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Oral In Situ Gel; A Novel Drug Delivery System for Oral Diseases

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ABSTRACT

The conventional dosage forms have the disadvantages like frequent administration, poor bioavailability, unpredictable doses etc. To overcome the problems of the conventional dosage forms, newer research in drug delivery systems directed towards a amalgamation of several technologies, leads to the development of in-situ oral gels, which extend the contact time and slows down the removal of the drug. To improve the bioavailability and to prevent rapid loss of drug, the drug can be formulated as oral in-situ gel using stimuli sensitive polymers. Gel dosage forms are successfully used as drug delivery systems to control drug release and protect the medicaments from a hostile environment. This review work gives information about oral diseases, in situ gel, approaches and polymers used for in situ gelation.

Keywords: In situ gel, sustained release, oral diseases.

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INTRODUCTION

The oral cavity provides a diverse environment for colonization of a wide range of microorganisms. Oral diseases are complex pathologies, deriving from the intersection of different components: the oral microbial flora (microbiome), environmental and behavioral factors and life style, the human genetic makeup (the genome), its transcription and translation.¹ Oral diseases ranging from cavities to cancer are all serious threats to oral health. Oral health is an important part of our overall health. Left unchecked, causes hidden threats to oral health such as gum disease, root cavities and infections and oral cancer, can lead to severe pain, loss of teeth and serious health implications.

Oral Candidiasis- also known as oral thrush, is a mycosis (yeast or fungal infection) of *Candida* species on the mucous membrane of the mouth.

Gum disease- Gum disease is one of the most common dental problems adults face, but gum disease can begin at just about any age.

Gingivitis- Gingivitis is a term used to describe inflammation of the gums.

Cavities- A cavity is a very small hole that forms on the surface of a tooth.

Oral cancer- Oral cancer is a disease resulting from abnormal cell growth in the mouth, lips, tongue or throat.²

The aim of dental healthcare is to control the population of microorganisms. Slowing or arresting of the oro-dental infections can be achieved by controlling bacterial plaque. The systemic administration of antibiotics is a useful method for controlling sub gingival flora but it has been found that discontinuation of systemic antibiotic therapy results in re-colonization of pathogens. Therefore long term antimicrobial therapy is required for complete eradication of microorganisms. High oral doses are required to achieve effective concentrations, but high doses given for long periods of time eventually causes development of resistant strains of bacteria, super infection, gastrointestinal and central nervous system disturbances. To overcome the disadvantages of systemic chemotherapy with antibiotics, recent technical advancements have led to the development of new drug delivery systems that provide controlled therapeutic activity by targeting the delivery of a drug to a particular site. If a particular drug is targeted to a desired site, it minimizes the distribution of drug to other body organs. Controlled drug delivery systems offer numerous advantages compared with conventional dosage forms.¹

The conventional formulations for the local delivery of drugs to the oral cavity are the mouth paints, rinses, troches, creams and suspensions. The reason for incomplete eradication of diseases

in most cases may be due to the short residence time of drug in the oral cavity. The other reason may be degradation of drug in salivary fluid. One way to improve the efficacy in eradicating the infection is to deliver the drug in the oral cavity. Therefore some researchers had prepared and reported new formulation such as gels, mucoadhesive tablets, pH sensitive excipients composition mucoadhesive microspheres, which were able to reside in oral cavity for an extended period for more effective eradication. As conventional drug delivery system does not remain in the oral cavity for prolonged period, they are unable to deliver the drug to the site of infection in effective concentrations and in fully active forms. Hence to prolong active drug concentrations in the oral cavity a newer drug formulation, oral in situ gel can be used. At the site of drug absorption, they swell to form a strong gel that is capable of prolonging the residence time of the active substance.

***In situ* gelling systems**

In situ gel forming systems are viscous, polymer based liquids which exhibits a sol-to-gel phase transition due to a change in specific physico-chemical parameter. The gelation occurs due to cross linking of polymer chains through covalent bond formation or non covalent bond formation.

Advantages of *in situ* gels:

It shows various advantages like

- Ease of administration.
- Improved patient compliance.
- Reduced dosing frequency.
- Site specificity and local action.
- Increased bioavailability.
- Sustained and prolonged release.

APPROACHES OF *IN SITU* GEL DRUG DELIVERY

❖ Physiological stimuli sensitive *in situ* gels systems.

• Temperature induced *in situ* gel systems

• pH induced *in situ* gel systems

❖ Physically induced *in situ* gel systems.

❖ Chemically induced *in situ* gel systems.

- Enzymatic cross linking

- Ionic cross linking

- Photo-initiated polymerization

Thermally Triggered System

Temperature-sensitive gelling system are triggered by change in temperature. 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 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 for trigger gelation. A useful system should be tailorable to account for small differences in local temperature, such as might be encountered in appendages at the surface of skin or in the oral cavity. Temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive, and thermally reversible gels.⁴

pH Triggered Systems

In this system change in pH causes formation of gel. In this approach, pH responsive or pH sensitive polymers are used. 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 a large number of ionizable groups are known as polyelectrolytes. The polyelectrolytes those are present in the formulation causes increase in external pH that leads to the swelling of hydrogel that leads to the formation of 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. The most of anionic pH-sensitive polymers are based on PAA (Carbopol®, carbomer) or its derivatives. Suitable polymers for pH triggered systems are the polymers that are having anionic groups. Polymers used for pH sensitive *in situ* gels are cellulose acetate phthalate (CAP), carbomer and its derivatives, Polyethylene glycol (PEG), Pseudo latexes and poly methacrylic acid (PMC) etc.⁵

PHYSICAL MECHANISM

Swelling

In situ formation may also occur when material absorbs water from surrounding environment and expand to occur desired space. One such substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some Bioadhesive properties and can be degraded *in vivo* by enzymatic action.

Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system.⁶

Chemically induced *in situ* gel systems

Chemical reactions that results in *in situ* gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

Ionic Cross-Linking

Polymers may undergo phase transition in presence of various ions. The ion sensitive polymers when comes in contact with cation present in the biological fluid, it gets converted to gel. This is because of the cross linking of the negatively charged helices by monovalent or divalent cations like Na⁺, Ca⁺ etc. Some of the polysaccharides fall into the class of ion-sensitive ones .While k-carrageenan forms rigid, brittle gels in reply of small amount of K⁺, i-carrageenan forms elastic gels mainly in the presence of Ca²⁺.⁷

Enzymatic Cross-Linking

In situ formation of gel is catalysed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators.

Photo-Polymerization

Photo-polymerization is commonly used for *in situ* formation of biomaterials. A solution of monomers or reactive macromer and initiator can be injected into a tissues site and the application of electromagnetic radiation used to form gel. Acrylate or similar polymerizable functional groups are used as the polymerizable groups on the individual monomers and macromers as they rapidly undergo photo polymerization in the presence of suitable photo initiator. Long wavelength ultraviolet visible wavelengths are commonly used as photo initiator. Short wave length ultraviolet radiation is not often used because of the limited penetration and biological harm.⁸

POLYMERS USED FOR *IN SITU* GELLING SYSTEM

Xyloglucan:

Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)- β -D-glucan backbone chain, which has (1-6)- α -D xylose branches that are partially substituted by (1-2)- β -D-galactoxylose. When xyloglucan is partially degraded by β galactosidase, the resultant product exhibits thermally reversible gelation by the lateral stacking of the rod like chains . The sol-gel transition temperature varies with the degree of galactose elimination. It forms thermally reversible gels on warming to body temperature. Its potential application in oral delivery exploits the proposed slow gelation time (several minutes) that would allow in-situ gelation in the stomach

following the oral administration of chilled xyloglucan solution. Xyloglucan gels have potentially been used for oral, intraperitoneal, ocular and rectal drug delivery.⁹

Carbopol:

Carbopol is a well known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. Carbopols, which are very high molecular weight polymers of acrylic acid, have been used mainly in liquid or semi-solid pharmaceutical formulations, such as gels, suspensions and emulsions, as a thickening agent, in order to modify the flow characteristics. HPMC is used in combination with carbopol to impart the viscosity to carbopol solution, while reducing the acidity of the solution. Various water soluble polymers such as carbopol system- hydroxypropylmethylcellulose system, poly (methacrylic acid)-poly (ethylene glycol) come under the category of pH-induced in-situ precipitating polymeric systems.¹⁰

Gellan gum:

Gellan gum (commercially available as Gelrite TM or Kelcogel TM) is an anionic deacetylated exocellular polysaccharide secreted by *Pseudomonas elodea* with a tetrasaccharide repeating unit of one α -L-rhamnose, one β -D-glucuronic acid and two β -D-glucuronic acid residues 30. It has the tendency of gelation which is temperature dependent or cations induced. This gelation involves the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water.¹¹

Sodium alginate:

Sodium alginate is a salt of Alginic acid - a linear block copolymer polysaccharide consisting of β -D mannuronic acid and α -L-glucuronic acid residues joined by 1,4-glycosidic linkages.¹²

EVALUATION AND CHARACTERIZATIONS OF *IN SITU* GEL SYSTEM

The *in situ* gel formulation and processing for specified purpose are characterized to ensure their predictable *in vitro* and *in vivo* performance. The characterization parameters for the purpose of evaluation are,

- Visual appearance and clarity
- Determination of pH
- Gelling Capacity
- Gel strength
- Drug release
- Viscosity Studies

- Gelation time
- Gelation temperature
- Syringe ability
- Spreadability¹³

CONCLUSION

Oral *in situ* gel can play a vital role in sustained drug delivery, more efficiently and on a target based approach. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the *in situ* gel dosage forms very reliable. As the oral *in situ* gel provides definite advantages, it is a better choice for drug delivery in to mouth. The current advancements in novel drug delivery systems are helpful in overcoming challenges offered by the traditional systems.

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