wjpmr, 2022,8(2), 137 – 145.

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH
www.wjpmr.com

SJIF Impact Factor: 5.922

Review Article
ISSN 2455-3301
WJPMR

REVIEW ON NIOSOMAL INSITUGEL AS AN SUITABLE VEHICLE FOR OCULAR DRUG DELIVERY SYSTEM

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Article Received on 14/12/2021 **Article Revised on 04/01/2022** **Article Accepted on 24/01/2022**

ABSTRACT

The common principle behind the success of pharmacotherapy is that the suitable drug should be present in proper concentration at the site of action for a sufficient period of time. Drug delivery in ophthalmic treatment is very challenging because of the distinctive anatomy and physiology of eye containing different barriers like many layers of cornea, sclera and retina, blood retinal, lachrymal fluid-eye barrier and drug loss from the ocular surface. To overcome those obstacles, vesicular systems especially Niosomes, a non-ionic surfactant-based vesicle are preferred due to their stability and ability to promote drug absorption by modifying the permeability of the conjunctival and scleral membranes of ophthalmic region. They provide prolonged duration of action by preventing ocular metabolism in the lachrymal fluid. Niosomes have wide access in the treatment of inflammation, dry eye, allergy, ocular hypertension, and glaucoma. In addition, it has the advantage of drug to be administered in the form of a drop, which shows significant advancement in prolonging the preocular retention on the eye surface and improvement of transcorneal penetration of novel therapeutic agents.

KEYWORDS: Niosomes, *In-Situ* Gel, Methods, Ocular Drug Delivery.

INTRODUCTION

The ocular globe is an inimitable organic structure which comprises spectacular anatomic, histological, and physiological features. Mainly, the ocular globe may be segmented in two chief parts—the anterior and posterior portions. The anterior portion pertains about one-third of the eye and is constituted by the aqueous humour, conjunctiva, cornea, iris, ciliary body and lens, with the remaining second-third occupied with the posterior portion, made up of the choroid, neural retina, optic nerve, retinal pigment epithelium, sclera, and vitreous humor. According with the segment of the eye, elicited, several diseases can be pointed out. For the anterior segment of the eye a diversity of illnesses can be named as conjunctivitis, anterior uveitis, or cataracts.[1]

Ocular drug delivery is an extremely important topic, especially with the recent development of new drugs for age-related macular degeneration. Drug delivery to the eye can vary in ease from the simple topical eye drop, which rapidly penetrates to the anterior chamber, to the complicated engineering skills required to develop intravitreal implants.[2]

Revolutionary new therapies for treatment of ocular diseases have emerged due to the recent advances in drug delivery approaches and materials sciences. Current drug delivery to the eye has been limited to topical application, redistribution into the eye following systemic administration or directs intraocular/periocular injections. Topical drops are more convenient, but wash away, delivering less than 5% of the applied drug into the anterior section of the eye, and a small fraction of that dose to the posterior section of the globe. Cross section of the human eye. Systemic administration of therapeutics to treat ocular disorders exposes the whole body to the potential toxicity of the drug. Hence, there is a need for development of effective drug delivery strategies for the eye.[3]

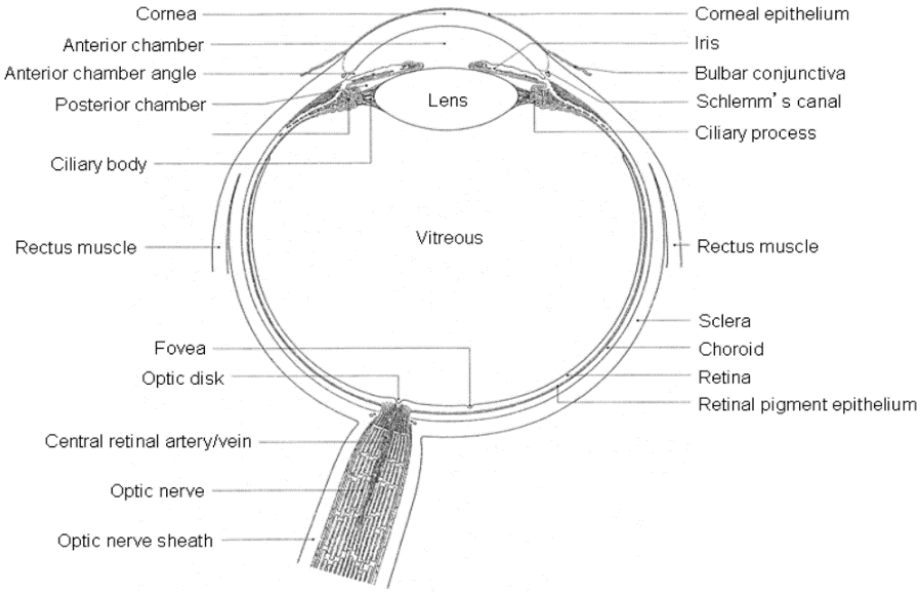

Fig. 1:

Drawbacks of ocular drug delivery

The major drawbacks of ophthalmic drug delivery systems are as follows

- Short contact time of drug solution and eye surface.
- Poor bioavailability.
- Instability for dissolved drugs.
- Use of preservatives
- Termination of the dosage form is not possible during an emergency.
- Interference with vision.
- Faces difficulty in placement and removal of the dosage form.
- During sleep or while rubbing eyes, there may be an occasional.[4]

Approaches in ophthalmic drug delivery systems

A number of approaches have been used in the early stages for better results. These approaches, categorized into two types, are:

- Bioavailability improvement and
- Controlled release drug delivery[4]

Traditional approaches like viscosity enhancers, gel, penetration enhancer, prodrug, liposomes improve the ophthalmic bioavailability of the drugs to the anterior segment of the eye. Various modern approaches like *in situ* gel, ocuserts, nanosuspension, nanoparticles, liposomes, niosomes, and implants improve the ophthalmic bioavailability of the drugs and controlled the release of the ophthalmic drugs to the anterior segment of the eye.

Moreover, approaches like intravitreal injections, iontophoresis, subconjunctival injection, and periocular route are used to deliver ophthalmic drugs to the posterior segment of the eye.[5]

Viscosity enhancers

Viscosity-increasing polymers are usually added to ophthalmic drug solutions on the premise that an increased vehicle viscosity should correspond to a slower elimination from the preocular area, which lead to improved precorneal residence time and hence a greater transcorneal penetration of the drug into the anterior chamber. It has minimal effects in humans in terms of improvement in bioavailability. The polymers used include polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose.[5]

Gel formulation

Gels are known to be significantly dilute cross-linked systems, which show rigidity in the steady-state. Gels are generally liquid, but behave like solids due to their three-dimensional cross-linked structure within the liquid The highly viscous solution even leads to blurred vision and matted eyelids, which substantially decrease patient's compliance. In aqueous gel, viscosity building agents, such as PVA, polyacrylamide, poloxamer, HPMC, Carbomer, polymethylvinylether, Maleic anhydride, and hydroxylpropylethylcellulose are incorporated, whereas hydrogel or swellable water-insoluble polymers give rise to controlled drug delivery systems.[4]

Penetration enhancers

Corneal epithelial membrane plays an important role in terms of permeability. So, by increasing its permeability, the transport property around cornea can be enhanced. Agents showing such properties are chelating agents, preservatives (like benzalkonium chloride), surfactants and bile acid salts, but due to local toxicity, they cannot be used in development ophthalmic formulation.[4]

Prodrug

The principle of prodrug is to enhance corneal drug permeability through modification of the hydrophilicity (or lipophilicity) of the drug. Within the cornea or after corneal penetration, the prodrug is either chemically or enzymatically metabolized to the active parent compound. Thus, the ideal prodrug should not only have increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility Some examples of suitable prodrug include the antiviral medications ganciclovir and acyclovir.[5]

Liposomes

Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments. Liposomes possess the ability to have an intimate contact with the corneal and conjunctival surfaces, which increases the probability of ocular drug absorption. This ability is especially desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility, or those with medium to high molecular weights. It provides the sustained release and sitespecific delivery. Liposomes are difficult to manufacture in sterile preparation. It has limitation like low drug load and inadequate aqueous stability.[5]

In situ-forming gel

The droppable gels are liquid upon instillation, and they undergo a phase transition in the ocular cul-de-sac to form a viscoelastic gel, and this provides a response to environmental changes. It improves the patient acceptance. It prolongs the residence time and improves the ocular bioavailability of the drug. Parameters that can change and trigger the phase transition of droppable gels include pH, temperature, and ionic strength. Examples of potential ophthalmic droppable gels reported in the literature include gelling triggered by a change in pH - CAP latex.[5]

Niosomes

Niosomes are chemically stable, bi-layered nanocarriers made up of nonionic surfactants and used as carriers for both hydrophilic and hydrophobic drugs. They do not have drawbacks like liposomes that are chemical instable, susceptible to oxidative degradation and made up of phospholipids that are very much unstable as well as expensive. Thus, niosomes have lots of advantages including that they are biodegradable, biocompatible and nonimmunogenic, which make them increase the contact time between drug and cornea, thereby increasing the bioavailability of drugs. Use of niosomal carrier as a drug delivery system has been reported for genciclovir,[42] cyclo-pentolate, or timolol.[4]

Nanoparticles/nanospheres

These are polymeric colloidal particles, ranging from 10 nm to 1 mm, in which the drug is dissolved, entrapped, encapsulated, or adsorbed. Encapsulation of the drug leads to stabilization of the drug. They represent promising drug carriers for ophthalmic application.[34] They are further classified into nanospheres (small capsules with a central cavity surrounded by a polymeric membrane) or nanocapsules (solid matricial spheres).

Alonso *et al*. have also reported that the nanoparticles of poly-e-caprolactone containing cyclosporin show a better corneal absorption with respect to the oily solution of the drug.[5]

Nanosuspension

Nanosuspensions are generated for poorly water-soluble drugs suspended at nano size range in a suitable dispersion medium. This technology can be utilized in a good way for drug moiety that forms crystals with high energy content, due to which they are insoluble in organic (lipophilic) or hydrophilic media. Polymeric nanoparticle suspensions are being formulated using inert polymeric resins, which can be used as vital drug delivery vehicles, having the capacity to increase drug release as well as improve its bioavailability. The carriers having such type of properties can be used as inert carriers for ophthalmic drugs, because they donot cause any irritation to the cornea, iris or conjunctiva. An example of such carrier is polymeric nanoparticle suspension having flurbiprofen (FLU) as an active ingredient and eudragit RS 1001 and RL 1001 are polymers used. Nanodispersions of alginate chitosan produced for sustained drug delivery and improved transcorneal permeation have been reported by Morsi *et al*.[4]

Method of preparation

The general method of preparation of niosomes involves organic solvents on evaporation leads to production of a lipid film followed by subsequent hydration with the aqueous medium. However there are various methods that are described in elaborate.[6]

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 PH gradient drug uptake
h) The bubble method

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.[8]

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 rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes film of lipid on the wall of rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.[8]

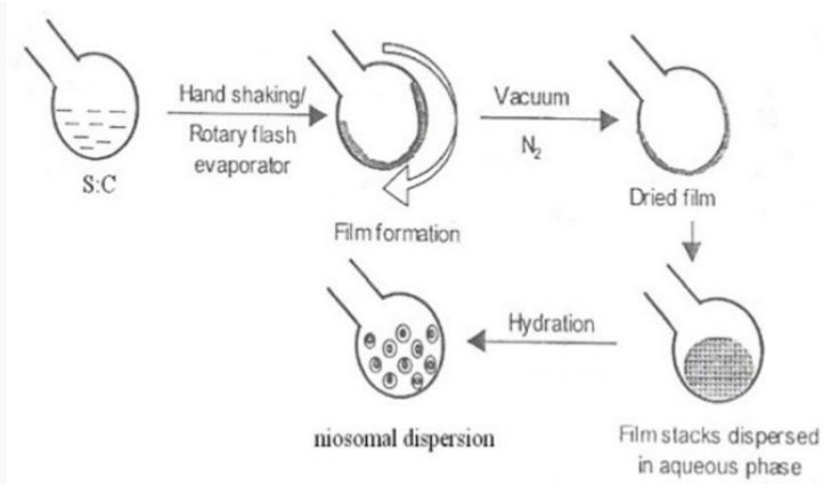

Fig. 2:

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 ultrahigh velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed.[9]

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 drug16. The resultant solution is extruded through poly carbonate membrane (0.1µm nucleophore) by using C16G12.[7]

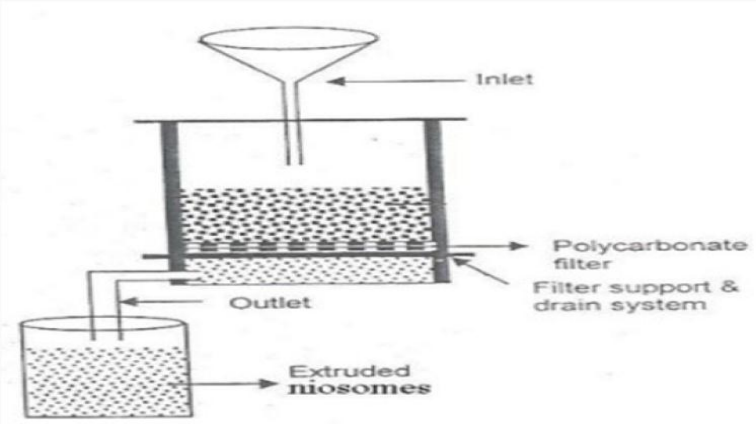

Fig. 3:

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 have reported the

preparation of Diclofenac Sodium niosomes using Tween 85 by this method.[8]

Sonication method

Bansal et al. used the sonication method to prepare niosomes of cefdinir. They added a mixture of surfactant and cholesterol to the solution of drug in the buffer. The resultant mixture is probe sonicated at 60 °C using a probe sonicator, to produce multilamellar vesicles. It could be further ultrasonicated to produce unilamellar vesicles.[4]

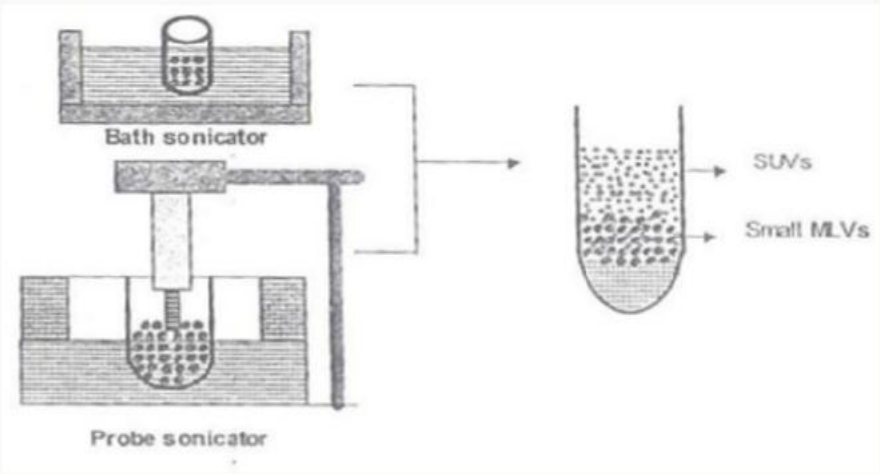

Fig. 4:

Transmembrane PH 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 (PH 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 PH between 7.0-7.2, phosphate buffer is used. Then the mixture is heated at 60ºc for 10 minutes to yield niosomes.[7]

The "Bubble" Method

It is one step technique by which liposomes and niosomes are prepared without the use of organic solvents. Round bottomed flask is used as bubbling unit with its three necks positioned in water bath to control the temperature. Water cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. At 70°C Cholesterol and surfactant are dispersed together in the buffer (pH 7.4) and mixed with high shear homogenizer for 15 seconds and immediately afterwards "bubbled" at 70°C using nitrogen gas.[11]

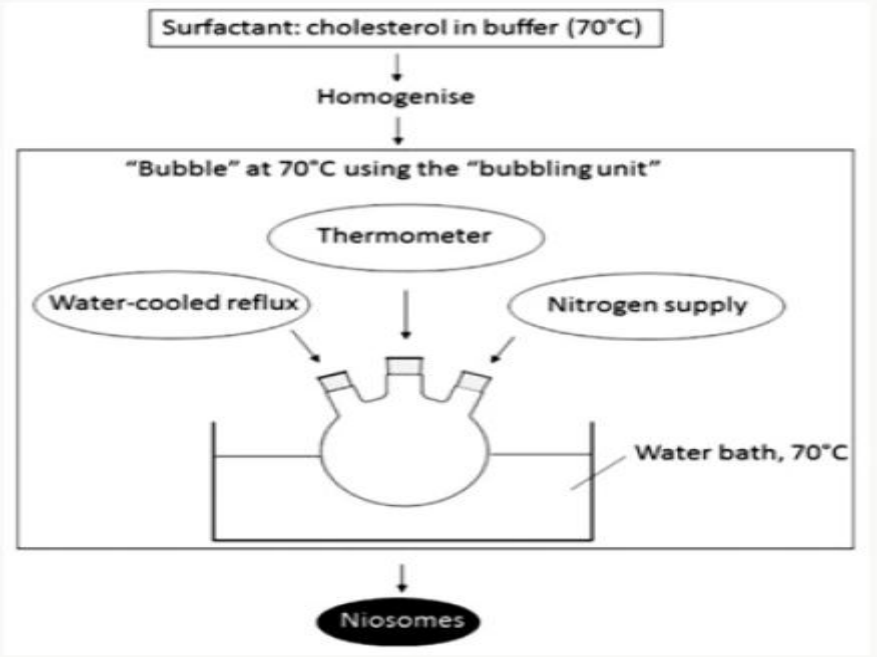

Fig. 5:

Evaluation test[12,13]
Table 1:

SL NO	EVALUATION METHODS	INSTRUMENTS
1.	Thickness of film	Dial caliper
2.	Folding endurance test	Schopper double fold tester
3.	Uniformity of weight	Digitial balance
4.	Uniformity of thickness	Verneir caliper
5.	Drug content	UV-VIS spectrophotometer
6.	Surface PH	Urine dipstick reagent strip
7.	Percentage moisture absorption	Moisture balance, moisture meter
8.	Percentage moisture loss	Moisture balance, moisture meter
9.	Swelling index	Bulk hydrophilicity and fluid uptake
10.	In vitro drug release study	Franz diffusion cell and dialysis membrane
11.	Sterility test	Membrane filtration techniques, direct – inoculation techniques

Application
The application of niosomes technology is widely varied and can be used to treat a number of diseases. The following are a few uses of niosomes which are either proven or under research.

Niosome as a carrier for hemoglobin
Niosomal suspension shows a visible spectrum super imposable onto that of free hemoglobin so can be used as a carrier for hemoglobin. Vesicles are also permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated haemoglobin.

Niosomes as drug carriers
Niosomes have likewise been utilized as transporters for iobitridol, a symptomatic operator utilized for X-ray imaging.

Ophthalmic drug delivery
It is difficult to achieve excellent bioavailability of drug from ocular dosage form like ophthalmic solution, suspension and ointment due to tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time.

Delivery of peptide drugs
Yoshida et al investigated the stability of peptide increased by niosomes. In Yoshida et al for oral delivery of 9-desglycinamide, 8-arginine vasopressin entrapped in niosomes in an *in-vitro* intestinal loop model and reported that the stability of peptide increased by niosomes.

Transdermal delivery of drugs by niosomes
In transdermal route of delivery, when drug is incorporated in niosomes penetration of drug through skin is enhanced.

Neoplasia
The anthracyclic antibiotic such as Doxorubicin which shows broad spectrum anti tumour activity, produces a dose depend antirreversible cardio toxic effect. This drug increased the lifespan and decreased the rate of proliferation of sarcoma when administered by niosomal delivery into mice bearing S-180 tumor.

Anti-inflammatory agents
Niosomal formulation of Diclofenac sodium with70% cholesterol exhibits greater anti-inflammator activity as compare to free drug. Niosomal formulation of Nimesulide and Flurbiprofen shows greater anti-inflammatory activity as compared to free drug.

Leishmaniasis
Niosomes can be utilized for focusing of medication in the treatment of maladies in which the contaminating life form lives in the organ of reticulo-endothelial framework. Leishmaniasis is such an infection in which parasite attacks cells of liver and spleen.

Immunological application
Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability.

Tetanus toxoid (TT)
Yoshika et al defined Span/CHOL/DCP niosomes containing lockjaw toxoid which was a vesicle-in water-in oil framework. Cottonseed oil was utilized and gave better immunological properties when contrasted with free antigen.

Niosomes in gene delivery
Novel niosome detailing in light of the 2,3-di (tetradecyloxy) propan-1-amine cationic lipid, joining with squalene and polysorbate 80 to assess the transfection productivity in rodent retinas. Lipoplexes at 15/1 proportion were 200 nm in measure, 25mV in zeta potential and displayed circular morphology.[14]

Table 2: Recently Reported Drug Carriers for Ocular Drug Delivery.

SI NO	AUTHOR	DRUG	METHOD	REMARKS
1	Sundaramurthy A (2018)	Metformin, Glipizide.	Thin film hydration technique.	Niosomal formulation for encapsulation and release of glipizide and metformin hcl for the treatment of diabetes is reported.[15]
2	Cosco D, Paolino D (2009)	5-Fluorouracil	Thin layer evaporation technique	A relatively small number of investigations are found in literature that treat the potential use of niosomes as drug delivery systems to be administered systemically for the treatment of cancerous diseases.[16]
3	Attia IA (2007)	Acyclovir	Thin film hydration method.	The prepared acyclovir niosomes have unilamellar spherical shape with average size of 0.95 μm and percentage drug Entrapment of 11%. The niosomal formulation showed sustained release characteristics with higuchi pattern of drug Release.[17]
4	Muller JM (2004)	Vasoactive Intestinal Peptide	Probe sonication method	The present study demonstrated that the administration of systemic glucose-bearing vesicles encapsulating vip could deliver intact vip to specific brain areas. Therefore, glucose-bearing vesicles represent a novel tool to deliver drugs across the bbb.[18]
5	Pardakhty A (2007)	Insulin	Thin film hydration method	The results of this study show that polyoxyethylene alkyl ether type of non-ionic surfactants can be used for preparation of insulin entrapping niosomes.[19]
6	Abdelbary G (2008)	Gentamicin Sulphate	thin film hydration technique	The results of this study show that cholesterol content, type of surfactant and the presence of charge inducer dicetyl phosphate, altered the entrapment efficiency %ee and release rate from gentamicin sulphate niosomes.[20]
7	Hashim F (2010)	Ribavirin	Thin film hydration method	The present study indicates that, the niosomal formulation significantly increased ribavirin liver concentration (6-fold) in comparison with ribavirin free solution.[21]
8	Gupta M (2011)	Fluconazole	Thin film hydration method	The type of surfactant altered the entrapment efficiency and size as well as modifi ed the drug release rate from niosomes.[22]
9	Pillai GK (1999)	Indomethacin	lipid hydration method	In addition to the action of indomethacin on the platelet receptor, some of the niosomal indomethacin may enter the platelets by fusion and endocytosis and act directly on the cyclo-oxygenase system to prevent thromboxane Formation.[23]
10	Paolino D (2007)	Ammonium glycirrhizinate	film hydration method	Bola-niosomes presented a certain safety and tolerability both *in vitro* on human keratinocyte NCTC2544 cells up to An incubation time of 72 h for the different concentrations investigated (0.01, 0.1, 1 and 10 μm) and *in vivo* on human Volunteers that showed no skin erythema when topically treated with the unloaded Bola-niosome formulation.[24]
11	Udupa N (1994)	vincristine sulfate	transmembrane pH gradient drug uptake process	Niosomal vincristine sulfate resulting in decreased toxicity And improved anticancer activity may be very Promising in cancer therapy.[25]
12	De A (2018)	Temozolomide	thin-film	The niosomal formulation

			hydration	Strategy not only enhances its stability and sustains release, it's also one of the unique formulations containing the charge inducer which has an electropositive characteristic to cross the BBB.[26]
13	Akbarzadeh I (2020)	Doxycycline	Thin layer hydration techinque	The niosomal formulation was optimized using a multi-objective response surface methodology to obtain a formulation with the highest encapsulation efficiency but the minimum size and PDI.[27]
14	Momekova D (2020)	Doxycycline hyclate	Thin film hydration method	The aim of the study several thermo-sensitive *in situ* gels were prepared and evaluated as a potential platform for incorporation of doxycycycline hyclate loaded niosomes for ophthalmic application.[28]
15	Ali J (2017)S	Lacidipine	Thin film hydration technique	The present study conclusively demonstrates the use of Box- Behnken design in formulation and optimization of LAC niosomes gel formulations to avoid its systemic toxicity.[29]

CONCLUSION

It has the advantage of drug to be administered in the form of a drop, which shows significant advancement in prolonging the preocular retention on the eye surface and improvement of transcorneal penetration of novel therapeutic agents.

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