IN-SITU GEL: A STUDY OF DENTAL DISEASES

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In-situ forming polymeric gelling systems has become prominent among novel drug delivery system (NDDS) in recent years due to advantages such as sustained and prolonged drug action, improved patient compliance and reduced frequency of administration of the drug in comparison to conventional drug delivery system (DDS). This is a type of mucoadhesive DDS where the polymeric formulation is in sol form before administration and once comes in contact with body fluids; it undergoes gelation to form a gel. The formulation of gel depends upon factors like temperature modulation, pH changes, presence of ions and ultraviolet irradiation from which drug gets released in sustained and controlled manner. Conventional formulation for the treatment of dental diseases has certain drawbacks. A new concept of *in situ* gel was develop to overcome the shortcoming of conventional formulation which deals with dental diseases. Conventional oral formulations like solution, suspension, and ointments have many disadvantages which result into poor bioavailability of drug in the buccal cavity. *In-situ* forming polymeric formulation drug delivery systems is in sol form before administration in the body, but once administered, undergoes gelation *in-situ* to form a gel.

Key words: *In-situ* Dental Gel, Periodental diseases, Gingivitis, Periodontitis

INTRODUCTION

Dental diseases are a major health problem in all parts of the world, common in all age groups, races and genders. The percentage of dental diseases has grown to a large extent in recent years. Around 70% of population suffers from dental problems. The human population is affected by major of oral diseases like periodontal infections, dental caries, dry socket. For most of the reasons tooth extraction is unavoidable and hence, post extractive complications like excessive bleeding, delayed wound healing, dry socket syndrome etc. are also of great concern [1]. According to estimates by Government of India-World Health Organization collaborative programme, about 50% of school children are suffering from Dental caries and more than 90% of adults are having periodontal diseases [2].

In-situ is a Latin word which means 'In its original place or in position' [3]. The gelation can be triggered by temperature, pH change, ionic change and also UV induced gelation, Solvent exchange induced gelation [4]. *In situ* drug delivery system offers advantages such as reduced frequency of administration, improved patient compliance, and comfort**.** An *in situ* gel formulation provides an interesting alternative for achieving effective plasma drug concentration, an advantage over conventional delivery systems [5]. The stimuli that induces various responses to form hydrogels includes: Physical stimuli such as change in temperature, electric fields, light, pressure, sound, and magnetic fields; chemical stimuli such as change in pH and ion activation from biological fluids; and biological or biochemical stimuli such as change in glucose level. Out of these different environmental conditions only pH, ion activated, and temperature stimuli are used for dental drug delivery system [6,7].

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Anatomy and physiology of oral cavity:

Oral cavity

The oral cavity is lined with mucus membranes with a total surface area of 200cm^2. The oral cavity has distinct areas:

1) The floor of mouth (sublingual)
2) The buccal area (Cheeks)
3) The gums (gingival), The palatal region.(Hard palate and soft palate) [8]. (Figure. 1)

DENTAL DISEASES

Periodontal Disease: The word "Perio" means around, and "dontal" refers to teeth. Teeth and their supporting (periodontal) structures are of main importance to oral health. Dental diseases are among the widest spread chronic disorder affecting mankind [9]. Periodontal disease are a group of clinical conditions which affect the supportive structure of the teeth and are characterized by infection and inflammation. The development of periodontotis involves periodontal tissue breakdown and result from an interaction between the affecting organisms. Conventional therapy, based on scaling, surgery and the use of antibiotics or antimicrobials has been proposed [10].

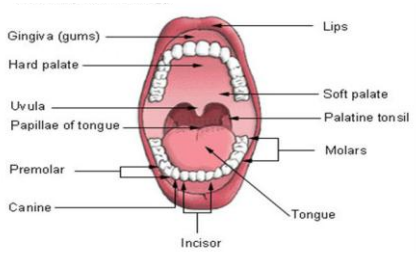

Figure 1: Anatomy of oral cavity

These conditions are characterized by a destruction of the periodontal ligament, a resorbtion of the alveolar bone and the migration of the junctional epithelium along the tooth surface. The clinical signs of periodontitis are changes in the morphology of gingival tissues, bleeding upon probing as well as periodontal pocket formation. This pocket provides an ideal environment for the growth and proliferation of anaerobic pathogenic bacteria [11]. (Figure. 2)

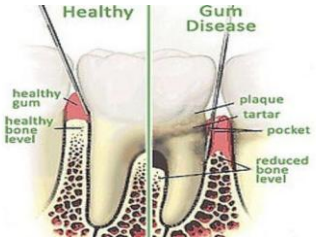

Figure. 2: Healthy V/S Gum Disease

Classification of Periodontal Disease:

The American Academy of Periodontology classification system identifies distinct types of periodontal diseases, clinical appearance, rate of disease progression, pathogenic microbial flora and systemic influences. The two major categories are Gingivitis and Periodontitis.

1. Gingivitis:

Gingivitis is a chronic inflammatory process limited to the gingiva without either attachment loss or alveolar bone loss. It is one of the most frequent oral diseases, affecting more than 90% of the population, regardless of age, sex, or race [12]. Gingivitis can usually be treated simply. Gingivitis is often caused by inadequate oral hygiene. Plaque and tartar are removed from teeth; the inflamed tissues around a tooth usually heal quickly and completely [13].

Types of gingivitis

a) Plaque-Associated Gingivitis

Gingival redness, edema, bleeding upon probing, enlargement and tenderness

b) Chronic Gingivitis

Inflammation of the gingival, resulting in loss of clinical attachment due to periodontal ligament destruction and loss of the adjacent supporting bone

c) Acute Necrotizing Ulcerative Gingivitis

Patients diagnosed with Acute Necrotizing Ulcerative Gingivitis may present with the following clinical findings: Papillary necrosis, bleeding, pain and fetor oris (odor).

d) Gingivitis Associated with Systemic Conditions or Medications

- Hormone-Induced Gingival Inflammation:-

Gingival redness, bleeding upon probing, edema and gingival enlargement associated with proliferation of blood vessels.

- Drug-Influenced Gingivitis

Fibrotic gingival response, pseudo pockets and bleeding upon probing

- Linear Gingival Erythema (LGE)

Patients that are HIV+ may exhibit this type of gingival response.

e) Gingival Manifestations of Systemic Diseases and Mucocutaneous Lesions

- Bacterial, Viral or Fungal: Two examples Acute Herpetic Gingivostomatitis or Candida Albicans

- Blood Dyscrasias (for example Acute Monocytic Leukemia): Clinical Findings: spontaneous bleeding upon probing or by simply touching the gingival tissues.
- Mucocutaneous Diseases (Lichen Planus, Cicatricial Pemphigoid): include; Lichen Planus, Pemphigus Vulgaris and Desquamative Gingivitis [14].

2. Periodontitis

Periodontitis is the common oral disease affecting many people around the world. It is defined as an inflammation and progressive destruction of the tooth-supporting structures (periodontium). Periodontitis involves progressive loss of the alveolar bone around the teeth, and if left untreated, can lead to the loosening and subsequent loss of teeth. A diagnosis of Periodontitis is established by inspecting the soft gum tissues around the teeth with a probe (i.e. a clinical exam) and by evaluating the patient's x-ray films (i.e. a radiographic exam), to determine the amount of bone loss around the teeth. This disease results from interaction between specific host defence mechanisms and dental plaque bio films that colonize on the tooth surfaces at or below the gingival margin [14, 15].

Types of periodontitis:-

a) Plaque-Associated Periodontitis:-

The presence of local factors such as plaque is usually comparable with the disease progression.

b) Early-Onset Periodontitis:-

• Prepubertal: A rare periodontal disease, onset is often during or immediately following eruption of the deciduous dentition and rapid destruction of bone.

• Juvenile Periodontitis: In these patients, there is rapid loss of attachment, bilateral symmetry is common, destruction of bone is often localized to first permanent molars, and mild to moderate inflammatory response.

• Rapidly Progressive: This case is a young female diagnosed with Rapidly Progressive Periodontitis.

c) Periodontitis Associated with Systemic Diseases:

With certain systemic conditions the inflammatory response is altered in the presence of local irritants thereby, accelerating the progression of periodontal disease.

d) Necrotizing Ulcerative Periodontitis:

Findings may include erythema, ulceration and necrosis of the gingival margin, with destruction of the supporting bone.

e) Refractory:

These types of cases normally do not respond to "well-executed" periodontal therapy.

f) Peri-implantitis:

This is a new category established by the AAP. Patients in this category have implants that exhibit a "periodontitis-like-process" similar to natural teeth.

Method of Preparation:

Polymerization in situ:-

This method is used for preparation of sheets of cross-linked polymer sheets in which drug can be incorporated. A liquid polymer or pre polymerized inside a suitable mould. The release from monolithic devices depends on diffusion of drug through matrix. By manipulating the system, selecting the ideal polymer, adjusting the cross-linking, fillers, plasticizers and by using co-polymers, release of some low molecular drug can be achieved. For an antimicrobial agent to be successful the pathogen must be known, it must be susceptible to the drug. It should not readily develop resistance for an adequate period of time. Also the drug should have little or no side effects[16].

EVALUATION AND CHARACTERIZATION OF IN SITU GELLING SYSTEM:

1. Clarity: The clarity of formulated solutions can be determined by visual inspection under black and white background [17].

2. Drug content: The drug concentration is determined by using a UV-visible spectrophotometer at suitable wavelength against a suitable blank solution [18].

3. Gelation temperature and gel time: 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 specific rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube [19].

4. Fourier Transforms Infrared Spectroscopy and Thermal analysis: During gelation process, the nature of interacting forces can be evaluated using this technique by employing potassium bromide (KBr) pellet method. Thermo-gravimetric analysis (TGA) can be conducted for *in-situ* forming polymeric system to calculate the percentage of water in hydro gel. Differential Scanning Calorimetry (DSC) is used to observe any change in thermograms as compared with pure ingredients used thus indicates the interaction [20].

5. Viscosity and Rheological studies: This is an important parameter for the in situ gels, to be evaluated. The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid (depending upon the route of administrations) instead of 5% mannitol, were determined with Brookfield rheometer or some other type of viscometers such as Ostwald's viscometer. The viscosity of these formulations should be such that no difficulties are envisaged during their administration by the patient, especially during parenteral and ocular administration [21].

6. *In vitro* release studies: *In vitro* drug release methods are frequently used to gain information about the release profiles of active ingredients when developing formulations. The amount of active ingredients released over time is analysed using a spectrophotometer or high performance liquid chromatography (HPLC)[22].

7. Gel Strength: This parameter can be evaluated using a rheometer. Depending on the mechanism of the gelling agent used, a specified amount of gel is prepared in a beaker, from the sol form. This gel containing beaker is raised at a certain rate, so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface [23]. (Figure. 3)

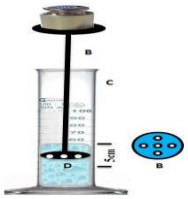

Figure 3: Gel strength measuring device

8. Texture analysis: The firmness, consistency & cohesiveness of formulation are assessed using texture analyzer which mainly indicates the syringability of sol so the formulation can be easily administered *in vivo*. Higher values of adhesiveness of gels are needed to maintain an intimate contact with surfaces like tissues [24].

9. Determination of mucoadhesive Force: The mucoadhesive force is calculated by taking a section of mucosa from the chicken cheek portion and instantly fixed with mucosal side out onto each glass vial using rubber band[25]. The vial with chicken cheek mucosa is connected to the balance in inverted position while first vial is placed on a height adjustable pan. Then the height of second vial is so adjusted that the mucosal surfaces of both vials come in intimate contact. Then weight was kept rising in the pan until vials get detached. Mucoadhesive force was the minimum weight required to detach two vials. The cheek mucosa was changed for each measurement [26].

experiments Detachment stress (dynes/cm^2) = mg/A

Where, m is the weight added to the balance in grams;
g is the acceleration due to gravity taken as 980 cm/s^2;
A is the area of tissue exposed, i.e 8.14cm^2.

Advantages of In-Situ Gel:[27]

a) Prolong drug release
b) Reduced systemic side effect
c) Reduced number of application
d) Ease of administration
e) Reduced frequency of administration
f) Better patient compliance

Approaches for in situ gelling system:[28]

The various approaches for in situ gelling system are:

1. Stimuli-responsive in situ gel system

a. Temperature induced in situ gel systems
b. pH induced in situ gel systems

2. Osmotically induced in situ gel systems (Ion activated systems)

3. Chemically induced in situ gel systems

a. Ionic cross linking
b. Enzymatic cross linking
c. Photo-polymerization

1. Stimuli-responsive in situ gel system:

Stimuli-responsive polymers are defined as polymers that undergo relatively large and abrupt, physical or chemical changes in response to small external changes in the environmental conditions [29].

a) Temperature induced in situ gel systems:

Temperature is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control, but also easily applicable both in-vitro and in-vivo[30]. 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 facilated 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 [31].

b) pH induced in situ gel systems:

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 a large number of ionizied groups are known as polyelectrolytes. 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 [32,33].

2. Osmotically induced in situ gel systems (Ion activated systems):

The polymer which shows osmotically induced gelation are gelrite or gellan gum, hyaluronic acid and alginates etc. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear gel in the presence of the mono or divalent cations typically found in the tear fluids. The electrolyte of the tear fluid and especially Na+, Ca2+ and Mg2+ cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in the conjunctival cul-de-sac [34].

3. Chemically induced in situ gel systems:

a. Ionic crosslinking: divalent cations, especially Ca^{2+}. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e. g. Ca^{2+} due to interaction with guluronic acid block in alginate chains [35].

b. Enzymatic crosslinking: In situ formation 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. Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Adjusting the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation [36].

Photo-polymerization: In situ photo-polymerization has been used in biomedical applications for over more than a decade. 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 typically used as the polymerizable groups on the individual monomers and macromers because they rapidly undergo photo-polymerisation in the presence of suitable photo initiator. Photopolymerizable systems when introduced to the desired site via injection get photo cured in situ with the help of fiber optic cables and then release the drug for prolonged period of time. A photo-polymerizable, biodegradable hydrogel as a tissue contacting material and controlled release carrier is reported by Sawhney et al [37].

FUTURE PROSPECT

• To find the other triggering factors for the *in-situ* gel formation

• To search for the penetration enhancers devoid of side effects

• To target the drug in the posterior chamber through non-invasive route [38]

CONCLUSION

Each drug having its own therapeutic effects can be administered through various routes as *in-situ* gels. *In-situ* gel having tremendous advantages of reducing systemic side effect, prolong drug release, Ease of administration is being used widely nowadays. *In-situ* gelling systems have transformed as conventional drug delivery systems because of its controlled delivery and convenient application. *In-situ* gel dosage forms are very reliable due to sustained and prolonged drug release and good stability. It had been a boon in pharmaceutical industry to develop such a delivery which could be delivered at great ease. Developments are still on and more formulation would be formulated in coming times.

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