NIOSOMAL IN-SITU GEL DRUG DELIVERY: A REVIEW

Sachin C. P.*, Gowtham M. and Vimal V. V.

*Department of Pharmaceutics, Rajiv Gandhi Institute of Pharmacy, Trikaripur, Kasaragod, Kerala, 671310.

Kerala University of Health Sciences, Thrissur.

ABSTRACT

Eye is the most vital organ of the body. Most ocular diseases are treated by topical drug application in the form of solutions, suspensions and ointment. The major drawback associated with conventional ophthalmic formulations is quick precorneal drug loss resulting in poor bioavailability and therapeutic response, because of high tear fluid turnover and dynamics. In-situ gelling ophthalmic drug delivery system is developed to overcome this bioavailability problems. In-situ forming gels are solutions, instilled as drops into the eye and undergo a sol-to-gel transition in the cul-de-sac. Drug delivery through niosome is one of the approaches to achieve localized action and it result in enhancement of efficiency of same drug and at the same time reduces its systemic toxic effects. Thus, niosomes entrapped through in-situ gel system has been developed to increase precorneal residence time, to minimize interference with blinking, enhance ocular bioavailability and reduce frequency of the administration of drug. The aim of this article is to present a concise review of niosomal in-situ gelling system to overcome conventional ophthalmic dosage forms problems.

KEYWORDS: Niosomes, In-situ gelling systems, Temperature sensitive, pH sensitive, Ion sensitive.

INTRODUCTION

The eye is a complex organ with a unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make
up the anterior portion. Back of the eye or posterior segment of eye include sclera, choroid, retinal pigment epithelium, neural retina, optical nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening diseases.\textsuperscript{[1,18,19]}

In the development of ocular drug delivery system lot of complications and difficulties are found. The conventional drug delivery such as suspension, ointment, solution, show some drawbacks like increase pre-corneal drainage, blurred vision, low bioavailability and low residence time. Most ocular diseases are treated with topical application of solutions administered as eye drops.\textsuperscript{[2]} Topical eye drops is the most convenient and patient compliant route of drug administration, especially for the treatment of anterior segment diseases. One of the major problems encountered with topical delivery of ophthalmic drugs is the rapid and extensive precorneal loss caused by drainage and high tear fluid turnover. After instillation of an eyedrop, typically less than 5% of the applied drug penetrates the cornea and reaches intraocular tissues, while a major fraction of the instilled dose is often absorbed systemically via the conjunctiva and nasolacrimal duct.\textsuperscript{[1]}

Drug delivery through niosomes is one of the approaches to achieve localized drug action. Since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. It results in enhancement of efficiency or potency of same time reduces its systemic toxic effects.

In-situ gelling systems are described as low viscosity solution that phase transition in cul-de-sac to form viscoelastic gel. Thus, niosomes entrapped through in-situ gel system has been developed to increase precorneal residence time, to minimize interference with blinking, enhance ocular bioavailability and reduce frequency of administration of drug.\textsuperscript{[3]}

**NIOSOMES**

Niosomes are microscopic lamellar structures formed on admixture of a nonionic surfactant, cholesterol and a charge inducing agent with subsequent hydration in aqueous media. They possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities. They have been evaluated in many pharmaceutical applications. In such therapeutic applications, important advantages of using niosomes include their ability to reduce systemic toxicity by encapsulation of treatment agents and minimize clearance of such agents from the body by slow drug release.\textsuperscript{[4]}
Advantages\textsuperscript{[5]}

1. Niosomes can accommodate a variety of drug moieties such as hydrophilic, lipophilic, as well as amphiphilic drugs.

2. Vesicle characteristics can be controlled by altering the composition of vesicle, size lamellarity, surface charge, tapped volume and concentration.

3. The drug can release in the sustained/controlled manner.

4. No special condition required for handling and storage of surfactants.

5. Due to the depot formulation, it allows controlled release of the drug.

6. Poorly soluble drugs have increased oral bioavailability.

7. Surfactants possess following response biodegradable, biocompatible, and non-immunogenic

8. They can protect the active moiety from biological circulation.

9. Drug protection from enzyme metabolism.

10. Improve the stability of entrapped drug.

PREPARATION OF NIOSOMES\textsuperscript{[5,6,15,16,17]}

A. Passive trapping techniques\textsuperscript{[5]}

This category includes most of the techniques used in preparation of niosomes in which drug is incorporated during the preparation of niosomes i.e. during their formation.

1. Ether injection method

The first step in niosome production by ether injection is through the dissolution of surfactant in diethyl ether. The solution is then injected through a 14-gauge needle into an aqueous solution of drug maintained at 60°C. Subsequently, single layer vesicles with diameters
ranging from 50 to 1000 nm are formed because of the vaporization of ether.

2. **Hand shaking method**
Also known as thin film hydration technique. Surfactant and cholesterol are dissolved in a volatile organic solvent and transferred to a rotary evaporator. After evaporation, a thin layer of solid mixture is deposited on the wall of the flask. The dried layer is then hydrated with an aqueous phase containing the drug of interest. This process may be carried out at room temperature with gentle agitation.

3. **Sonication**
Niosomes can also be produced through sonicating a mixture of surfactant, cholesterol and aqueous containing the drug at 60°C for 3 min. The vesicles produced through this method are usually small and uniform in size.\(^6\)

4. **Reverse phase evaporation technique**
Cholesterol and surfactant (ratio of 1:1) dissolves in the mixture of organic solvent (ether and chloroform). Addition of the aqueous drug solution to this and water in oil emulsion is formed; two phases are sonicated at 4-5°C. The emulsion is dried in a rotary evaporator at 40°C to form a semisolid gel of large vesicles. Small amounts of phosphate buffered saline (PBS) are added to the clear gel and sonicate again. The organic phase is removed at 40°C and lower pressure. Viscous niosomal suspension is further diluted with phosphate buffered saline, then heat on a water bath at 60°C for 10 min to form niosomes.\(^5\)

5. **The bubble method**
Bubbling unit involves round-bottomed flask with three neck position in water bath to control the temperature. Water-cool reflux is positioned in the first neck and thermometer is positioned in the second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed in the buffer (pH 7.4) at 70°C. Dispersion mixing for 15 seconds with high shear homogenizer. “Bubbled” at 70°C using nitrogen gas.

6. **Multiple membrane extrusion method**
Mixture of surfactant, cholesterol and diacetyl phosphate in chloroform forms thin film by rotary evaporator. The film hydrates with aqueous drug polycarbonate membranes. Solution and resultant suspension extrude through poly carbonate membrane and placed in series for up to 8 passages. It is a good method for noisome size control.
7. **Ethanol injection method**

An ethanol solution of surfactant is injected rapidly through a fine needle. Then in to excess of saline or other aqueous medium. Vaporization of ethanol take place. Vesicles are formed.

8. **Micro fluidization**

In this technique the principle involves is submerged jet principle in which two fluidized streams interact with each other at ultra-high velocities and in the micro channels within the interaction chamber. Thin liquid sheet impingements along with common front are arranged such as that the energy supplies remain same within the area of niosomes formation, formation of niosomal vesicles of greater uniformity, smaller size and better reproducibility.

B. **Active trapping techniques**

This includes includes the loading of drug after the formation of niosomes. The niosomes are prepared and then the drug is load of maintaining a pH gradient or ion gradient to facilitate uptake of drug into niosomes. Various advantages of noisome form are 100% entrapment, high drug lipid ratios, absence of leakage, cost effectiveness and suitability for labile drugs.

1. **Trans membrane pH gradient drug uptake process**

In remote loading process surfactants and cholesterol are dissolved in organic solvent (chloroform). Film hydrates with 300mM citric acid (Ph 4.0) by vortex mixing. Multilamellar vesicles are frozen and thawed 3 times and later sonication. For niosomal suspension, aqueous solution containing 10mg/ml of drug is added and vortex. Sample Ph is raises to 7.0-7.2 with 1M disodium phosphate. The mixture is later heated at 60°C for 10 minutes to yield niosomes

INSITU GELLING SYSTEMS\(^{7,8,9,10}\)

The word *in-situ* is derived from latin which means ‘in its original place or in position’.

*In-situ* gelling systems are described as low viscosity solution that phase transition in *cul-de-sac* to form viscoelastic gel. This *sol-to-gel* phase transition happens due to conformational changes of polymer in response to a physiological environment. *In-situ* formulations are more acceptable for patient because they are administered as solution or suspension which immediately undergoes to gelation as coming in contact with the eye.\(^{7,10}\)
Advantages of *in-situ* forming gels[^8,12,13]

1. Less blurred vision as compared to ointment.
2. Decreased nasolacrimal drainage of the drug which may causes undesirable side effects due to systemic absorption
3. The possibility of administering accurate and reproducible quantities, in contrast to already gelled formulations and moreover promoting precorneal retention.
4. Sustained, prolonged drug release and maintaining relatively constant plasma profile.
5. Reduced dosing frequency compared to preformed gel. Reduced number/frequency of applications, hence improved patient compliance and comfort.
6. Generally, more comfortable than insoluble or soluble insertion.
7. Increased bioavailability due to increased precorneal residence time and absorption.
8. Avoidance of hepatic first pass.

Approaches for *in-situ* gelling system[^8,9]

Depending on the method chosen to cause sol-to-gel phase transition on the surface of eyes, three types of *in-situ* gelling system are,

1. **Temperature dependant system**
   The use of a material whose transition from sol-gel is triggered by increase in temperature is an attractive way to approach *in-situ* formation. The ideal critical temperature range for such system is ambient and physiologic temperature, such that clinical manipulation is facilitated and no external source of heat other than that of body is required to trigger gelation. For convenience, temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive and thermally reversible gels. Negative temperature sensitive hydrogels have a lower critical solution temperature (LCST) and contract upon heating above the LCST. Poly (N-isopropyl acrylamide) (PNIPAAm) is used as polymer.

2. **pH dependant system**
   Another formation of *in-situ* gel based on physiologic stimuli is formation of gel is induced by pH changes. All the pH sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. The polymers with large number of ionizable groups are known as polyelectrolytes. The most of anionic pH sensitive...
polymers are based on PAA (Carbopol®, carbomer) or its derivatives. Basic method of preparation for pH triggered (induced) in-situ gelling systems.\textsuperscript{[7,34]}

![Diagram](image)

3. **Ion activated system**

In this the phase transition from gel to sol is triggered by change in ionic strength. The most common polymer used for ion sensitive in-situ gel is gellan gum i.e. gelrite which is linear anionic heteropolysaccharide secreted by microbes sphingomonas elodea.

**IN-SITU GELLING POLYMERS**\textsuperscript{[8]}

A polymer used in in-situ gels should have following characteristics:

1. It should be biocompatible.
2. It should be capable of adherence to mucus and non-irritating.
3. It should have pseudo plastic behaviour.
4. It should influence the tear behaviour.
5. The polymer should be capable of decrease the viscosity with increasing shear rate there by offering lowered viscosity during blinking and stability of the tear film during fixation.
6. It should have good optical activity.
7. It should be tolerable.

**CONCLUSION**

The primary requirement of a successful controlled release product focuses on increasing
patient compliance which the in-situ gel offer. The development of in situ stimuli activated gel-forming systems for ophthalmic drug delivery provides simplest and best gel-forming systems and have been proved advantageous over other conventional dosage forms. Drug delivery through niosomes is one of the approaches to achieve localized drug action. Since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. It results in enhancement of efficiency or potency of same time reduces its systemic toxic effects. Thus, niosomes entrapped through in-situ gel system has been developed to increase precorneal residence time, to minimize interference with blinking, enhance ocular bioavailability and reduce frequency of administration. The advantages of in situ gel include sustained and prolonged release of drug, good stability, biocompatibility, ease of instillation, etc. It is an ideal system that maintains effective level of drug for the longer duration following a single application and offers the primary requirement of a successful controlled release product. Use of biodegradable and water-soluble polymers for the in-situ gel formulations can make them more acceptable and excellent drug delivery systems with minimum chances of irritation, and hence improved patient compliance.

REFERENCES


