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AN OVERVIEW ON NIOSOMES AS EFFICIENT DRUG CARRIERS

RIZWANA KHAN[*1] AND RAGHUVEER IRCHHAIYA[2]

*[*1]PhD scholar Department of Pharmacy, Monad University, Hapur,U.P.*
[2]Institute of Pharmacy,Bundelkhand University,Jhansi, U.P.

ABSTRACT

Over the past years the treatments of disease have undergone a revolutionary change. With the advancement of pharmaceutical science not only novel drug delivery system have been developed but also emphasis has been laid to deliver the active constituent to the diseased site.The basic component of such a system is a suitable carrier that protects the active medicament from degradation or clearance from the body.Niosomes are one such vesicular drug delivery system which are composed of non-ionic surfactant vesicles formed by self-association of hydrated surfactant. Being biodegradable, non-toxic, stable and inexpensive, these are becoming increasingly popular in cosmetic and in pharma industry.Various reports have shown promising future of niosomes by oral, ocular,parentral and transdermal route.The first report on surfactant vesicles came from the cosmetic applications devised by L'Oreal.Since then, there has been increasing interest in the use of niosomes in the pharmaceutical, cosmetic, and food industries.This article reviews the current widening interest of noisomes in medicine.The present review compiles the types of niosomes,their basic structure.It also attemps to provide exhaustive collection of recent research on niosomal preprations with special emphasis on strategies used to enhance the delivery of drugs via oral,occular and transdermal route with their reported preclinical and clinical studies illustrating enhanced safety and efficacy.

KEY WORDS: *Niosomes,research,surfactant, carrier, bioavailability*

RIZWANA KHAN

PhD scholar Department of Pharmacy, Monad University, Hapur,U.P.

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INTRODUCTION

Niosomes are novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of bilayer of non-ionic surfactant and hence the name noisomes. Their size lies in the nanometricscale[1].Such a novel drug delivery system facilitates encapsulation of both hydrophilic and lipophilic drug[2,3,4].Such a delivery system offers numerous advantages such as the vesicle suspension being water–based vehicle offers high patient compliance in comparison with oily dosage forms. Due to the unique infrastructure consisting of hydrophilic, and lipophilic moieties together they can accommodate drug molecules with a wide range of solubilities. The vesicles may act as a depot, releasing the drug in a controlled manner. The characteristics of the vesicle formulation are variable and controllable, altering vesicle composition,size, lamellarity, tapped volume, surface charge and concentration thus controlling the vesicle characteristics. They are osmotically active and stable, and also increase the stability of entrapped drug thereby improving its bioavailability.Handling and storage of surfactants requires no special conditions.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,occular as well as topical routes[5].

Basic structure of niosomes

The main components of niosomes are non-ionic surfactants,hydration medium and lipids such as cholesterol. The list of materials used in the preparation of niosomes has been shown in Table 1.The self-assembly of nonionic surfactants in aqueous media results in closed bilayer structures (Figure 1).A high interfacial tension between water and the hydrophobic tails of the amphiphile causes them to associate.The steric and hydrophilic repulsion between the head groups of non-ionic surfactant ensure that hydrophilic termini point outwardsand are in contact with water while the hydrophobic tails are oriented inwards therefore the hydrophilic drugs can be encapsulated in the internal aqueous compartment while lipophilic and hydrophobic drugs can be associated with the bilayers of the vesicles. The assembly into closed bilayers usually requires some input of energy such as mechanical or heat[6].Additionally some charge inducing agents can also be added to increase the stability of the vesicles. They increase surface charge density and thereby prevent vesicles aggregation. Dicetyl phosphate,sodium de oxycholate and phosphatidic acid are most used negatively charged molecules for niosome preparation and, similarly, stearylamine and stearyl pyridinium chloride are well-known positively charged molecules used in niosomal preparations. Normally,the charged molecule is added in niosomal formulation in an amount of 2.5–5%.However increasing the amount of charged molecules can inhibit niosome formation[7].

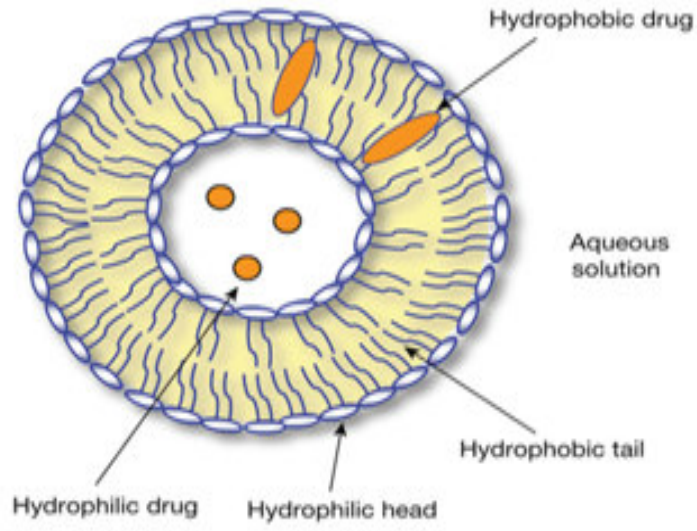

Figure 1
Structure of Niosomes[73]

Table 1
Materials used in the preparation of niosomes

Non ionic surfactant	Example	Reference
Alkyl Ethers		
(i) Alkyl glycerol ethers	Hexadecyldiglycerol ether (C16G2)	[8]
Ii Polyoxyethylene glycol alkyl ethers(Brij)	Brij 30, Brij 52, Brij 72, Brij 76, Brij 78	[9,10]
Crown ethers	Bola	[11,12]
Alkyl esters		
(i) Sorbitan fatty acid esters (Spans)	Span 20, Span 40, Span 60, Span 80, Span 65, Span 85	[13,14]
(ii) Polyoxyethylenesorbitan fatty acid esters (Tweens)	Tween 20, Tween 40, Tween 60, Tween 80, Tween 65, Tween 85	[15]
Alkyl amides		
(i) Glycosides	C-Glycoside derivative surfactant (BRM-BG)	[16]
(ii) Alkyl polyglucosides	Octyl-decylpolyglucoside (OrCG110), decyl polyglucoside (OrNS10)	[17]
Fatty alcohols or fatty acids		
(i) Fatty alcohols	Stearyl alcohol, cetyl alcohol, myristyl alcohol	[18]
(ii) Fatty acids	Stearic acid, palmitic acid, myristic acid	[18]
Block copolymer		
(i) Pluronic	Pluronic L64, Pluronic 105	[19]
Lipidic components		
Cholesterol		[20]
l-α-Soya phosphatidyl choline		[21]
Charged molecule		
Negative charge	Diacetyl phosphate, phosphatidic acid, lipoamino acid, dihexadecyl phosphate	[22, 23]
Positive charge	Stearylamine, stearylpyridinium chloride cetylpyridinium chloride	

Types of niosomes

Niosomes can be divided into three groups on the basis of their vesicles size and lamellarity:

i. Small Unilamellar Vesicles (SUV, size(10–100 nm),
ii. Large Unilamellar Vesicles (LUV, Size (100–3000 nm),
iii. Multilamellar Vesicles (MLV) where more than one bilayer is present[6].

Small Unilamellar Vesicles (SUV)

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of dicetylphosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60based niosomes.

Large Unilamellar Vesicles (LUV)

Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

Multilamellar Vesicles (MLV)

It consists of a number of bilayer surrounding the aqueous /lipid compartment separately. Multilamellar vesicles are the most widely used niosomes.These vesicles are highly suited asdrug carrier for lipophilic compounds[24].

Preclinical And Clinical Aspects Of Drugs Delivered Via Niosomal Carriers

To determine the clinical efficacy and safety of the niosomal carriers loaded with drug, various authors have performed preclinical and clinical studies on this. Given below(table no 2) is a view of various drugs such as anticancer, immunosuppressant, NSAIDS, antibiotics, antibacterial etcdelivered through niosomal vesicular carriers focusing mainly on preclinical and clinical studies[25].

Table 2
Delivery of drugs via Niosomal drug delivery system with their reported preclinicaland clinical studies

Drug	Route of administration	Preclinical and clinical study	Result	Reference
Methotrexate	oral	In-vivo absorbtion study	Enhanced absorption	[26]
Flurbiprofen and Piroxicam	Oral & transdermal	Bioavailability &*in vivo* anti-inflammatory activity	Enhanced bioavailability & effective anti-inflammatory activity	[27]
Erythromycin	Topical	In vivo CLSM(confocal laser-scanning microscopy)	Enhanced penetration	[28]
Sumatriptine Succinate	Nasal	*In vitro* release &*ex-vivo* study	Enhanced nasal absorption & prolonged release.	[29]
Enoxacin	Topical	*In vitro* permeation study	Enhanced permeation	[30]
Insulin	vaginal	*In vivo* Hypoglycaemic activity	Insulin became active and therapeutically effective for vaginal delivery	[31]
Propylthiouracil	Topical	*In vitro* drug release	Controlled drug delivery from Niosomes	[32]
Minoxidil	Topical	*in vitro* skin penetration and permeation study	Increased drug absorption and bioavailability as compared to commercial formulation	[33]
Rofecoxib	Topical	*In vitro* permeation study	Prolonged drug release with improved permeation	[34]
Clobetasol Propionate	Topical	*In vivo* pharmacodynamic study (anti-inflammatory activity	Enhancement in the % reduction in paw oedema exhibited by niosomal gel	[35]
Lornoxicam	transdermal	*In vitro* permeation &*in vivo* inflammatory activity.	Enhanced permeation and better anti-inflammatory activity as compared to solution of drug.	[36]
Silymarin	Hepatic	*In vivo* hepato protective activity & histopathological study.	Improved hepato protective efficiency & was found to be safe.	[37]

Research on niosomal formulation for oral drug delivery

The oral route is usually preferred by most patients. Thus, many studies are conducted to evaluate orally active formulations that may provide potential plasma level[38].Moreover, controlled and sustained release formulations are designed to produce a longer effect in comparison with conventional oral dosage forms. The encapsulation of drugs in niosomes can decrease drug metabolism and increase drug level in blood circulation. Consequently, the use of niosomes can alter the bio-distribution of drug to provide a potential targeting and sustained release effect[39].The delivery of drugs and biopharmaceuticals to the systemic circulation through oral administration is hindered by numerous barriers, including pH gradients, proteolytic enzymes and low epithelial permeabilityetc but delivery of such compounds by encapsulating them in niosomal formulation has proved a possible solution to the problem[40].

Insulin

The oral delivery of recombinant human insulin using niosomal formulations was demonstrated by a study involving polyoxyethylene alkyl ethers based niosomes. Entrapment of insulin in bilayer structure of niosomes protected it against proteolytic activity of α-chymotrypsin, trypsin and pepsin in vitro. Significantly higher protection activity was seen in Brij 92/cholesterol (7:3 molar ratios) in which only 26.3±3.98% of entrapped insulin was released during 24 h in simulated intestinal fluid (SIF)[41]. It thus appears that niosomes could be developed as sustained release oral dosage forms for delivery of peptides and proteins such as insulin.

Peptide drugs

Manosroi*et al*., had demonstrated the enhanced entrapment of charged peptide drugs, bacitracin, insulin and bovine serum albumin in niosomes by modifying the vesicular charge compositions. Cationic, anionic and neutral niosomes were prepared from sorbitan monostearate (Span 60) or polyoxyethylene sorbitan monostearate (Tween 60), cholesterol (CHL), dimethyl dioctadecyl ammonium bromide (DDAB) and/or dicetyl phosphate (DCP). Anionic niosomes were oligolamellar membrane structure with the sizes of 40-60 nm whereas neutral niosomes and cationic niosomes showed the sizes of 0.1-1.3 μm and 100-150 nm, respectively. The highest entrapment efficiency of bacitracin, bovine serum albumin and insulin at 90.88, 72.94 and 87.15 was observed in anionic, neutral and cationic niosomes,respectively . The results suggested the niosomal formulation are appropriate to entrap the peptides with different charges and polarity for pharmaceutical application [42].

Ovalbumin

In one of the first studies of its kind sucrose ester niosomes loaded with ovalbumin were found to cause a modest but significant increase in the level of specific antibodies after oral administration [43].

Zidovudine

Ranga et al formulated Niosomes of Zidovudine by ether injection method by varying ratios of span 80 and span 20 with cholesterol in ratio of 1:1,2:1and 3:1.and dicetyl phosphate added to the formulation to prevent aggregation of vesicles, the prepared vesicles were characterized for their size ,entrapment efficiency leakage studies ,osmotic shock and invitro drug release profile.The study conclusively states that the niosomal formulations of Zidovudine were stable at refrigeration temperatures and can be considered advantageous over the conventional drug deliveries like Zidovudine tablets, since the niosomes provide zero-order release kinetics which is essential for prolonged action of the drug. It can be further concluded that where the drug therapy requires longer duration of treatment as in HIV infections Zidovudine niosomal formulations can be considered ideal[44].

Metformin

Metformin an oral hypoglycaemic encapsulated drug niosomes were designed using thin film hydration technique using Span 40, 60,cholesterol and DCP.The study concluded that the Molar concentration and molar ratio of cholesterol and surfactant, the charge inducer DCP and the volume of hydration used should be in optimized value and greatly influence the entrapment of drug in the vesicles and also alters the performance of niosomes. The optimized formulation (cholesterol: surfactant, 100:100 molar concentration) with DCP (5mg) and 15 ml volume of hydration showed the most sustained release of drug and was found to be the best formulation.The careful control of all the above factors allow the production of a dosage form with sustained release capable of combating the side effects and also reducing the dosing frequency with the greater patient compliance. Suggesting metformin loaded niosomes to be an efficient oral drug carrier system in treatment of Type II Diabetes [39].

Colchicine

Colchicine niosomes were prepared using(Span20,40,60,80), cholesterol and DCP .To obtain the highest encapsulation efficiency, several factors including the structure of surfactant,level of lipid, content of drug and cholesterol were investigated and optimized. The results indicate that Span 60 is the most ideal surfactant among four kinds of Span. Furthermore, the release studies of colchicine and 5-fluorouracil (5-FU) in vitro from niosomes exhibited a prolonged release profile as studied over a period of 24 h. The results demonstrated that niosomes prepared in this way not only have high encapsulation capacity but also is expected that side effects of drugs may be reduced. Totally, the proposed niosomes preparation may be a promising candidate and could be used with a potential application to treat gout [45].

Acyclovir

Acyclovir an antiviral drug frequently used to treat chicken pox has a short biological half life of 2.5h and oral bioavailability is (15%-30%), which necessitates multiply daily dosing and hence a novel delivery system such as niosomes was formulated by Rangasamy et al to increase the oral bioavailability. Acyclovir entrapped niosomes were prepared by hand shaking and ether injection process with different ratios of (1:1, 1;2and 1:3) of cholesterol (CHOL) and Span-80 (Non-ionic surfactant). The vesicles were quite stable and the drug release was extended upto 1 day, 16h. Niosomes could be used as a drug carrier for Acyclovir, for producing prolonged activity and simultaneously reducing side effects and improving its oral bioavailability[46].

Tenofovir disoproxil fumarate

Nonionic surfactant vesicles (niosomes) were formulated with an aim of enhancing the oral bioavailability of tenofovir disoproxil fumarate (TDF), an anti-HIV drug. Niosomes were formulated by conventional thin film hydration technique with different molar ratios of surfactant (Sorbitanlaurate ,Sorbitan monopalmitate, Sorbitan monostearate,Sorbitanoleate), cholesterol, and dicetyl phosphate. All the formulated niosomal vesicles were found to be spherical in shape ranging from2.95 μmto 10.91 μmin size and have zeta values within range. The percentage of drug entrapment was found to be higher with surfactant :CHOL ratio 1 : 1 with all grades of surfactants but sorbitan monostearate showed the highest drug entrapment compared to other grades. *In vitro* study revealed that formulation (with sorbitan monostearate) showed maximum 99.091% drug release at the end of 24 hours. Further, the *in vitro* release profile was fitted to various release kinetics models to predict the release mechanism of drug from the niosomes and the results revealed that all the formulations were best explained by zero order release.The In vivo study was performed on rats to predict the average plasma drug concentration time profile in rats after a single oral dose of TDF (95mg/kg)as plane drug solution and niosomal dispersion (containing both entrapped and unentrapped drug) results showed more than two fold increase in the oral bioavailability of TDF by niosomal formulation and a significant increase in mean residential time (MRT) was also found, reflecting release retarding efficacy of the vesicles. In conclusion, niosomes could be a promising delivery for TDF with improved oral bioavailability and prolonged release profiles[47].

Diclofenac sodium and Lornoxicam

Diclofenac sodium and Lornoxicam are broadly used non-steroidal anti-inflammatory drug for the treatment of inflammatory conditions such as rheumatoid arthritis,osteoarthritis and ankylosing spondilytis but they suffer the drawbacks due to their short half life , frequent dosing and gastric mucosal damage. To avoid these drawbacks Gawhari encapsulated Diclofenac sodium into niosomes by sonication method to develop a suitable niosomal formulation with an optimal encapsulation efficiency and drug release extended over a prolonged period with avoiding its side effect[48],While D.Akhilesh et al formulated Lornoxicam encapsulated niosomes by lipid film hydration technique. Study suggests that niosomal formulation can provide consistent and prolonged release of lornoxicam from different niosomal formulations. It will lead to sustained action of the entrapped drug that reduce the side effects associated with frequent administration of the drug and potentiate the therapeutic effects of the drug[49].

Research on niosomal formulation for ocular drug delivery

An eye is the most precious and easily accessible organ of the body. It possesses easy route to local drug delivery and is a way to non-invasive clinical treatment of ocular diseases. Ocular delivery in spite of possessing various advantages has the limitation of poor bioavailability and low permeability across the cornea thus, limiting the efficacy of drugs.Therefore, various carrier systems have been developed to overcome these limitations. Most recently, niosomes have been developed as efficient vesicular carrier for ophthalmic drug delivery. Large number of drugs of various therapeutic categories have been incorporated in these vesicles enumerated in table no 3. These systems exhibited enhanced permeability required for the treatment of ocular diseases, initiating a new era in vesicular research for ocular delivery. Given below are various reports showing promising future of niosomes

for ocular delivery of various therapeutically active agents more effectively and providing better *in vivo* data thus suggesting the need of the clinical testing of these carriers for their widespread utility.

Brimonidine tartrate

Prabhu*et al* formulated and evaluated Brimonidine tartrate which is used to treat glaucoma, loaded niosomes for *in vitro* and *in vivo* intra ocular pressure lowering activity on male albino rabbits. To observe this activity, acute glaucoma was firstly induced in the rabbits by infusing 5% dextrose solution through the marginal ear vein and then the basal intraocular pressure was measured by tonometer. The formulation containing drug (20 µl, drug equivalent to pure drug solution 0.2%) were administered to rabbits in three different levels. Ocular hypotensive activity was calculated as the intraocular pressure difference between treated and controlled eye of the same rabbit. Niosomes showed better reduction in intraocular pressure due to the better partitioning of drug between vesicle and eye corneal surface. However, it was observed that delivery of drug via niosomes enhanced the local drug concentration at the corneal surface. Prolonged contact time at the desired site of action also improved the bioavailability of the drug. Thus, ocular drug delivery via niosomes modifies the rate as well as extent of absorption, which ultimately resulted in reducing the intraocular pressure. Thereby, exhibiting the controlled ocular drug delivery[50].Maiti*et al* had formulated nanovesicular formulation of brimonidine tartrate for the treatment of glaucoma and evaluated them for in vivo efficacy and eye irritation test. *The intraocular* pressure measurement study was conducted by the authors on normotensive albino rabbits(2-3 kg) which demonstrated intraocular pressure-lowering activity more significantly for a prolonged period of time in comparison to a marketed formulation. It was revealed by the authors that the vesicles increased the absorption of drug by altering the corneal permeability of drug.The authors also evaluated the ocular irritancy effects of optimized niosomal formulations by Eye Irritation Test.The test results confirmed that the Selected niosomal formulations did not showed any sign of irritant effect. Further, a confirmatory test concluded that animals did not showed any ocular lesion in 3 days of study. Thus, it was concluded by the authors that the optimized niosomal formulation were non-irritant and safe for the ocular delivery[51].

Fluconazole

Kaur*et al* had formulated and evaluated elastic surfactant based niosomal vesicular carriers loaded with anti fungal drug fluconazole for effective ocular delivery. These were designed by the authors to prolong the drug release as well as to enhance its effect. These vesicles were prepared by using sorbitan (spans) with an edge activator by ether injection method and characterized for vesicular size, shape, and entrapment efficiency, *ex vivo* corneal permeability and safety test. It was observed by the authors that niosmal formulation showed improved permeability as compared to the marketed formulation. The prepared vesicles were also found to be more stable under stability study of two months. Safety studies were reported as genotoxicity (Ames test), cytotoxicity (MTT assay), and eye irritation revealed that the niosomes loaded with fluconazole were safe. Thus, exhibiting itself an effective carrier for the ocular drug delivery [52].

Chloramphenicol

Yasin *et al* had designed niosomes of chloramphenicol for the treatment of conjunctivitis and compared it with the marketed chloramphenicol eye drop. Niosomes were prepared by ether injection method and evaluated for particle size, zeta potential, viscosity, entrapment efficiency, and stability study, *in vitro* and *in vivo* studies. *In vivo* study was conducted on twelve rabbits divided into two groups, each containing six rabbits. Ist group was treated with ophthalmic drops of chloramphenicol and second group with niosomal suspensions loaded with chloramphenicol. Sample (aqueous humour) was drawn periodically up to 8 hrs and analyzed by HPLC (High performance liquid chromatography) and the study was done in duplicate. Result was then recorded by visualizing the sign of conjunctivitis and the recovery of the rabbits. It was observed that from both the studies , each group of rabbits showed similar recovery pattern from conjunctivitis. But, niosomal suspensions exhibited better treatment efficacy with less toxic effect as compared to commercial drops. Thereby, improving the patient compliance. No sign of irritation or redness was observed with the niosomes containing chloramphenicol. Thus, it was concluded that niosomes were appropriate as a carrier for the treatment of conjunctivitis for ophthalmic sustained release[53].

Acetazolamide

Acetazolamide, a carbonic anhydrase inhibitor is used orally (no topical formulation being available in the market) for the reduction of intraocular pressure (IOP) in patients suffering from glaucoma. Two major reasons responsible for the failure to develop a topically effective formulation of acetazolamide are its low solubility (0.7mg/ml) and its low permeability coefficient. It is assumed that topical acetazolamide formulation possessing efficacy similar to that achieved upon oral administration would be a significant advancement in the treatment of glaucoma. In order to enhance the bioavailability of acetazolamide by topical route and to improve the corneal permeability of the drug, the niosomes of acetazolamide were prepared (by reverse phase evaporation method) and coated with Carbopol for the latter's bioadhesive effect.*In vivo* pharmacodynamic studies performed in male albino rabbits, reported reduction in intraocular pressure by 33%. The selected niosomal formulation exhibited four times higher concentration as compared to the dorzolamide (Dorzox, a topical marketed product). The concentration of acetazolamide absorbed in the aqueous humor from both control and selected niosomal formulation was determined by microdialysis. The peak concentration of amount of drug absorbed in the aqueous humor via niosomal formulation was reported to be twice of that obtained via control suspension, after 20 min. of instillation. Thus, depicting the fact that enhanced penetration was achieved with niosomal formulation. Therefore, it was revealed that niosomes were effective in enhancing the bioavailability of acetazolamide, effective in the treatment of glaucoma [54].

Table 3
Ocular delivery of variety of drugs via Niosomes

Drug encapsulated	Therapeutic category	Conclusion	Reference
Ofloxacin	antibiotic	Improved corneal Penetration and bioavailability in a controlled manner	[55]
Gentamycin	antibiotic	Occular irritancy test results showed no Signs of redness or inflammation and was found effective for ophthalmic delivery.	[56]
Naltrexone	Narcotic antagonist	conjunctival and corneal toxicity test, hen"s egg test-chorioallantoic membrane (HET-CAM), bovine corneal opacity and permeability (BCOP) test as well as corneal histopathological test showed better ocular tolerability and less ocular irritation, effective system for safe and effective drug delivery across cornea for the treatment of diabetic keratopathy.	[57]
Flupirtine Maleate	Non Opoid Analgesic	Ocular irritancy test, *In vivo* trigeminal neuralgia test showed that niosomal formulation was capable of delivering the drug with reduced dosing frequency as well as side effect.	[58]
Cyclopentolate	anticholinergic used to produce pupil dilation(mydriasis)	*In vitro* absorption study, *in vivo* mydriatic activity results showed enhanced absorption of cyclopentolate by altering the permeability across conjunctiva and sclera.	[59]
Timolol Maleate	Antiglaucoma, antihypertensive, antiarrhythmic and antiangina, agent.	niosomal vesicles exhibited sustained controlled ocular drug delivery	[60]

Research on niosomal formulation for transdermal drug delivery

Niosomesare receiving much attention as potential transdermal drug delivery systems due to their properties such as enhanced drug penetration, local depot for sustained drug release, and a rate-limiting membrane for modulation of systemic absorption of drugs via the skin.Niosomal carriers are suitable for the transdermal delivery of numerous pharmacological agents, including antioxidant, anticancer, anti-inflammatory, antimicrobial, and antibacterial molecules etc. Niosomes were introduced for use in the cosmetic industry. The first report on surfactant vesicles came from the cosmetic applications devised by L'Oreal[61].Since then, there has been increasing interest in the use of niosomes in the pharmaceutical, cosmetic, and food industries. Drug reaching the bloodstream is the aim of transdermal targeting, and is becoming a focus of interest for many pharmaceutical research groups studying diseases such as inflammation, cancer, psoriasis, alopecia, and acne [62]. The transdermal route has several advantages over the conventional routes of drug administration: peak and trough levels in serum (a risk and inconvenience of intravenous therapy) are avoided; first-pass hepatic metabolism and gastrointestinal degradation (pH, enzymatic activity, and interactions with food, beverages, and other orally administered drugs), are avoided, leading to an increase in drug bioavailability and efficacy; and it can serve as an alternative to oral drug administration when that route is unsuitable (eg, vomiting and diarrhea). Other advantages of the transdermal route include the accessibility of the skin, the relatively large surface area for absorption, and the fact that it is noninvasive, making the patient more compliant. Recent collection of investigation in this field are given below and in table no 4.

Sulfadiazine sodium

Non-ionic surfactants belonging to the class of Pluronic and sucrose esters were used both as components of niosomal systems and in the form of sub-micellar solutions containing Sulfadiazine sodium.The results proved that only direct treatment of the skin with sulfadiazine loaded niosomes increased the percutaneous permeation of the drug, confirming the role of niosomes as enhancers. Direct contact between the vesicles and the skin is essential for efficient delivery, although surfactants apparently do not penetrate into the deeper skin layers, and the presence of drug and vesicular carriers must be simultaneous. Only in this case the intercellular lipid barrier in the stratum corneum would be dramatically changed to be more permeable[63].

Aceclofenac and Meloxicam

Niosomes containing nonsteroidal anti-inflammatory drugs (NSAIDs) have been prepared by different groups of researchers, as these drugs may cause local mucosal irritation and undergo first-pass metabolism in the liver after oral administration, which leads to partial inactivation. Thus, only 50% of the drug reaches the circulation. Transdermal dosage forms are desirable for long-term use of this drug, especially when used to treat rheumatic symptoms. The efficacy of topical NSAIDs depends greatly on their capacity to penetrate through the skin[64].Nasr et al reported better stability and efficacy of their newly developed aceclofenac niosomes when compared with liposomes for targeting of aceclofenac via the skin. The anti-inflammatory effect of aceclofenac vesicles was assessed using the rat paw edema technique. The data showed that the entrapment efficiency and in vitro release of aceclofenac from the vesicles can be manipulated by varying the cholesterol content, the type of surfactant used, and the type of charge. Both vesicular systems had significant sustained anti-inflammatory activity when compared with the marketed product, with niosomes being superior to liposomes, as manifested by edema and inhibition percentages, suggesting their effectiveness as transdermal anti-inflammatory delivery systems[65]. Similarly El-Badry formulated meloxicam an anti-inflammatory drug loaded niosomal gel using poloxamer-407, chitosan, and carbopol-934 results

showed the superiority of niosomal gels over conventional gels[66].

Baclofen

Niosomes loaded with baclofen, a centrally acting muscle relaxant, were prepared by lipid film hydration technique to improve the low skin penetration and poor bioavailability of conventional topical formulations containing this drug. Vesicles were prepared using nonionic surfactant (Span 20) and cholesterol in different molar ratios which resulted in improved muscle relaxant activity[67].

Papain

Papain is a protease enzyme from Carica papaya latex, which is widely used in dermatology for the treatment of scars. Manosroi et al compared the transdermal release of papain from gel formulations containing niosomes or nanospheres. They demonstrated that niosomes (especially elastic niosomes obtained from Tween 61/cholesterol with sodium cholate as an edge activator) could enhance transdermal absorption of papain through rat skin and improve scar reduction in a rabbit ear model, which would be beneficial for development of topical products for the treatment of scars[68]

Table 4
Transdermal delivery of variety of drugs via Niosomes

Drug encapsulated	Therapeutic category	Conclusion	Reference
vinpocetine,	anti-inflammatory agent, potential role in the treatment of Parkinson's disease and Alzheimer's disease.	High efficiency of enhanced systemic transdermal delivery with lack of irritation and excellent safety profiles.	[69]
Resveratrol,alpha-tocopherol,and curcumin	Anti-oxidant	In vitro percutaneous permeation profiles for the antioxidants appeared to be controlled and improved.Resulted in an improved ability for inhibition of free radicals due to a synergistic antioxidant action.	[70]
Simvastatin	lipid-lowering agent	Significantly improved the bioavailability of drug and hypocholesterolemic effect in the treatment of hypercholesterolemic rats.	[71]
Lopinavir	protease inhibitor used in the treatment of AIDS	Ability to improve the overall bioavailability of lopinavir with lack of irritation and safety	[72]

CONCLUSION

The investigation conclusively supports that niosomes have been demonstrated to be promising controlled delivery systems for oral,ocular and transdermal administration of both hydrophilic and lipophilic drugs.There is lot of scope to encapsulate toxic anti-cancer, anti-infective, anti-HIV, anti-inflammatory, anti-viral drugs etc. in niosomes and to use them as promising drug carriers to achieve better bioavailability and targeting properties and for reducing the toxicity and side effects of these drugs. The potential of niosomes can be enhanced by using novel preparation, loading, and modification methods. These areas need further exploration and research for the development of niosomal preparations that can be made available commercially. Special attention should be given for appropriate selection of suitable surfactants for preparation of niosomes as the type of surfactant used is the main parameter for determining the successful formulation of these vesicles, along with their toxicity, stability, and potential applications.So far only animal experimentation of niosomal products are reported but further clinical investigations in human volunteers, may open new gateways for newer commercially available niosomal products.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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Reviewers of this article

Dr. Rishikesh Gupta, M.Pharm, Ph.D

Assistant Professor, Department of Pharmacy, Institute pf Pharmacy, Bundelkhand University, NH 25,Jhansi-Kanpur Road, Jhansi, Uttar Pradesh 284128, India

G. Bakhya Shree M.S. (Research)

Coordinator and Trainer, Department of Biotechnology and Life Sciences, Dexter Academy, Madurai, Tamilnadu

Prof.Dr.K.Suriaprabha

Asst. Editor , International Journal of Pharma and Bio sciences.

Prof.P.Muthuprasanna

Managing Editor , International Journal of Pharma and Bio sciences.

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