REVIEW ARTICLE

Thermosensitive *in situ* Otic Gel: A Modern Approach for the Topical Management of Otitis Media with Its Formulation Aspects

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Abstract

An increasing number of *in situ* forming systems for many biomedical applications have been published in the literature in recent years. Otitis media (OM), most common condition which is caused due to the infection of virus and bacteria. Otitis media is classified into two types: acute and chronic. The most often isolated pathogens in OM are *Streptococcus pneumoniae*, *non-typeable Haemophilus influenza, and Moraxella catarrhalis*. Otalgia, ear drainage, fever, restlessness, earache, headache, mild deafness, and difficulty sleeping are all symptoms of otitis media. The global impact of Chronic Suppurative OM sickness includes up to 330 million people having issue of draining ears, 60% (up to 200 million) have significant hearing difficulty. Thailand had prevalence rates ranging from 0.9 to 4.7%, whereas India has a high frequency of 7.8%. Ear drop has drawbacks such as a shorter residence time frame in the ear. Semisolid preparation includes drawbacks such as administrative complexity. Both of these issues can be solved by developing a solution that forms an *in situ* gel after administration. Solvent exchange, UV-irradiation, ionic cross-linkage, pH alteration, and temperature modulation are few examples of the mechanisms. Because it does not involve the use of organic solvents, copolymerization agents, or a locally applied gelation trigger, the thermosensitive technique may be desirable for some applications. The benefits of *in situ* polymeric delivery methods include ease of administration and minimized frequency of administration, in addition to improved patient compliance and comfort. At body temperature, poloxamer 407 aqueous solutions (more than 18% w/v) can produce *in situ* gel.

Key words: *In situ* gel, sustained release, temperature sensitive

INTRODUCTION

Otic refers to hearing problems.[1] The human ear is one of the most remarkable aspects of the human body, not only for the beauty and uniqueness of its form but also for its extraordinary sensitivity to sound sensation.[2,3] The ear is traditionally split mainly into three sections, namely, the exterior, middle, and inner ear.[4]

- External or outer ear-Which absorbs and directs sound waves inside.
- Middle ear (tympanic cavity)-This delivers sound waves to the elongated window.
- Inner ear-Which houses the receptors for hearing and equilibrium.[5]

OTIC DRUG DELIVERY SYSTEM[6-10]

There are many diseases and disorders which can affect hearing of patients. Problem includes:

i. Disputes of the outer ear
   Otitis externa, swimmers ear, and perforated ear drum.
ii. Disputes of the middle ear
   Otitis media, glue ear in children, burst eardrum in children, and burst eardrum in adults.
iii. Disputes of the inner ear
   Hearing and nerve damage, tinnitus, and vertigo.

The most frequent of these is "Otitis Media," which is caused by the infection of virus and bacteria and has a

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high morbidity rate worldwide.[11] Otitis medium (OM) is a collection of fluids in the middle ear, whether or not there are inflammatory symptoms.[12,13] The infection is brought on by eustachian tube malfunction or blockage and is mostly found in youngsters younger than 2 years old.[14-17] *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*, and *Moraxella catarrhalis* are the often pathogens that have been isolated in otitis media.[18-20]

Otitis media is classified into two types: (a) acute and (b) chronic.

a. Acute otitis media indicates that the middle ear and tympanic membrane are inflamed. The eardrum will be red and frequently bulging in this situation.[21] Children with this condition frequently complain of pain, are irritable, and may have high fevers.[22] Analgesics and antibiotics are frequently required. Normally, the fluid drains through the Eustachian tubes.[23] This is characterized as medial otitis with an effusion and is also when it occurs, it is termed as "glue ear."[24]
b. Chronic suppurative otitis media is caused by aerobic bacteria (e.g., *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, Streptococcus, and species) or anaerobic bacteria (e.g., *Bacteroides*, *Peptostreptococcus*, and *Propionibacterium*).[25-28]

IN SITU GELLING SYSTEMS

Various polymers are used by the researchers that have the ability to undergo phase transition at physiological conditions of the eye and remain as a liquid at non-physiological conditions.[29,30] The phase transition could be triggered by any of the following mechanisms:

i. Temperature sensitive-At physiological temperature (35–37°C), it is liquid at room temperature (20–25°C) and forms a semisolid gel, for example, xyloglucan, methyl cellulose, poly oxy ethylene-polypropylene copolymer (Poloxamer), and n-isopropyl acrylamide.[31-34]
ii. Ion sensitive-Liquid under non-physiological conditions forms semisolid gel after coming in the contact with monovalent and divalent ions present in the tears, for example, gellan gum and sodium alginate.[31-34]
iii. pH sensitive-Liquid under non-physiological conditions and forms semisolid gel after instillation into the eye due to the physiological pH (7.4) conditions, for example, cellulose acetate phthalate (CAP latex) and carbomer (carbopol).[35-37]

Out of these systems, the temperature-mediated phase transition system is most suitable and beneficial for delivery of drug in ear by ototopical route.[36,37] The formulation is administered in the form of solution but when come in contact with ear temperature, it forms gel and give sustained release effect.[38-40] There are several reasons behind formulation of *in situ* gel for otic drug delivery system.

NEED BEHIND FORMULATION OF *IN SITU* GEL

- Ear drop has drawbacks such as a shorter residence period in the ear. Semisolid preparation includes drawbacks such as administrative complexity.[41] Both of these problems can be overcome by formulating a solution which forms *in situ* gel after administration.[42] To overcome the disadvantages of solutions and semisolids gel, *in situ* gel is preferred.[43]
- Higher concentration is achieved at site of action.
- Prolonged duration of action.
- Patient comfort and compliance have improved.
- A smaller amount of drug is necessary.
- Reduction in the instillation or application frequency.
- Packing compatibility in standard dropper containers used for solutions.

MECHANISM OF POLOXAMER 407

At low concentrations (10.4–10.5%), they form monomolecular micelles, but at higher concentrations, they form multimolecular aggregates with a hydrophobic central core and hydrophilic polyoxyethylene chains facing the external medium.[44-47] Micellization occurs in dilute solutions of block copolymers in specified solvents above the micellar concentration at a specific temperature.[48,49] Micelles have the ability of forming a lattice concentrations rising, exceeding a critical gel concentration.[50]

Poloxamer aqueous solutions are stable in the acidic, alkaline environment, as well as in the presence of metal ions. The 188 (F-68 grade), 237 (F-87 grade), 338 (F-108 grade), and 407 (F-127 grade) poloxamers are water soluble.[51] The "F" designation refers to the product's flake shape. Due to its high solubility and low toxicity, PF-127 is an ideal medium for drug delivery systems. PF-127 is a commercially available polyoxyethylene-polyoxypropylene triblock copolymer having the general formula E106 P70 E106 with an average molar mass of 13,000. It is hydrophilic because it includes roughly 70% ethylene oxide. It is one of a class of poloxamer ABA block copolymers with the following chemical formula:

Ethylene oxide and propylene oxide are combined to form polymers. Due to increased solvation and hydrogen bonding at lower temperatures, PF-127 is more soluble in cold water than

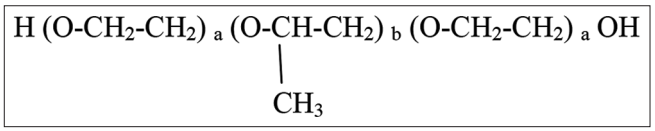

Figure 1: Pluronic F-127 chemical structure (a, ethylene oxide portion b, propylene oxide portion)

in hot water, as shown in Figure 1.[52] PF-127 aqueous solutions containing 20–30% w/w exhibit the intriguing property of reverse thermal gelation, which means that they are liquid at cold temperatures (4–5°C), but gel when warmed to room temperature. When cooled, the gelation is reversible.[53-55]

In aqueous solutions at low temperatures, PF-127 molecules are surrounded by a hydration layer.[56] However, as temperature rises, the copolymer's hydrophilic chains become desolvated due to the breakdown of the hydrogen bonds created between these chains and the solvent.[53] This effect promotes hydrophobic interactions between polyoxypropylene domains, resulting in the formation of gel. The hydroxyl groups become more accessible as a result of the dehydration process.[52] The gel is assumed to be micellar in nature. At low temperatures, a liquid micellar phase is stable, but as the temperature rises, it converts into a cubic structure. At higher temperatures, a hexagonal-packed cylinder phase forms. Surface active chemicals produce micelles and liquid lyotropic crystalline phases. Over a temperature range of 10–40°C, ultrasonic and light scattering measurements revealed a micellar association for PF-127.[54] NMR, rheology, and fluorescence have also revealed the micellar configuration of block copolymers. Gelation of PF-127 is considered to occur as a result of polymer dehydration, which causes increased chain friction and entanglement, resulting in a hydrophobic association [Table 1].[57,58]

Table 1: Otitis media prevalence by age

Age (years)	Prevalence (%)
Neonate	0–12
1	12
2	7–12
3–4	12–18
5	4–17
6–8	3–9
9	0–6

PF-127 is utilized as a viable medicine distribution method in humans has been based on reverse thermal gelation and minimal toxicity. It has been studied for topical administration of lidocaine, anti-cancer medicines, and burn wound dressing. Pilocarpine as the model drug and PF-127 as the vehicle were used in studies on ophthalmic usage. PF-127 has been studied as a potential injectable vehicle using both intramuscular and subcutaneous injection techniques.[59] Finally, using ciprofloxacin and other cytotoxic and other drugs, PF-127 has been investigated as a potential vehicle for otic drug delivery system. PF-127 is of particular importance because concentrated copolymer solutions (>20% w/w) are available, when heated to body temperature, convert from low viscosity clear solutions to solid gels. The reversible thermal behavior of PF-127 solutions, both dilute and concentrated, has been widely researched. As a result of this phenomenon, when the gel preparation is injected into a body cavity or applied on the skin, it forms a solid artificial barrier as well as a sustained release depot. Furthermore, of the commercially available copolymers, PF-127 is the least hazardous.[60]

APPLICATION OF POLOXAMER 407 AS OTIC DRUG DELIVERY SYSTEM

The special thermos-reversible and prospective drug release features of PF-127 make it appealing choice as a pharmaceutical vehicle for medications administered through the otic route.[61,62] Several authors have proposed PF-127 gels as an anticipated otic drug delivery. Advantages over standard bases include ease of application and medication release characteristics.[63,64] It is worth noting that numerous studies have concentrated on the otic formulations development.

- Mali *et al*. (2011) have investigated the use of poloxamer in the development and testing of metronidazole *in situ* gelling otic compositions. The goal of this study was to create sustained release *in situ* gel formulations for

Table 2: Otic formulations

Otic formulations				
Ear sprays and Eardrops	Ear formulations of semi-solid category	Ear powders	Ear washes	Ear tampons

Table 3: Gel classification and description in general

Class	Description	Example
Inorganic	Usually two-phase systems	Aluminum hydroxide gel; bentonite magma
Organic	Usually single phase systems	Carbopol®; tragacanth
Organogels	Hydrocarbon type Animal/vegetable fats Soap bases greases	Petrolatum lard, cocoa butter aluminum stearate
	Hydrophilic	Carbowax®
Hydrogels	Organic hydrogels Natural and synthetic gums Inorganic hydrogels	Pectin paste methylcellulose, Sodium CMC, PF-127® bentonite gel, Veegum®

chronic suppurative otitis media to improve medication concentration in middle ear fluid. The formulation's viscosity increased as the concentration of Poloxamer 407 increased. In the formulation having a constant amount of Poloxamer 407, as the concentration of viscosity enhancing chemical was increased, the viscosity increased.[4]

- Harnish *et al*. (2011) have investigated the *in situ* gel system to enhance patient compliance and comfort. Temperature change, pH alteration, ions presence, and irradiation (ultra violet) all contribute to the production of gels, in which case the medicine gets released in a controlled and consistent manner. The results show that they have high sustained release qualities, and in the future, using biodegradable and water soluble polymers in *in situ* gel formulations may improve their acceptability and efficacy as drug delivery vehicles.[13]
- Rathore (2010) have studied ophthalmic gelling *in situ* medication delivery system. Improved patient compliance is a fundamental condition for a successful controlled release solution, which *in situ* gels provide. Polymeric *in situ* gels for controlled drug release have various advantages over standard dosage forms. Due to their continuous and prolonged drug release, as well as their great stability and biocompatibility, *in situ* gel formulations have proven their high reliability. Utility of water soluble polymers and biodegradable polymers into *in situ* gel compositions can boost their acceptability and performance as drug delivery methods.[12]
- Nirmal and Bakliwal (2010) have investigated the *in situ* gel: New trends in Controlled and Sustained Drug Delivery System. They concluded that the main criterion of a controlled release product success is increased patient compliance, which is provided by situ gels. Controlled drug release using polymeric *in situ* gels offers several advantages in comparison to traditional formulations. Due to their continuous and prolonged drug release, also due to their optimum stability and biocompatibility, *in situ* gel dosage forms are highly reliable. Because biodegradable and water soluble polymers are used in the *in situ* gel formulation scan, they are more acceptable and excellent drug delivery systems.[15]
- Dicks *et al*. (2009) have examined the otitis media: A review, with a focus on alternative treatments. This study describes the condition OM, outlines existing treatment options, and offers another safe and herbal remedies that should be investigated.[1]
- Murphy *et al*. (2005) have investigated the vaccines for otitis media: ideas for overcoming roadblocks. Vaccine development for the prevention of otitis media, this has a substantial human as well as economic impact. There has been a conspicuous lack of progress in the discovery, manufacture, and clinical testing of vaccinations to prevent otitis media over the past decade. This assessment provides a number of specific ideas aimed at advancing otitis media vaccine development.[2]
- Eve and Leroux (2004) have investigated formation of *in situ* in hydrogels in temperature-sensitive systems. The focus of this research is on polymeric aqueous solutions that generate implants *in situ* in reaction to temperature variations, typically from room temperature to temperature of the body. It focuses on the applications and characterization of polysaccharides, N-isopropylacrylamide copolymers, poloxamer, and other polymers.[16]
- Klein (2000) have investigated the impact of otitis media. The goal of this review is to provide an overview of the burden of otitis media, including acute infection morbidity, the sequelae of severe and recurring infections, and the costs of the illness, not only in monetary terms for medical and surgical care but also non-medical expenses associated with lost work and higher costs of new drugs needed to manage various infections (not just otitis media) due to multidrug-resistant pathogens resulting from the extensive.[3]

ADVANTAGES OF *IN SITU* GEL[65-69]

- On comparing to already formed gel, the main advantage is the ability to administer accurate and reproducible amounts.
- Ease of administration.
- Reduced frequency of administration.
- As the drug's effect lasts longer, it is not necessary to administer the drug on a regular basis.
- Patient compliance and comfort have improved.
- It has a sustained and longer effect when compared to typical medicine delivery techniques.
- In compared to standard medicine administration systems, the effect is sustained and prolonged.

CLASSIFICATION OF OTIC FORMULATIONS

There are number of dosage forms which are intended to be used in treating ear diseases, as shown in Table 2. They are as follows:[70-76]

Otic preparation formulation considerations: Otic formulations, like other pharmaceutical formulations, can be manufactured as aqueous or non-aqueous solutions and comprise one or more medicinal agent categories. The following aspects should be considered while developing ear drops or solutions.

i. Vehicle

For the preparation of otic formulation, the following vehicles can be used:

a. Aqueous
   Ex. Purified water
b. Non-aqueous
   - Mineral oil
     Ex. Liquid paraffin
   - Vegetable oil
     Ex. Arachis oil
c. Glycols are non-aqueous but miscible with water
   Ex. Propylene glycol, glycerol

Vehicles that are non-aqueous are commonly utilized as vehicles in ear wax removal formulations due to their lipophilic nature aids as a wax solubilizer. The medicinal agent's solubility in each of these determines whether an aqueous or non-aqueous solvent is used as the vehicle.[77] In some cases, the medication may be manufactured as a suspension, utilizing the vehicle's solvents/solvent combinations. Surprisingly, the hygroscopic ability of glycerol and propylene glycol is used in otic formulations to minimize swelling and remove exudate from inflamed areas.

ii. Preservative

Since otic formulations are usually multidose and watery systems, to prevent microbial growth, a preservative is required.[78] The following preservatives are used in otic formulations and are similar to those utilized in ocular and nasal formulations:

- Chlorobutanol
- Combinations of parabens
- Benzalkonium chloride
- Thimerosal

Benzalkonium chloride and thimerosal are often utilized in otic formulations. Preservatives are not required in low-water-content otic formulations.

iii. Viscosity modifiers

The management of formulation viscosity is critical while designing the otic products since it influences both the simplicity of administration as well as retention at the application site.[79] The viscosity of aqueous-based compositions can be altered. Hydrophilic polymers such as methylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose, and poly (acrylic acid) can be used to create ocular, nasal, and otic dosage forms. Because glycol-based formulations have a higher viscosity than aqueous counterparts, viscosity modification with polymeric components may not be necessary.[80]

The viscosity-modifying substance should have the following ideal properties:

- Easy filtration: During the manufacturing process, all ear drop solutions are filtered.[81] This could be simple particle removal (e.g., clarity with 0.8-m filter) either clarifying in tandem with filtration sterilization.
- Easily to sterilize: Ear drop solution is often sterilized using filtration or heat. If heat sterilization is employed, the viscosity altering chemicals must be chemically and physically sustainable at these temperatures.[81]
- Must be compatible with other excipients: The combination of hydrophilic polymers with some of the preservatives is a renowned phenomenon that is normally addressed by increasing the preservative concentration. However, the pharmaceutical scientist must ensure that no or only minor interactions occur between the therapeutic medication and the viscosity-modifying agent, for example, basic therapeutic drugs and polyacidic polymers.[82]

iv. Antioxidants

To enhance the stability of drugs that are susceptible to oxidative degradation, antioxidants may be incorporated in otic formulations. An antioxidant typically used for this purpose is sodium metabisulfite (about 0.3%). The antioxidant is chosen based on the formulation's solubility qualities.[83]

v. Gels

Gels are widely known to be swelling networks with both solid-like cohesive capabilities and liquid-like diffusive transport features. Gels are employed as elastomers made of thermoplastic polymers for pressure sensitive adhesion and impact modification. Reversible gels are those that can create, break, and change the bonds that maintain the network together.[84]

GEL CLASSIFICATION

Gels along with jellies are semisolid liquid-interpenetrated solutions of tiny inorganic particles or large organic molecules. If the particle size of the dispersed phase is large, gels are often categorized as two-phase systems, or single-phase gels are formed when organic macromolecules are uniformly distributed throughout a liquid with no visible boundaries between the dispersed macromolecules and the liquid, as shown in Table 3.[85-87]

CONCLUSION

Thermoreversible gel PF-127, with its distinct properties, can be considered a promising drug carrier for otic drug delivery systems. Due to its micellar characteristics and gelation behavior, the system has good solubility and an appropriate delivery rate. Thus, *in situ* gel systems play an essential role in the delivery of otic drugs, allowing for prolonged drug release while reducing toxic effects. *In situ* gel system specially temperature-mediated system has superior as compared to traditional system such as ear drops, ear sprays, and ear powders, the formulations that are administered in

the form of solution and come in contact with ear temperature that it becomes gel and gives sustained release effect.

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