infection either single or in combination. Niosomes, a vesicular

formulation, has been explored extensively for topical application to enhance skin penetration as well as to improve skin retention of drugs. In the present investigation, Roxithromycin was entrapped into niosomes by a thin film hydration technique and various process parameters were optimized by partial factorial design. The optimized niosomal formulation was incorporated into carbopol gel and extensively characterized to Percentage Drug Entrapment (PDE) and *in-vitro* release performance. The stability of the above formulation was studied at different temperatures. The present study demonstrates prolongation of drug release after encapsulation of Roxithromycin into niosomal topical gel.[16]

Jivrani Shilpa D *et al.* (2014) formulate and evaluate niosomal drug delivery system for Clindamycin phosphate to increase its effectiveness by increasing penetration through skin and reducing its side effects Sorbitan esters which are Non-ionic surfactants were the key ingredient which form vesicles upon hydration with aqueous media. Cholesterol was used to make the vesicle stable and rigid. Different formulations were prepared by using different sorbitan esters and changing the ratio of surfactant and Cholesterol. A 3^2 factorial design was applied to evaluate the effect of various surfactants and surfactant:cholesterol ratio on dependent variable i.e. Entrapment efficiency and Vesicle size. Regression analysis and analysis of variance were performed for dependent variables. The results of the F-statistics were used to select the most appropriate model. Batch F21 was selected as the optimized batch which contained span 60 as non-ionic surfactant and 2:1 surfactant:cholesterol ratio. It was incorporated into carbopol 934 as gelling agent and compared for *in-vitro* release profile and *in-vitro* skin penetration with marketed gel. *In-vitro* release data were fitted to various models to ascertain the kinetic of drug release. The study indicates that the formulation increased the effectiveness of drug and reduce the side effects of drug.[17]

S. Indira *et al.* (2014) was formulated and evaluated the ocular niosomal *in-situ* gels of Linezolid. Linezolid is a potent synthetic oxazolidinone derivative active against a broad range of gram positive and gram-negative aerobic and anaerobic bacteria. Niosomes were prepared using various surfactants (span 20, span 40, span 60 and span 80) in different ratios using thin film hydration technique. They were evaluated for particle size, entrapment efficiency and *in-vitro* drug release. Niosomes prepared using cholesterol and span 60 in the ratio 1:2 showed higher entrapment efficiency and better *in-vitro* drug release. The optimized formulation was formulated as *in-situ* gels using Carbopol 971P and HPMC K4M in different ratios and evaluated for gelling capacity, pH, viscosity, *in-vitro* drug release, drug content, antimicrobial activity and ocular irritation test. The gels retained their antimicrobial efficacy and were proven to be safe and non-irritant on rabbit eyes. The niosomal *in-situ* gel is a viable alternative to conventional eye drops by virtue of its ability to enhance bioavailability through its longer precorneal residence time and ability to sustain drug release.[18]

Ujwala A. Shinde *et al.* (2014) have prepared a Primaquine phosphate niosomes for the treatment of malaria. Primaquine phosphate (PQP) is the most preferred drug in the treatment of malaria, which cause the complete eradication of parasites and prevention of relapse by destruction of the exo-erythrocytic liver stages of *P.vivax* and *P.ovate*, However, wider use of the PQP in the prophylactic therapy is limited by toxic side effects. REV method was selected which entrap higher aqueous phase containing the drug. Among different blends of solvents tried diethyl ether and chloroform in a 1:1 ratio provided stable emulsion in presence of drug and niosomes were formed in size ranges between 200-250 nm approximately.[19]

Navya M. N. *et al.* (2014) were aimed to develop sustain release formulation of Flutamide niosomes in order to provide better therapeutic effect. Flutamide niosomes was prepared by thin film hydration method using drug, span 60 and cholesterol in different ratios. The formulations were optimized from the above method with respect to vesicle shape, entrapment efficiency,

drug content, compatibility studies and *in-vitro* drug release. The FT-IR spectra shows the drug and excipients were compatible. The *in-vitro* release studies indicates that all the formulation exhibits retarded release for 24 hrs and its release mechanism was followed by Higuchi order kinetics.[20]

Dina Fathalla *et al.* (2014) was prepared and characterized niosomal gel formulations for sustained delivery of aceclofenac. Aceclofenac is the most widely used anti-inflammatory agent in the treatment of rheumatoid arthritis. It has a narrow therapeutic index and short biological half-life. Aceclofenac-loaded niosomes were prepared using reverse phase evaporation technique. The effects of concentration of non-ionic surfactant, cholesterol and concentration of drug on the encapsulation efficiency were studied. The formulations were characterized using different techniques, such as Differential Scanning Calorimetry (DSC), Fourier-Transform Infrared Spectroscopy (FTIR), Optical Microscope and Transmission Electron Microscope (TEM). Selected formulations of niosomes were incorporated into carbopol 934 (1%w/w), sodium alginate (7%w/w), sodium carboxy methyl cellulose (3% w/w), pluronic F127 (20%w/w) and HPMC (3% w/w) gels. The niosomal gel formulations were evaluated for *in-vitro* drug release and skin permeation. Optimum niosomal gel formulation was evaluated *in-vivo* using carrageenan-induced rat paw edema test and compared to a gel containing the drug alone. TEM analysis confirmed that niosomal samples were spherical in shape and have a definite internal aqueous space. Niosomes of span60 showed a higher percent drug entrapment and larger particle size. *In-vitro* drug release and skin permeation of different gel preparations showed sustained release and enhanced permeation compared to gel formulations containing free drug. Among the niosomal gel formulations, HPMC gel showed the highest release rate of the drug. The *in-vivo* anti-inflammatory activity of the selected niosomal gel formulation was significantly higher and more sustained than the corresponding non-niosomal gel formulation containing free drug. These results suggest that the niosome-containing gels are promising formulations for sustained local delivery of aceclofenac.[21]

Hasansathali Abdul *et al.* (2014) formulated topical niosomal gel of clobetasol propionate to extend the duration of action. Firstly, niosomes of clobetasol propionate were prepared by three different methods i.e. Ether injection method, Thin film hydration method and Handshaking methods by altering the ratio of various non-ionic surfactants (span 40,60,80) and cholesterol. Prepared niosomes were evaluated using various parameters like drug content analysis, entrapment efficiency, size analysis, and *in-vitro* drug release studies. Niosomes prepared by thin film hydration method showed higher entrapment efficiency (91.37%) and were further formulated as niosomal gel which was then compared with marketed gel. The results revealed that carbopol-based gel was found to be suitable for niosomal delivery of clobetasol.[22]

Nwakile C.D. *et al.* (2013) formulated Benzyl Penicillin niosomes using thin film hydration technique. Prepared niosomes were evaluated for various physicochemical parameters i.e. surface morphology, particle size distribution, encapsulation efficiency, *in-vitro* antimicrobial activity, *in-vivo* bioavailability. Particle size of the niosomes ranged between 1.67µm to 2.22µm. the encapsulation efficiency was with batch A higher (82.42%) in comparison to batches B and C which showed slow release, oral stability and good bioavailability *in-vivo*. For *In-vitro* and *in-vivo* studies, batch b containing span 80, tween 65 and cholesterol was particularly stable and released its drug content in a controlled manner. The Cmax of the pure drug (55.04 mg/ml) lower than that of niosomal preparation, all the batches have shown high antimicrobial activity than pure drug against *S. typhi*, *P. vulgaris* and *P. Aereuginosa* and prepare formulation were found stable.[23]

Shivhare UD *et al.* (2013) prepared niosomal gel as a vesicular drug carrier system of carvedilol by thin film hydration method. These formulations were optimized by using 3^2 full factorial design

and evaluated using various parameters i.e. vesicle size, entrapment efficiency, pH, viscosity, drug content uniformity *in-vitro* release and stability studies of the gel. The effect of span 60 and cholesterol on entrapment and release profile of carvedilol was also appraised. The prepared gels were entrapped in transdermal patches by using different polymers. Such as Eudragil RS 100 and PVP .it was concluded that optimized formulation slowed entrapment and release 94.38% up to 12 hr. Thus novel drug delivery system was found to be a promising carrier system for carvedilol because of ease in formulation and stability for a prolonged period.[24]

Salih Omar S. *et al.* (2013) prepared niosomal formulation of rosuvastatin calcium using non-ionic surfactants (span 20, span 60, span 80), cholesterol and lecithin in different ratios by film hydration method. Prepared formulations were subjected to various evaluation parameters viz; entrapment efficiency, particle size, morphology, *in-vitro* drug release and *ex-vivo* permeation study. The selected batches have undergone characterization by drug excipients compatibilities were assessed by fourier transform infrared (FTIR). Niosomal formulations with span 60 showed more entrapment efficiency in comparison to other formulas. TEM results revealed that vesicle size of optimized formulation was found to be 150 nm. FTIR showed compatibility of pure drug with excipients used.[25]

K. Srikanth *et al.* (2013) aimed to develop the niosomal nystatin gel for transdermal administration. Nystatin is a bacterial-originated polyene antifungal agent. Formulations were developed using thin film hydration technique. Developed formulations were characterized for particle size, shape, % entrapment efficiency, *in-vitro* drug release, etc. After analyzing the results, best formulation is optimized and its zeta potential, stability were determined. Niosomal gel was prepared with optimized formulation using carbopol as gelling agent. *In-vitro* drug release from formulated niosomal gel and marketed preparation was carried out. The niosomes appeared spherical in shape and the size range of niosomes in all formulations was found to be 278±1.4 to 431±1.2nm. Highest and least % entrapment was shown by FN3 (72.5±1.9) and FN5 (51.2±2.2) respectively. *In-vitro* drug release of all formulations was carried out using an exhaustive dialysis method. FN3 formulation was selected as an optimized formulation because of its good entrapment efficiency and drug release pattern. *In-vitro* & *Ex-vivo* drug release studies of niosomal gel and marketed formulation show that niosomal gel sustains the drug release more than the marketed gel.[26]

Tejaswi lella *et al.* (2013) was formulated the olanzapine niosomal suspensions with a view to targeting the drug to the brain and producing a sustained release to increase the retention time of the drug in the brain. Olanzapine Niosomal suspensions were formulated by the Thin film hydration technique. Relationship between type and molar concentration of surfactants, cholesterol and characterization parameters of niosomes was established. The influence of Span 20, Span 60 and Span 80 surfactants with different molar concentrations of cholesterol were studied. Particle size and scanning electron micrographic analysis reveal the presence of well-identified and nearly perfect spheres within nanosomal size range. The higher values of entrapment efficiency (50.83-61.42%) were observed for the niosomes made with span 60 surfactant. Span 20 niosomal formulations showed better entrapment efficiency than span 80 formulations. Drug entrapment efficiency was found to be increased with the increase in molar concentration of cholesterol. The highest percentages of drug released (72.57% and 75.30%) were obtained with F5 and F4 formulations which were prepared with Span 60. The drug release from Span 20 and 80 formulated niosomes seem slower than Span 60 formulations. *In-vitro* diffusion studies of the formulations followed first-order kinetics and ascertained peppa's mechanism, governed by non-Fickian diffusion. Zeta potential value of the formulation F5 was found to be -78.8mV indicating high negative surface charge on niosomes indicating high stability. From the results, it can be concluded that the niosomal formulation F5 could

be a better choice in the view of entrapment efficiency and drug release rate for the effective management of psychotic disorders.[27]

P. Aravinth Kumar *et al.* (2013) was encapsulated Pregabalin in niosomes for achieving prolonged release and longer duration of action. Niosomes containing Pregabalin were formulated using two surfactants such as span 40 & span 60 and evaluated for various parameters. The microscopic examination of the prepared niosomes revealed spherical small unilamellar vesicles of 80-120 nm and 250- 280 nm for F I and F II. *In-vitro* release studies showed that the percentage amount of free drug released was 99.04% within 2.5 hours. FI showed 84.99 % of drug release within 19 hours. F II showed 93.48 % of drug release within 20 hours. Storage under refrigerated condition showed greater stability with 97.23% of drug content at the end of 3 months.[28]

Geeta M. Patel *et al.* (2013) have prepared the Alitretinoin niosomes using SPAN 60 and cholesterol for skin delivery. Various ratios of SPAN 60 and cholesterol were tried and optimized for the preparation of niosomes. Various process parameters were also optimized for the rotary flask evaporation method. The niosomal dispersion was incorporated into carbopol 971NF gel. The gel was kept for 6 weeks for accelerated stability studies. The niosomal dispersion was evaluated for various parameters like vesicle size, shape and morphology by Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM). *In-vitro* and *ex-vivo* studies were carried out. The drug release pattern from gel was evaluated on the basis of *in-vitro* studies and skin irritation studies on rat skin. The *in-vitro* study shows sustained release gel effects whereas the *ex-vivo study* shows no signs of irritation on the applied skin area.[29]

M. Madhavi, *et al.* (2013) formulated a metformin niosomal drug delivery system and evaluated its *in-vitro* performance. The formulations were prepared with different types of surfactants. The study is based on formulation of metformin niosomes which provide most promising oral bioavailability of metformin. An optimal or best niosome formulation is claimed to be one with high entrapment efficiency, i.e., SPAN20. Entrapment efficiency was shown to be cholesterol: surfactant ratio-dependent in this investigation. *In vitro* oral bioavailability of the medicine was shown to be improved by formulations. Based on these findings, it is possible to infer that niosomes may be a potential strategy for increasing metformin oral bioavailability. [30]

Palash Das, *et al.* (2012) was formulated niosomal suspension containing diclofenac sodium multilamellar vesicle (MLVs). Diclofenac is a drug with a narrow therapeutic index and a short biological half-life. This study was aimed at developing and optimizing niosomal formulation of diclofenac in order to improve its bioavailability. In evaluation study, the effect of the varying composition of non-ionic surfactant and cholesterol on the properties such as encapsulation efficiency, particle size and drug release was studied. Moreover, the release of the drug was also modified and extended over a period of 72 h in all formulations. Different ratios of cholesterol and surfactant (span 20, span 40 and span 60) were used. The optimized ratio was 1:2:1 with highest entrapment efficiency. The *in-vitro* release of the drug was consistent. The time course of drugs and their effects on the body are assessed through pharmacokinetics which was provided by mathematical basis. The data collected from the release were incorporated into release kinetic analyses which are Higuchi equation and Korsmeyer-Peppas equations. Further, release of the drug from the most satisfactory formulation NF-6 was evaluated through a dialysis membrane to get the idea of drug release. The mechanism of drug release was governed by the Peppas model.[31]

SB Shirsand, *et al.* (2012), to improve low skin penetration and to minimize the side effects associated with topical conventional drug administration, Ketoconazole niosomes were prepared by a thin film hydration method using

different ratios of non-ionic surfactants (Span 40, 60 and Tween 60) along with cholesterol (CHO). Ketoconazole is a broad-spectrum Imidazole derivative useful in the treatment of superficial and systemic fungal infections. The formulations were evaluated for size, shape, entrapment efficiency and *in-vitro* drug release. Niosomes appeared spherical in shape and size range was found to be 4.86 ± 1.24-7.38 ± 3.64 μm. The entrapment efficiency was found in the range of 55.14 ± 2.29-78.63 ± 0.91% and *in-vitro* drug release in the range of 46.63 ± 0.95-72.37 ± 0.59% in 24 h. Ketoconazole niosomes formulated with Span 60 and CHO in the ratio of 1:0.2 were found to be promising and were incorporated into 1% Carbopol gel. The formulated gel was evaluated for various physicochemical parameters and antifungal activity. The *in-vitro* drug release study was carried out using phosphate buffer saline pH 7.4 and was found to be 36.18 ± 1.50% in 12 h. Gel formulations containing niosomes loaded with Ketoconazole showed prolonged action than formulations containing Ketoconazole in non-niosomal form and it can be developed successfully to improve the antifungal activity.[32]

Punitha Sundaresan *et al.* (2012) were aimed to develop sustained release formulation of aceclofenac niosomes in order to minimize gastrointestinal disturbances and to provide a better therapeutic effect. Aceclofenac niosomes were prepared by different techniques namely Ether injection method (F1), Ethanol injection method (F2), Sonication method (F3), Thin film hydration (F4) and Reverse phase evaporation technique (F5) using 1:1:1 ratio of drug, cholesterol and surfactant (Span 60). The formulations were optimized from the above methods with respect to vesicle shape, particle size, entrapment efficiency, drug content, compatibility studies and *in-vitro* drug release. The well-spherical shaped niosomes were obtained in all the methods. FT-IR Spectra show the drug and excipients were compatible. The *in-vitro* release studies indicate that all the formulations exhibit retarded release for 24hrs but the thin film hydration method and reverse phase evaporation method were found to be most satisfactory with respective to niosomes particle size, drug entrapment efficiency, *in-vitro* drug release and its release mechanism was followed by zero-order kinetics r2=0.9948 and 0.9913.[33]

A. Abdul Hasansathali *et al.* (2012) were developed Brimonidine tartrate niosomal *in-situ* gels for glaucoma treatment. Poor bioavailability of drugs from the ocular dosage form is mainly due to tear production, nonproductive absorption, transient residence time and impermeability of corneal epithelium. These problems can be minimized by the use of a niosomal vesicular system. Niosomes were formulated by using different ratios of span series and cholesterol. Span 60 (S/C 2:1) niosomes had highest entrapment efficiency and showed prolonged drug release. Small unilamellar vesicles were observed and had a size of about 50-100 nm. *In-situ* gelling of niosomal drops was formulated by using HPMC K 15 M and carbopol 940 to maintain the drug localization for an extended period of time. The niosomal formulation was transformed into a gel when it was installed into the eye. All the gel formulations exhibited pseudoplastic rheological behavior and slow drug release pattern. Anti-glaucoma activity of the prepared gel formulations showed a more significant and sustained effect in reducing intra-ocular pressure than marketed and niosomal drops. Hence, niosomal *in-situ* gelling may have potential applications than conventional ocular therapy and improve the ocular bioavailability with minimal loss of drug.[34]

Vinod Gaikwad *et al.* (2012) incorporated niosomes in *in-situ* gel formulation for the ocular delivery. Conventional liquid ophthalmic formulations are most convenient from patient point of view. But these formulation shows low bioavailability because of a constant lachrymal drainage in the eye which leads to frequent dosing. Moreover, the absorption of the drug drained through the nasolacrymal duct may result in undesirable side effects. To overcome these limitation different approaches has been applied such as ointment, gel, cream etc. These ophthalmic formulations also fails to show

desired therapeutic responses because of their own disadvantages such as ointment makes blurred vision. So two different systems was combined together as niosomes and *in-situ* gel by incorporating niosomes in *in-situ* gel formulation so that it is easy to administered and retain at the site for prolong period of time. The Ofloxacin (OFL), a second generation fluoroquinolone derivative used in eye infections needs frequent dosing in its solution form. Vesicular system reported prolonged and controlled action at corneal surface but it has again limitation of drainage along tear produced. In this, first niosomes containing ofloxacin were prepared by applying 3^2 full factorial designs and evaluated for their vesicle size, percent entrapment, *in-vitro* drug release kinetics and their stability. Also, *in-situ* gel formulation was prepared by dispersing the niosomes in a solution of carbopol 940 and Hydroxy Propyl Methyl Cellulose (HPMC) K4M. *In-vitro* drug release kinetics from niosomal *in-situ* gel formulation indicates that the minimum inhibitory concentration (MIC) of a drug (4 µg/ml) was achieved within 1-2 hrs (batch G1-G9).[35]

Sakthivel M, *et al.* (2012) prepared oxcarbazepine niosomes for the treatment of epilepsy. Oxcarbazepine niosomes were prepared by thin film hydration method using span60 in order to achieve prolonged circulation time and sustained release. The prepared niosomes were evaluated for size, shape, degree of drug entrapment, drug content and stability studies. *In-vitro* drug release studies were performed and drug release kinetics was evaluated using linear regression method. From this study it was observed that the formulation F-II showed satisfactory particle size 230-275nm, entrapment efficiency 58.87% and *in-vitro* release 78.08% for the period of 16 hours. Thus the niosomal formulation could be a promising delivery system for Oxcarbazepine with improved anticonvulsant activity, stability and sustained drug release profile.[36]

Vijay S. Jatav. *et al.* (2011) prepared niosomes containing rifampicin by using various nonionic surfactants of sorbitan ester class and cholesterol in 50:60 (1:1.2) percent mol fraction ratios for sustained release. To improve the dissolution rate of noisome prepare a handshaking method using Surfactants and cholesterol (150 µmol) in 50:60 (1:1.2) percent mol fraction ratio. The percent of drug estimated to be entrapped was noted to decrease progressively for various sorbitan esters used in the order of Span-85>Span-80>Span-60>Span-40>Span-20. *In-vitro* release rate studies revealed that the cumulative percent rifampicin released was maximum for Span-20-based niosomes and minimum for Span-85-based niosomes. The handshaking method is a simple and efficient technique for designing functional niosomes for hydrophobic or amphiphilic drugs.[37]

P.S. Salve *et al.* (2011) developed and evaluated the topical drug delivery system for terbinafine hydrochloride using niosomes. Fungal infection caused by a fungus called dermatophyte infects the top layer of skin, hair or nails. An allylamine antifungal agent terbinafine hydrochloride is used topically and orally. Its topical administration is preferred but barrier properties of stratum corneum decrease absorption and require frequent application. It has low oral bioavailability due to hepatic first-pass metabolism and many systemic adverse effects. Niosomes have been reported to enhance the residence time of drugs in stratum corneum and epidermis while reducing systemic absorption and improving penetration of entrapped drugs across skin. Niosomes of terbinafine hydrochloride were prepared by film hydration method in a size range of 0.24 to 9.4 µm. Maximum entrapment efficiency was observed in a formulation containing span 60 at 1:1 molar ratio of cholesterol and surfactant. Zeta potential values of niosomes containing span 60 (1:1) were more stable than other niosomal formulations. Niosomes were incorporated in 1.5 %w/v carbopol gel at pH 6.8-7.0. In *in-vitro* antifungal study against candida albicans, vesicular systems were found to be more effective than conventional gel. The formulations containing tween 60 (1.5:1) and span 80 (1:1) were found to have a maximum zone of inhibition. In *ex-vivo* percutaneous permeation studies, niosomal formulations have shown

superior skin penetration and drug deposition as compared to the conventional formulation. The formulation containing tween 80 has shown higher drug deposition in rat skin as compared to other formulations. The niosomal vesicles can be used to enhance penetration and deposition of terbinafine hydrochloride in skin.[38]

Firthouse Mohamed P.U. *et al.* (2011) prepared niosomes of miconazole using varying ratios of cholesterol and surfactant (1:0.5, 1:1, 1:1.5) by thin film hydration technique. Prepared formulations were evaluated for percentage of drug entrapment and drug release. Preparation with 1:1 CHOL: SA ratio, the concentration of SA was increased and it has revealed 92.10% drug released in 24 hours. The results revealed that the required amount of drug release per day as well as extended for the required day is the optimized formulation. Thus B formulation was the optimized.[39]

Vyas Jigar *et al.* (2011) formulated erythromycin niosomes by thin film hydration technique and various process parameters were optimized by partial factorial design . the optimized niosomal batch was formulated as gel and characterized for percentage drug entrapment and *in-vitro* release performance. The stability of the prepared formulation was analysed at various temperature ranges. The present study revealed that encapsulation of erythromycin into niosomal topical gel has led to prolonged drug release, enhanced drug retention and improved penetration through skin.[40]

Meenakshi Chauhan *et al.* (2009) have prepared niosomes with different molar ratios of surfactant and cholesterol and their morphological properties have been determined by scanning electron microscopy. Different batches of Fluconazole niosomal preparations were prepared by changing the surfactant concentration but keeping the cholesterol concentration constant. The surfactant used was Span 60 and the five batches of niosomal preparations prepared were in the ratios 1:1:1, 1.5:1:1, 2:1:1, 2.5:1:1 and 3:1:1 (surfactant: cholesterol: drug). Furthermore, the release profile, entrapment efficiency, size distribution and stability of these niosomes under various temperatures were studied.[41]

Zerrin Sezginbayindir *et al.* (2009) formulated the niosomal Paclitaxel (PCT), using different surfactants (Tween 20, 60, Span 20, 40, 60, Brij 76, 78, 72) by film hydration method. Encapsulation efficiencies of prepared formulations ranged between 12.1-1.36% and 96.6-0.482%. Z-average sizes of the niosomes were between 229.3 and 588.2 nm. The drug was released by diffusion-controlled mechanism at a very slow rate resulting in reduced toxic effects of the same. It was concluded that niosomes prepared with span 40 showed improved stability of drug in git when compared with other formulations. Among all formulations, gastrointestinal stability of PCT was well preserved with Span 40 niosomes.[42]

Tokerserdar *et al.* (2009) evaluated the effect of topical Atorvastatin for the treatment of wound in streptozotocin-induced diabetic rats. Two wounds (15×15mm size) were created in 28 rats and in total 56 diabetic wounds were created in 8 groups (n=7). First and second groups did not receive any treatment (lasted for 7 and 14 days respectively) while third and fourth groups were administered with 1:1 mixture of lanolins and Vaseline therapy for some time period. Atorvastatin (1%) with 1:1 mixture of lanolin and Vaseline was used in 7th and 8th groups and on 7th and 14th day, 5% statin with 1:1 mixture of lanolin and vaseline was administered. The state of wound healing and percent of wound healing was determined by measuring its size on 7th and 14th day. Results showed that the rate of wound healing were 14%, 40%, 96.5% and 96.5% in the first, second, third, and fourth group respectively. It was concluded that local atorvastatin therapy was useful for healing wounds in diabetic rats.[43]

Manivannan Rangasamyet *et al.* (2008) prepared Acyclovir entrapped niosomes by hand shaking and ether injection processes with cholesterol (CHOL) and Span-80 in different ratios (1:1, 1:2, 1:3). The size range of niosomes lied between 0.5-5µ and 0.5-2.5 using hand shaking method and ether injection processes,

respectively. The entrapment efficiency of niosomes was increased by increasing the concentration of span 80. *In-vitro* dissolution study indicated that formulation prepared with CHOL Span 80(1:1) showed 76.64% release in 16 hr.[44]

Conclusion:

Niosomes have been investigated for drug delivery through the most common routes of administration, such as intramuscular, intravenous, subcutaneous, ocular, oral, and transdermal. Niosomes appear to be multilamellar surfactant structures, and are thus best suited for hydrophobic or amphiphilic drugs. Niosomes are promising vehicle for drug delivery and being non-ionic; it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Recently, niosomes have been studied by many researchers for various routes and different disease treatment which is summarized in this review.

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