IN-SITU GEL DRUG DELIVERY SYSTEMS FOR THE TREATMENT OF PERIODONTITIS

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ABSTRACT

Periodontitis is an inflammatory disease characterized by progressive destruction of periodontal soft and hard plaque tissues leading to permanent tooth loss. The incidence of these diseases can be reduced by mechanical plaque removal or scaling and root planning (SRP) along with systemic and locally delivered antimicrobial agents or statins. In-situ gels are the drug delivery systems that are in solution form before administration in the body, but once administered in to the body undergoes gelation in-situ to form gel. Mechanisms involved in in-situ gel formation are solvent exchange, UV-irradiation, ionic cross-linkage, pH change, and temperature modulation. Polymers exhibit solid-gel phase transition and thus trigger drug release in response to external stimuli. The polymers used must be biocompatible, adhere properly to mucus, and exhibit pseudo plastic behavior. The main advantages of this route of drug administration is that it can deliver the active agents directly to the site of action at bactericidal concentration and it can facilitate prolong drug delivery.

KEYWORDS: In situ gel, Periodontitis, Thermo-sensitive modulation, pH change and Statins.

INTRODUCTION

Periodontitis (PD) is an immuno-inflammatory disease of tooth supporting tissues (the gingiva, bone and periodontal ligament), which results in progressive destruction of surrounding soft and hard tissues with eventual tooth mobility and exfoliation. PD starts as an
inflammatory reaction confined to the gingival tissue (gingivitis), but when left untreated it spreads to periodontal ligament, cementum and supporting alveolar bone, resulting in pocket formation which provides a favourable environment for the growth of pathogenic anaerobic microorganisms. Chronic periodontitis primarily affects adults, but aggressive periodontitis may intermittently occur in children. Perioceutics, involves the delivery of a right therapeutic agent via systemic and local means as an adjunct to mechanical therapy.\textsuperscript{[1,2]}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{a) Signs of Gum Disease/Periodontitis b) Stages of Periodontitis.}
\end{figure}

\textbf{Classification of Perioceutics}

Based on the application

1) Personally applied (in patient home self-care)
   a. Subgingival non-sustained drug delivery: Home oral irrigation jet tips, Traditional jet tips, Oral irrigation (water pick), Soft cone rubber tips (pick pocket).
   b. Sustained subgingival drug delivery

2) Professionally applied (in dental office)
   a. Nonsustained subgingival drug delivery - Professional pocket irrigation
   b. Sustained subgingival drug delivery.\textsuperscript{[1,2]}

\textbf{Drugs used for the treatment of PD}

1. Antimicrobial agents or Antibiotics: Tetracycline, Minocycline, Doxycycline, Chlorhexidine, Clarithromycin, Clindamycin, Ciprofloxacin, Ampicillin, Fluoroquinolones (Ciprofloxacin), Erythromycin, Azithromycin, Metronidazole.\textsuperscript{[12,15]}

2. The pleiotropic effects of statins have been evaluated to assess their potential benefit in the treatment of various inflammatory and immune-mediated diseases including periodontitis.\textsuperscript{[4,7,25]}
Local drug delivery systems used for the treatment of PD

Local drug delivery systems (LDDS) exhibit several advantages over systemic agents, which include minimally invasive and direct application at the site of infection, avoidance of gastrointestinal issues and presystemic metabolism, reduction in the dosage regimen, improved patient compliance and serves as ideal means to incorporate agents, which are not suitable for systemic administration eg. Chlorhexidine.\[^1\]

Limitations of LDDS into periodontal pocket include, local irritants cannot be administered and potent drugs are used because of relatively small area, enzymes like peptidase and esterase may cause presystemic metabolism, peptide administration is not practicable due to peptidase.

An ideal LDDS must be easy to administer, release the drug in a controlled manner, sustain the drug release for prolonged period, should be biodegradable, biocompatible and donot cause any sensitization and irritation to the tissues. Various LDDS aims to deliver therapeutic agents to sub-gingival diseased sites are fibres, films, injectable systems, gels, strips, compacts, vesicular system, microparticles and nanoparticles.\[^3,4\]

![Fig. 2: Local drug delivery systems used for the treatment of PD.\[^3\]](image-url)
Gels
Gels are transitional state of matter containing both solid and liquid dosage forms. The solid phase comprises a three dimensional network of interconnected molecules or aggregates (polymer) which immobilizes the liquid continuous phase.[6] Based on the nature of the bonds involved in the three-dimensional solid network, gels can be classified into.

1. **Physical gels**: They arise when weak bonds like hydrogen bonds, electrostatic bonds and vanderwaal bonds constitute together to maintain the gel network.

2. **Chemical gels**: They arise when strong covalent bonds constitute to maintain the gel network. The network indicates the presence of cross-links which helps to avoid the dissolution of the hydrophilic polymer in an aqueous medium.

3. **Hydrogels**: These are three dimensional polymeric networks that can absorb and retain large amounts of water and biological fluids and swell, still maintaining their integrity. These polymeric networks contain hydrophilic domains that are hydrated in an aqueous environment, thereby creating the hydrogel structure.[1,2]

**Advantages of hydrogels over other drug delivery systems**
1. They exhibit good mechanical and optical properties and biocompatibility.
2. The degradation products of hydrogels are usually non-toxic or have lower toxicity.
3. Lower interfacial tension between the surface of the hydrogel and the physiological fluid helps to minimize protein adsorption and cell adhesion on the hydrogel's surface.
4. The soft rubbery nature of hydrogels also can minimize mechanical irritation when used as in-vivo implants.[11]

Hydrocolloids are polymers having the ability to swell in water or aqueous solvent and induce transition of a liquid to gel. Gels are viscous preparations, which are formed when high molecular weight polymers or high polymer concentrations are incorporated in the drug formulations.[12,13] In addition, the ability of hydrogels to release an entrapped drug in an aqueous medium and to regulate the release of such drug by control of swelling and by cross linking makes them particularly suitable for controlled release applications. Hydrogels can be designed for the controlled release of hydrophilic and hydrophobic drugs and charged solutes.

**Classification of hydrogels**
Hydrogels are of two types. They are
1. Preformed hydrogels are defined as simple viscous solutions which do not undergo any modification after administration.
2. *In-situ* gels are the solutions or suspensions that undergo gelation after reaching the particular site due to physico-chemical changes.\[^1,2\]

**In-situ gelling systems**

*In-situ* is a Latin word which means ‘in position’. *In-situ* gels are the formulations that are in solution form before administration in the body, but once administration undergo gelation to form gel. There are triggered by different mechanisms such as pH change, temperature modification, UV radiation, presence of specific molecules or ions and solvent exchange to form in-situ gel.\[^21\] They provide sensor properties and can undergo reversible sol-gel phase transitions upon changes in the environmental condition. Intelligent or smart polymers play a vital role in drug delivery by dictating not only site of drug delivery, but also rate of drug release.\[^5\]

**Routes administration of in-situ gelling systems**

Oral, nasal, ophthalmic, vaginal, injectable, intraperitoneal and rectal route.

**Advantages**

1. It provides ease of administration and good patient compliance.
2. It shows increased gastric retention with slow drug release.
3. It reduces dosing frequency.
4. It shows local action and site specificity by acting directly onto the targeted site.
5. It shows less adverse effects compared to other pharmacological dosage forms.
6. It improves local bioavailability of drugs.

**Disadvantages**

1. It is more susceptible to stability problems due to chemical degradation.
2. It requires high level of fluids.
3. It leads to degradation due to storage problems.\[^6\]

**Suitable drug candidates for in-situ gel formulations**

1. Narrow absorption window in GI tract, e.g., Ofloxacin
2. Primarily absorbed from stomach and upper part of GI tract, e.g., Amoxicillin.
3. Drugs that act locally in the GI tract, e.g., Chlorhexidine HCl.
4. Drugs that degrade in the colon, e.g., Metronidazole.
5. Drugs that disturb normal colonic bacteria, e.g., Amoxicillin trihydrate.
Ideal characteristics of In-situ gelling polymers

1. Biocompatible.
2. Capable of adherence to mucus.
3. Exhibit pseudo plastic behavior.
4. Exhibit good tolerance and optical activity.\[26\]
5. Capable of decrease the viscosity with increasing shear rate offering lowered viscosity during blinking and stability of tear film during fixation.

Eg.: Natural: Gellan gum, Xyloglucan, Guar gum, Xanthan gum, Carrageenan, Lambda carrageenan Chitosan, Thiolated chitosan, Pectin, Carbopol 934P, Gellan gum.

Synthetic: Poloxamers or pluronics, poly (lactic acid), poly (glycolic acid), poly (lactide-coglycolide), poly (decalactone), poly ε-caprolactone.\[6,7\]

Mechanism involved in formation of in-situ gels

The in-situ gelling systems utilises various polymers that converts from solution and gel due to change in physicochemical properties. In this system when low viscosity solution comes in contact with body fluids undergo changes in confirmation of polymers and a viscous gel. There are three mechanisms used for triggering the in-situ gel formation of biomaterials.

1. Physiological stimuli (e.g., temperature and pH)
2. Physical changes in biomaterials (e.g., solvent exchange and swelling)
3. Chemical reactions (e.g. enzymatic, chemical and photo-initiated polymerization)

I. Based on physiological stimuli

Thermoresponsive gels: The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach in-situ formation. The ideal critical temperature range is ambient and physiologic temperature for these systems, therefore no external source of heat other than that of body temperature is required for trigger gelation.

1. Negatively thermo sensitive gels: They have lower critical solution temperature (LCST) and contract upon heating above the LCST and transition between ambient and physiologic temperature.

Eg: poly(N-isopropylacrylamide), Pluronics are poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPOPEO).\[26,28\]
2. **Positively thermo sensitive gels:** They have an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST.

Eg: Polyacrylic acid and poly(acrylamide-co-butyl methacrylate).\[^{26,28}\]

3. **Thermoreversible gels:** When injected as a solution into the body, the material forms a firm, stable gel within minutes and remains at the site of injection providing absorption and its action from less than one week to many months. These systems are very convenient and easy to administer into desired body cavity.

Eg: Poloxamer, Pluronics, Tetronics.\[^{12,13}\]

![Fig. 3: Schematic of temperature triggered in situ gelling system.](image)

**pH triggered systems**

In this approach, pH responsive or pH sensitive polymers are used to change pH liquid formulation to gel. Polyelectrolyte pH sensitive polymers have acidic or alkaline ionisable functional groups, used to increase external pH that leads to the swelling of hydrogel and then in-situ gel. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups.\[^{12,13}\]

Eg.: Cellulose acetate phthalate (CAP), Carbomer and its derivatives, Polyethylene glycol (PEG), Pseudo latexes and poly methacrilic acid (PMC) etc.\[^{26,28}\]
II. *In-situ* formation based on physical mechanism

1. **Swelling**: In this approach, the polymers that are surrounding the polymer imbibe the fluids that are present in the external environment and swell from inside to outside and slowly release the drug.

   Eg: Myvero18-99 (glycerol mono-oleate), which is a polar lipid that swells in water to form lyotropic liquid crystalline phase structures.[29]

2. **Diffusion**: This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix.[14]

   Eg: N-methyl pyrrolidone (NMP)[27]

III. *In-situ* formation based on chemical reactions: It involves precipitation of inorganic solids from supersaturated ionic solutions or enzymatic processes or photo-polymerization.

**Ionic cross-linking**: Polysaccharide polymers may undergo phase transition in presence of ions. Eg.: k-carrageenan forms rigid, brittle gels in presence of small amount of K⁺ whereas i-carrageenan forms elastic gels in the presence of Ca²⁺. Gellan gum (Gelrite) is an anionic polysaccharide form *in-situ* gel in the presence of mono-and divalent cations, including Ca²⁺, Mg²⁺, K⁺ and Na⁺.[26]
Enzymatic cross linking: In this approach, gel is formed by cross linking with the enzymes that are present in the body fluids.

Photo polymerisation: In this method, polymerisable functional groups in polymers undergo dissociation in the presence of photo initiators like acrylates or other polymers contain long wavelength ultraviolet and visible wavelengths are used. Eg.: 2,2-dimethoxy-2-phenyl acetophenone is used as the initiator for ultraviolet photo polymerization.

Characterization of in-situ gel formulations

In-situ gelling systems can be evaluated for various characterization parameters such as clarity, pH measurement, gelling capacity, drug content, rheological study, in vitro diffusion study, isotonicity and accelerated stability studies.

1. Physical Appearance
The formulations should be observed for general appearance i.e. color, odor and presence of suspended particulate matter. Preferably the gels should be transparent in appearance.

2. Gelling capacity
The gelling capacity of formulations can be observed by time taken for gel formation in a vial containing 2.0 ml of freshly prepared simulated salivary fluid.

Fig. 5: Schematic of mechanism of ion triggered in situ gelling systems.
3. Determination of pH
The pH of formulations must be evaluated by using pH meter and they should preferably be near to salivary pH to avoid irritation and enhance patient compatibility and tolerance.

4. Viscosity and rheological properties
These parameters may be assessed by using Brookfield viscometer and Cone and Plate viscometer. Viscosity of these formulations should be such that no difficulties are arise during their administration to the patient. It should be 5-1000 m Pas, before gelling and after formation of gel viscosity should have about 50-50,000 m Pas.[29]

5. Sol-gel transition temperature and gelling time
For in-situ gel forming systems incorporating thermoreversible polymers, the sol-gel transition temperature may be defined as that temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at a specified rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube. Gelling time is the time for first detection of gelation as defined above.[22]

6. Texture analysis
The gel strength, firmness, consistency and adhesiveness of in situ gel is measured by texture profile analyzer, which mainly indicates the syringeability of sol so the formulation can be easily administered in-vivo. Higher values of adhesiveness of gels are required to maintain an intimate contact with surfaces like tissues.

7. Drug polymer interaction studies
Interaction between drug and polymer must be observed to check the compatibility between various ingredients of the formulation by suitable method such as Fourier Transform InfraRed (FTIR) spectroscopy analysis of their physical mixture or Differential Scanning Calorimetry (DSC) method.

8. In-vitro drug release studies
In-vitro release study of in situ gelling system can be carried out using Franz diffusion cell to check the duration of drug release from the formulation.[14,15]

9. Drug content
It is an important parameter to be measured as the formulation should contain the accurate amount of the drug as directed by the physician.
10. Accelerated stability studies
These studies are used to check the shelf-life the formulation and performed as per International Conference on Harmonization (ICH) Guidelines.

Recent advancements in in-situ gelling systems\textsuperscript{[27,28,29]}
Various novel drug delivery systems are used for sustained drug delivery by in-situ gelling system such as in-situ gel implants, mucoadhesive polymers, polymer coated nanoparticles and liposomal formulations are used.

1. Liposome incorporated in-situ gel
Active ingredients encapsulated in lipid vesicles like liposome allow not only improved solubility but also transport of drug through dental cone and provide controlled delivery of drug. The bioadhesive polymer such as poly (vinyl alcohol) and polymethacrylic acid derivatives were used for gel preparation and lecithin and α-L-dilplsmithyl-phosphatidyl choline provided the encapsulating agent for drug into liposome. Encapsulation of the drug into liposomes prolonged the in-vitro release of the antibacterial agent from liposomal vesicles and by use of liposomal formulation, higher drug concentration can be achieved at the site of action along with prolonged contact time, thus bioavailability can be improved.

2. Micelles incorporated in-situ gel
Micelles incorporated in reverse thermal gel (RTG) as an injectable drug delivery system for sustained release of drug for upto one year. The RTG chemistry exhibits a novel \{poly (nisopropylacrylamide), PNIPAAm\} polymer coupled to a \{poly (serinol hexamethylene urea), PSHU\} backbone, for complete physiological clearance of system during degradation. PEGylated polyurethane triblock copolymer based micelle system was fabricated through a filter extrusion method with favorable drug encapsulation capacity. Then micelles were incorporated in RTG.

3. Nanoparticles incorporated in-situ gel
Nanoparticles have been employed to address issues related to topical formulations. They provide prolonged release of active ingredient by particle degradation or erosion, drug diffusion or a combination of both, depending on the biodegradable or inert nature of the polymer.
4. Nanoemulsified *in-situ* gels

Nanoemulsions (NE) have been widely used as controlled drug delivery systems due to its intrinsic advantages such as sustained release of drug, higher penetration into the deeper layers of the tissue. They showed better biological performance, faster onset of action, and prolonged effect as compared to drug solution.

5. *In-situ* gel implants

These are novel biodegradable, injectable polymeric liquid formulations that form semi-solid or solid depots after injection at the site of injection due to phase separation and provide a sustained release over weeks to few months duration. It consists of blend of drug and biodegradable polymers dissolved or suspended in pharmaceutically acceptable water-miscible organic solvents. After administration at the injection site, depot (gel) is formed when water penetrates in; organic solvent dissipates into the surrounding tissue and leads to phase separation and precipitation of the polymer. The drug entrapped in the gel is released into the surrounding body fluid by degradation of the polymers and reaches the systemic circulation, which ensures patient compliance. Three triggers are used to stimulate this sol to gel transformation: (1) *in-situ* cross-linking, (2) *in-situ* solidifying organogels, and (3) *in-situ* phase separation.

**ATRIGEL Technology**

Two new products, ATRIDOX periodontal treatment and ATRISORB guided tissue regeneration (GTR) barrier designed based on the unique ATRIGEL technology used for treatment of periodontal diseases. It consists of a solution of a resorbable polymer in a biocompatible carrier and upon administration; the polymer undergoes a phase transition from a liquid to gel formed implant. Being in liquid form, it initially provides the advantage of in vivo placement by simple means, such as syringes to form implants at the site of use. The system is biocompatible and has the capability of serving as a biomaterial and a drug delivery system. Drug Release periods ranging from one week to four months have been achieved with one month being the most often desired. For these reasons the ATRIGELÔ system is being applied to a number of medical applications ranging from site and systemic oncology to post-operative pain control and bone regeneration using growth factors.\[^{30}\]
Fig. 6: Atrigel technology based product design.

Marketed products based on Atrigel technology\(^{[30]}\)

<table>
<thead>
<tr>
<th>Marketed Product</th>
<th>Active ingredient</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atridox</td>
<td>8.5% Doxycycline</td>
<td>Sub gingival delivery used for the treatment of periodontitis</td>
</tr>
<tr>
<td>Atrisorb</td>
<td>-----------</td>
<td>GTR barrier product without any drug for guided tissue regeneration of periodontal tissue</td>
</tr>
<tr>
<td>Atrisorb D</td>
<td>4% Doxycycline</td>
<td>Periodontal tissue regeneration</td>
</tr>
</tbody>
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CONCLUSION

The present review concludes that ‘in-situ gel’ drug delivery system has emerged as one of the best novel drug delivery systems for the treatment of periodontitis, by providing sustained and controlled release of the drugs, improved patient compliance and comfort. Use of biodegradable and water soluble polymers for the in situ gel formulations can make them more acceptable and excellent drug delivery systems. There is high extent for research work on in-situ gel system in order to provide advanced techniques in drug delivery systems.

REFERENCES


