

Sustained release: In situ forming ophthalmic gel

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Date of Submission: 01-11-2021

Date of Acceptance: 09-11-2021

ABSTRACT

In Situ ophthalmic gels provide sustained release in the eye. They increase the residence time of drug in the eye however they can be instilled as eye drops in the eyes. The formulation of in situ gels can be employed using various approaches like ion sensitive, pH sensitive and temperature sensitive approach. The combination of gelling agents and the viscosity increasing agents are being used which have led to release of drug in controlled manner. Thus in situ ophthalmic gels are area of interest in the field of ophthalmic drug delivery.

Keywords: Phase transition, in situ gel, sustained release, controlled release

INTRODUCTION

Eye is quite an amazing organ due to its peculiar characteristics. It is lodged in the orbit of the skull, thus giving eyes the protection. It is rounded, soft organ that measures about 2.5cm in diameter. It is held in position by the adipose tissue and protected from dust by the eye lashes and eye brows. Mostly topical application is preferred due to ease of application. Major challenge is to see off those eye barriers which do provide hindrance. More and more research had been carried out in this field and trying to develop a novel drug delivery is under process. Formulations like eye drops and eye suspensions have poor ocular bioavailability. Therefore a combined information of drug molecule and the various constraints there should be studied and known beforehand while formulating¹. The various approaches that are being employed are first one is sustained release drug delivery system and second one to increase corneal absorption. Major ophthalmic drug delivery should be able to provide sustained release and remain in the vicinity of eye for a prolonged period. The eye is protected against the foreign particles by blood ocular barriers. These barriers have two parts blood aqueous barrier and blood retina barrier. The anterior blood eye barrier is composed of endothelial cells in the uvea. It consists of iris, ciliary body and choroid. The barrier prevents plasma albumin into aqueous

humour and also limits the entry. Then there is posterior chamber which consists of RPE (Retinal Pigment Epithelium) and retinal capillaries are also present. Another, major loss is due to nasolachrymal drainage

Figure 1: barriers in ocular drug delivery

Barriers in ocular drug delivery are listed as below

1. Lacrimal Fluid Barriers:

Corneal epithelium is the main culprit behind this. They form closely knitted junctions. Thus lipophilic drugs have more permeability than the hydrophilic drugs. Conjunctiva is more leakier epithelium than cornea and that too surface area is greater than nearly 20 times than the corneal epithelium and thus offers resistance to them. Lipophilic have performed better in penetration than the hydrophilic drugs.

2. Blood Ocular Barriers:

The eye is protected against the foreign particles by blood ocular barriers. These barriers have two parts blood aqueous barrier and blood retina barrier. The anterior blood eye barrier is composed of endothelial cells in the uvea. It consists of iris, ciliary body and choroid. The barrier prevents plasma albumin into aqueous humour and also limits the entry.

Another one major loss is due to nasolachrymal drainage. It is drained as soon as it is instilled into eyes. Thus one main concern is that there is systemic absorption instead of ocular absorption. Systemic absorption takes place from conjunctival sac via local blood capillaries. Even ocular Drug Absorption occurs in two ways that is drug diffuses directly from cornea or there are certain non-corneal routes. The permeation of drug in the corneal absorption takes from the precorneal space. The movement of drug molecule across the biological membrane depends on physicochemical properties of the molecule. Cornea further consists of three distinct layers (epithelium, stroma, endothelium). The epithelium and endothelium are much higher in lipid content than the stroma³. Whereas in the case of non-

corneal absorption drug permeation is through sclera. Generally it offers less resistance than the cornea. It is composed of epithelial layer like the other layers. The absorption of ophthalmic drugs is due to phenomenon of diffusion.

Various Eye Diseases

1. Conjunctivitis It is inflammation of membrane which lines the eyelids. It is characterized by exudation. Staphylococcus aureus is the most common bacteria which causes conjunctivitis.

2. Keratitis It is known as inflammation of cornea and then there may be corneal oedema, ciliary congestion. Cornea is in contact with external environment and is prone to infection. Common bacteria causing corneal ulceration are Staphylococcus aureus, E. coli, Proteus etc.

3. Endophthalmitis In this disease there is inflammation of intraocular cavity i.e. (purulent uvetis) & inner coat of eye ball. The various organisms are E.coli, Pseudomonas, Streptococci. There are various antibacterials which are used to treat such diseases like sulfonamides, aminoglycosides, flouroquinolones, been widely recognized as drug of choice and is widely acclaimed. Recently it has been shown to be efficacious against various ocular diseases. Because of flouroquinolones wide range of spectrum and that is too highly effective in clearing away major bacterial information. Flouroquinolones have shown better results than the counterparts and particularly the fourth generation like Moxifloxacin Hcl, Gatifloxacin are drug of choice

In Situ Gel:

An in situ gel is free flowing liquid which have low viscosity so that they can be instilled as an eye drops and gel is formed immediately after its administration. Optimally it should be able to withstand shear forces in the eye and have a sufficient contact time of the drug in eye then only it can give such a sustained action^{4,5}. Thus in a way in situ gel possess such characters as to provide desired sustained release.

Advantages of in situ forming gel:

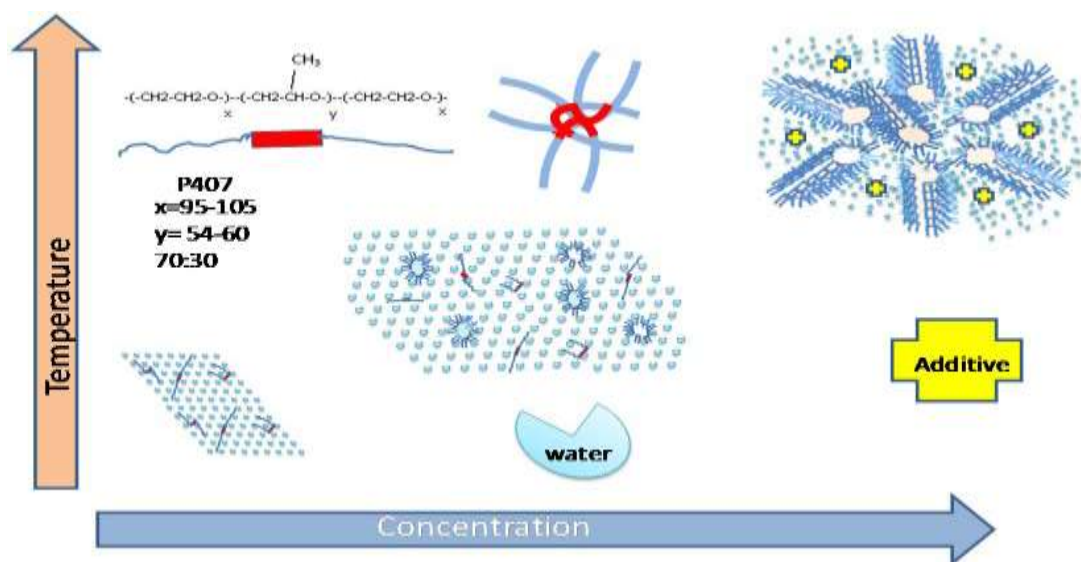
- Generally more comfortable than insoluble or soluble insertion. Less blurred vision as compared to ointment.
- Increased bioavailability due to – Increased precorneal residence time Decreased nasolacrimal drainage of the drug which cause undesirable side effects arising due to systemic absorption of the drug through naso-lacrimal duct is reduced.
- Drug effect is prolonged hence frequent instillation of drug is not required.
- The principle advantage of this formulation is the possibility of administering accurate and reproducible quantities, in contrast to already gelled formulations and moreover promoting precorneal residence time.

Various approaches of in situ gel

Temperature Sensitive Gel

pH Dependent In situ Gel:

Ion-activated In situ-Gel:



Evaluation:

1. Clarity: Gels formed are checked for clarity against light under white and black backgrounds.

2. Gelling Capacity: The gelling capacity is determined by placing 2ml of formulation in simulated tear fluid and then noting time for gelation. Generally Simulated Tear Fluid consists of Calcium Chloride, Sodium Bicarbonate and Sodium Chloride¹⁰.

3. Drug Content: The drug content is determined by taking 1ml of sample and then diluting it with 50ml of STF maintained at buffer 7.4. Then further 5ml was taken and then again diluted with 50ml. Then samples were analysed at 295nm using UV visible spectrophotometer¹¹.

4. Rheological Studies: Rheological studies of the formulation, was carried out by using brookefield viscometer using spindle S2 at liquid formulations at ph 5.5. Alternately using T-bar spindle at ph 7.4 in the gel form¹². The viscosity of the formulation was measured at different speeds 5, 6, 10, 12, 20, 30, 50 rpm.

5. Sterility Studies: Ophthalmic preparations should be sterile. Direct inoculation method was used. Samples was taken out with sterile pipette or with sterile syringe and then aseptically transferred into the Fluid thioglycolate medium and soyabean casein digest medium and then incubated at 30-35 degrees for 7 days for fluid thioglycolate medium and at 20-25 degrees for soyabean casein digest medium¹³.

6. Antimicrobial Studies: Antimicrobial efficiency studies were carried out to ascertain the biological activity of sol-to-gel systems against microorganisms. This was determined in the agar diffusion medium employing Cup plate technique. Sterile solution of marketed Moxifloxacin Hcl eye drops was used as a standard. The standard solution and the developed formulations (test solution) were taken into separate cups bored into sterile SCDM Agar previously seeded with organisms like (Staphylococcus aureus and Pseudomonas aeruginosa). After allowing diffusion of solutions for two hours, the plates were incubated for 24hrs at 37°C. The zone of inhibition (ZOI) was compared with that of the standard 17, 19, 22^{14,15}. Each sample were tested in triplicate

7. In Vitro drug Release Studies: The in vitro drug release studies, was studied through a cellophane membrane using modified USP XIII dissolution testing apparatus. The dissolution

medium employed was artificial tear fluid prepared pH(7.4). Cellophane membrane used was soaked overnight in dissolution medium was tied to one end of glass cylinder (which was open at both ends and of 5cm diameter). A 1ml of the formulation was accurately pipette into the cylinder. The cylinder was then attached to metallic driveshaft and then suspended in 50 ml of the dissolution medium maintained at 37 degrees and was stirred by magnetic stirrer at 50 rpm employing a magnetic stirrer. Aliquots each 1ml volume was withdrawn after hourly intervals and then it was analysed at 290 nm using Uv spectrophotometer¹⁶.

8. Ocular Irritancy Test -Draize Test: Take three male rabbits weighing 2-3 kgs. Eyes drops were instilled into lower cul-de-sac of rabbits. The measured dose amount was 50 ul instilled into lower cavity of eyes in cul-de-sac. It was instilled for a period of 7 days. Each day single dose of 50 ul was given and then after 24 hours another dose was given. This was continued for one week. Eyes were checked in for any redness, swelling, inflammation etc¹⁷.

9. Accelerated Stability Studies: Then the formulation was subjected to stability studies. Sterilized formulations were filled in glass vials stoppered with grey butyl rubber closures sealed with aluminium caps. Short term accelerated stability studies, was carried out for a period of 45 days. The samples were stored at room temperature and at elevated temperature such as 40 degrees at 75% RH and refrigerator at (2-8) degrees. Samples were withdrawn on weekly interval and analysed for drug content, visual appearance, clarity, pH

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