

ORODENTAL DELIVERY SYSTEMS: AN OVERVIEW

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Received: 09 Apr 2013, Revised and Accepted: 23 May 2013

ABSTRACT

Oral cavity can be used for local drug delivery as in for periodontitis, dental caries or for oral mucosal drug delivery as for alveolar osteitis, analgesia or transmucosal systemic effect as for smoking cessation or delivery of biotechnological products like proteins and peptides. This article gives an overview of basic structure, function, biochemistry, and permeability of the oral cavity. Different diseases affecting orodental region along with conventional as well as new and emerging drug delivery and technologies that address the unmet patient and market needs for improved local drug therapy to this region are discussed in this article. Regulatory and Clinical aspects of this type of drug delivery are very important and are taken into consideration in this article. The aim of this review is to provide the reader a general and inspiring prospect on recent and promising fields of innovation in oral drug delivery.

Keywords: Periodontitis, Alveolar osteitis, Oral mucosal, Transmucosal, Oro-dental.

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 [1, 2]. It has been observed that poor oral hygiene increased risk of cardiovascular diseases in patients suffering from periodontitis also poor maternal oral hygiene showed babies with low birth weight. 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. Also, the wide array of habitat renders the mouth a microbial paradise, offering preferred accommodations on the cheek, back of the tongue and in the moist, oxygen deprived area between the tooth surface and the adjacent periodontal tissues [3, 4]

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.

A considerable number of products are now recommended for use in the oral cavity. The high incidence of caries and periodontal disease is common especially in the children and elderly respectively. A number of products have been available for the treatment of dental disorders but little work has been done on the sustained delivery of the products to the oro-dental cavity [5].

Chemotherapy of periodontal and other dental diseases faces several formidable challenges and obstacles. Because of the unique anatomical and physiological features of the oral cavity such as large fluid production (saliva and gingival fluids) and relative motions or friction between the dosage form and tissues and food, the retention of dosage form is poor and clearance of active agents is rather large, resulting in the need for frequent dosing. Currently marketed pharmaceutical products for the treatment of various dental diseases require procedures that are time consuming or inconvenient, limiting the widespread usage of the products. These problems also compromise physician/patient compliance. Therefore, for the new products to be successful in the market it is essential that the products embody significant improvement in one or more of these attributes associated with the current dosage forms [6,7].

Anatomy and physiology of oral cavity

Oral cavity

The oral cavity is lined with mucus membranes with a total surface area of 200cm². The oral cavity has distinct areas:

- 1) The floor of mouth (sublingual)
- 2) The buccal area(Cheeks)
- 3) The gums(gingival)
- 4) The palatal region.(Hard palate and soft palate).

The buccal and sublingual are the commonly used routes for producing local or systemic effects [8].

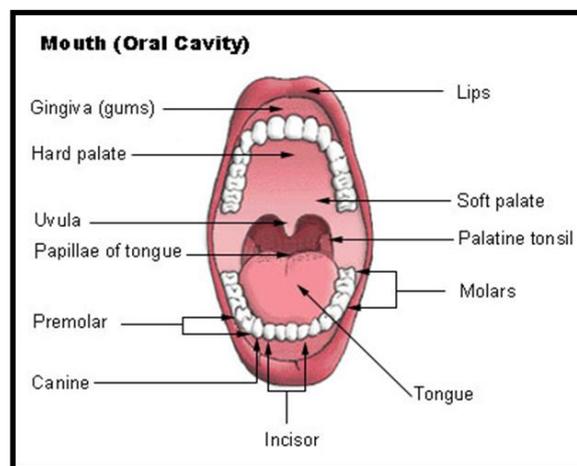


Fig. 1: (Source: V.Sankar et al) Anatomy of oral cavity [9]

Oral mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The permeability of buccal mucosa is 4-4000 times greater than that of skin. In general, the permeability of the oral mucosa decreases in the order of, sublingual greater than buccal, and buccal greater than palatal. This is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized [10].

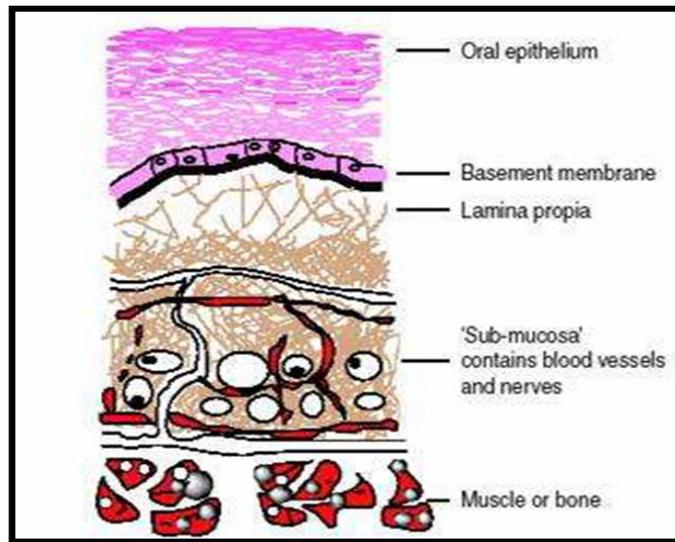


Fig. 2: (Source: J.D. Smart et al) Structure of oral mucosa [11]

Table 1: Characteristics of oral mucosa

Tissue [12]	Structure	Thickness (µm) [12]	Turnover time (days) [13]	Surface area (cm ²) ± SD [13]	Permeability [15]	Residence time [15]	Blood flow* [14]
Buccal	NK	500-600	5-7	50.2 ± 2.9	Intermediate	Intermediate	20.3
Sublingual	NK	100-200	20	26.5 ± 4.2	Very good	Poor	12.2
Gingival	K	200	-	-	Poor	Intermediate	19.5
Palatal	K	250	24	20.1 ± 1.9	Poor	Very good	7.0

NK is nonkeratinized tissue, K is Keratinized tissue and * In rhesus monkeys (ml/min/100 g tissue)

The relative impermeability of oral mucosa is predominantly due to intercellular materials derived from Membrane Coating Granules (MCG). The MCG's are present in both keratinized and non-keratinized epithelia [16]. The components of the membrane coating granules in keratinized and non-keratinized epithelia are however different. The membrane coating granules of keratinized epithelium are composed of lamellar lipid stacks, whereas the non-keratinized epithelium contains membrane coating granules that are non-lamellar. The membrane coating granule lipids of keratinized epithelia include sphingomyelin, glucosylceramides, ceramides, and other non-polar lipids, however for non-keratinized epithelia, the major membrane coating granule lipid components are cholesterol esters, cholesterol, and glycosphingolipids. These MCG's release lipophilic material into the intercellular spaces to ensure epithelial cohesion. This lipophilic material slows the passage of hydrophilic materials across the epithelium [17].

There are two permeation pathways for passive drug transport across the oral mucosa:

Para cellular and Trans cellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage [18].

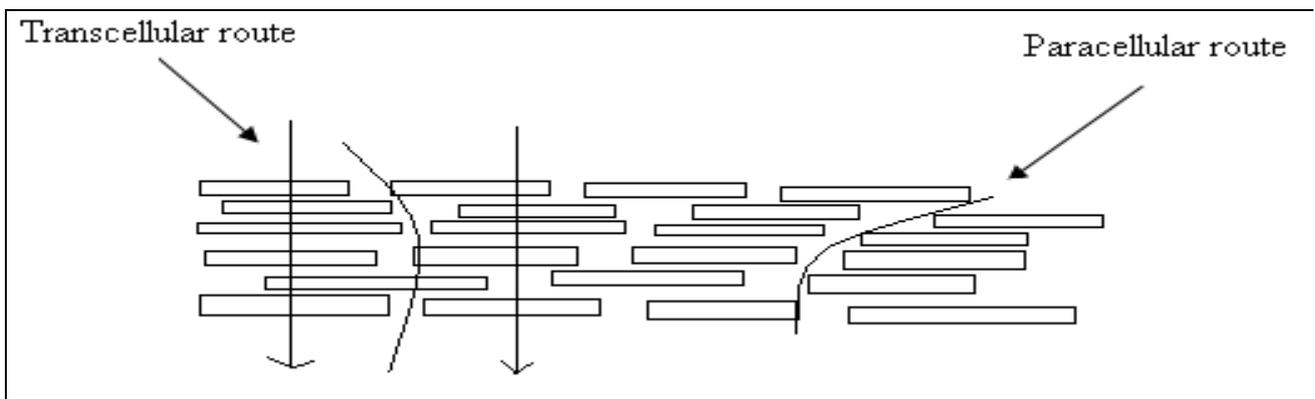


Fig. 3: (Source: M. Rathbone et al) Permeation pathways for passive drug transport across the oral mucosa [18]

Structure, function and composition of Mucus

The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness ranging from 40µm to 300µm. Although most of mucus is water (≈95–99% by weight) the key macromolecular components are a class of glycoprotein known as mucins (1–5%). Mucins are large molecules with molecular masses ranging from 0.5 to over 20 MDa. They contain large amounts of carbohydrate (for gastrointestinal mucins 70–80% carbohydrate, 12–25% protein and upto≈5%ester sulfate). Undegraded mucins from a variety of sources are made up of multiples of a basic unit (≈400–500 kDa), linked together into linear arrays to give the macroscopic mucins with molecular masses claimed to be as high as ≈50 MDa. It serves as an effective delivery vehicle by acting as a lubricant allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery systems. Pendant sialic acid (pKa = 2.6) and sulphate groups located on the glycoprotein molecules result in mucin behaving as an anionic polyelectrolyte at neutral pH. Other non-mucin components of mucus include secretory IgA, lysozyme, lactoferrin, lipids, polysaccharides, and various other ionic species. Some of these non-mucin components are believed to be responsible for the bacteriostatic action observed in mucus[19]. At buccal pH, mucus can form a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer. Mucus molecules are able to join together to make polymers or an extended three-dimensional network. Different types of mucus are produced, for example G, L, S, P and mucus, which form different network of gels. A thorough understanding of the glycoprotein mucin component is very important with regard to understanding the properties of mucus. Mucin glycoproteins may be described as consisting of a basic unit made from a single-chain polypeptide backbone with two distinct regions:

(1) A heavily glycosylated central protein core to which many large carbohydrate side chains are attached, predominantly via O-glycosidic linkages.

(2) One or two terminal peptide regions where there is little glycosylation. These regions are often referred to as 'naked proteins regions'[20].

Mucosal membrane is the main administration site for bioadhesive systems. Mucosal membranes of human organism are relatively permeable and allow fast drug absorption. They are characterized by an epithelial layer whose surface is covered by mucus. Mucus is a

complex viscous adherent secretion which is synthesized by specialized goblet cells. These goblet cells are glandular columnar epithelium cells and line all organs that are exposed to the external environment. Mucus is found to serve many functions within these locations such as lubrication for the passage of objects, maintenance of a hydrated epithelium layer, a barrier function with regard to pathogens and noxious substances and as a permeable gel layer allowing for the exchange of gases and nutrients to and from underlying epithelium. From an engineering point of view, mucus is an outstanding water-based lubricant whose properties are extensively exploited within nature[21]. Mucin itself is stored in both submucosal and goblet cells, wherein the negative charges of the mucin glycoprotein are shielded by calcium ions, this allows for the compact packing of such molecules. During release into luminal space, outflux of calcium exposes these negative charges resulting in electrostatic repulsion and an approximate 400-fold expansion of the molecule. These now elongated mucin chains entangle and form non-covalent interactions such as hydrogen, electrostatic, and hydrophobic bonds leading to the development of a viscoelastic gel. In the presence of water, these mucin chains begin to overlap, interpenetrate and form a structured network that mechanically functions as mucus. The overall rheological behaviour of mucus is a result of flow resistance exerted by individual chain segments, physical chain entanglement and non-covalent intermolecular interactions[22].

The exact composition of mucus may vary with the site of secretion, its physiological or mechanical role, and the presence of any underlying disease state. One particular point of interest is the strategic position of mucus in many disease processes in which the interactions of epithelial cells and their surroundings have gone astray such as is seen in inflammatory and infectious diseases, cancer and metastasis. Such scenarios may allow a means of targeting therapeutics to such conditions more effectively [23].

Functions of Mucus Layer [22]

- 1. Protective:** resulting particularly from its hydrophobicity.
- 2. Barrier:** The role of the mucus layer as a barrier in tissue absorption of the drugs and influence the bioavailability.
- 3. Adhesion:** Mucus has strong cohesion properties.
- 4. Lubrication:** mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules.

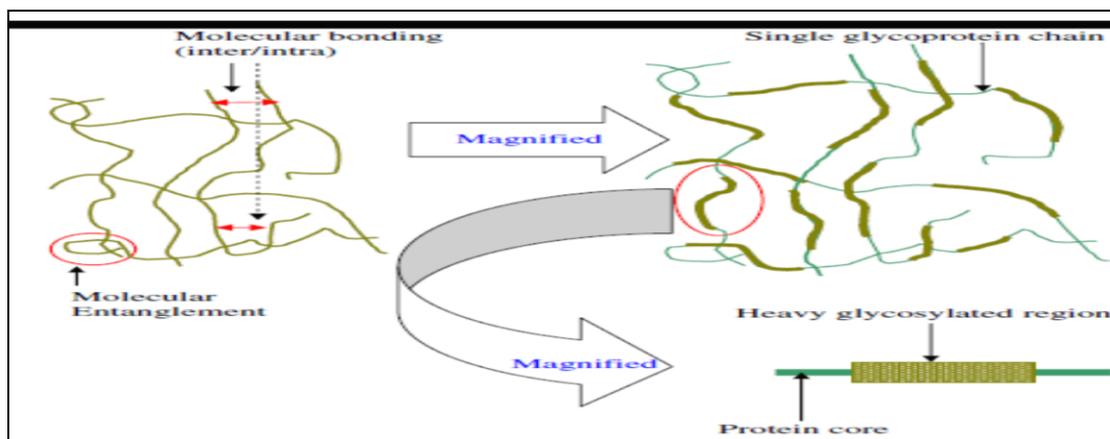


Fig. 3: (Source: C. Dawes et al) Molecular bonding and molecular entanglement in mucus [22]

Composition and functions of Saliva

Saliva forms a vital component of oral cavity. The surface of the oral cavity is constantly bathed with a stream of saliva (approximately 1 litre per day) produced by the salivary glands. The major salivary glands, producing up to 90% of the saliva, are the pairs of parotid, submaxillary (submandibular) and sublingual glands. The parotid glands are situated some way from, but drain into, the oral cavity via

long ducts that open onto the inner surface of the cheek. The submaxillary glands lie below the lower jaw and release saliva through ducts on each side of the floor of the mouth. The sublingual glands are located below the tongue with several ducts emptying onto the floor of the mouth. Minor salivary glands, i.e. the buccal glands exist in or below the oral mucosa [24]. Chemically, saliva consists of 99.5% water with 0.5% solutes. The solutes include ions (sodium, potassium, calcium, magnesium, phosphate, bicarbonate

and chloride), dissolved gases, urea, uric acid, serum albumin, globulin, mucin, and enzymes (lysozyme and amylase (ptyalin)). The nature of the secretions varies from gland to gland; the parotid glands produce predominantly an amylase-containing watery secretion while the buccal and sublingual glands produce mainly a viscous saliva containing mucin with little enzymatic activity. The submaxillary glands have an intermediate secretion containing both amylase and mucin. Ordinarily just enough saliva is secreted to keep the oral mucosa moist, 70% of which originates from the submaxillary gland. When food is ingested, secretion increases so that the saliva can lubricate, dissolve and bring about the chemical breakdown of food. The nature of the salivary secretion may alter from viscous to watery (and the enzyme content is also variable). The salivary pH will also vary from 6.2 to 7.4 (from low to high flow rates) although bacteria around the teeth may produce a lower localised pH. The glycoproteins in saliva can be divided into two groups: those of mucous cell origin which have a high molecular weight and are heavily glycosylated and those of serous cell origin which have a lower molecular weight and contain less than 50% carbohydrate. The salivary mucin glycoprotein MG1 consists of several disulphide-linked subunits containing a protein core with 4-16 oligosaccharide side-chain units. Its molecular size is over 1000 kDa, and it contains approximately 15% protein, 78% carbohydrate with about 5-10% covalently bound fatty acids. A smaller mucin glycoprotein (MG2) has been identified from submaxillary and sublingual saliva. This contains 30% protein and 68% carbohydrate and has a molecular weight of 200-250 kDa. It consists of a single peptide chain with 2-7 oligosaccharide side-chain units. Another important glycoprotein found in human parotid saliva is proline-rich glycoprotein (PRG). This contains 60% protein and 30% carbohydrate and is 38.9 kDa in size. It also consists of a single peptide chain with 14 oligosaccharide side-chain units. Components of saliva are adsorbed onto the surface of the oral mucosa to form a salivary pellicle 0.1-0.7 mm thick. This pellicle coats all surfaces in the mouth

and is a multilayered structure. Initially, salivary macromolecules are selectively adsorbed onto the mucosal surface, then these molecules complex with other molecules in the ambient saliva. It has been proposed that these salivary components may be covalently crosslinked to the epithelial cell surface and to each other by the actions of transglutaminases. It has been speculated that MG1 functions at the hard and soft tissue interfaces to provide a permeability barrier for protection against environmental insult and desiccation. The nature of the salivary pellicle (i.e. its effectiveness in increasing the wettability of a surface) has been seen to change throughout the day. It has been suggested that the lubricating properties of biological fluids depends on the ability of glycoproteins to form a boundary layer on opposing surfaces, thus reducing friction, and it was found, using a modified lubometer, that on a molar basis MG1 is a better lubricant than MG2, with PRG being the least effective[25]

Physiological Functions Of Saliva [24]

Modulation of the oral flora

Remineralisation of the teeth with calcium phosphate salts

Neutralisation of acid in the oral cavity and oesophagus

Lubrication and cleansing of the oral, pharyngeal and oesophageal mucosae

Assistance in bolus formation

Stimulation of epithelial proliferation

Initiation of fat and starch digestion

Diseases of oro-dental region

There are more than 250 different type of disease that affect oral cavity. The most frequently seen diseases in young adults are dentinoma, dental caries, periodontitis, dentinal sclerosis, root resorption, aphthous stomatitis (mouth ulcers), gingivitis, fungal infection, chronic bacterial infection etc. If these conditions remain untreated they may lead to various complications affecting different

body organs. Sometimes these complications may be lethal. Recent advances in molecular biology, microbiology, immunology and genetics have lead researchers to resume the study of the relationship between oral and systemic diseases with a more scientifically oriented approach[26].

Hence there is a need for targeting the orodental region to provide efficient treatment. Common diseases of orodental region are discussed below-

Periodontal diseases

Periodontitis is a localized inflammatory response caused by bacterial infection of a periodontal pocket associated with subgingival plaque. This periodontal pocket provides ideal conditions for the proliferation of microorganisms. The disease may then require extensive treatment, failing which the teeth may be lost. The therapeutic goal can be achieved by removing bacteria, by mechanical cleaning of plaque and topical application of antimicrobial agents. In periodontal diseases the supporting structures become infected and as a result loose the strength to hold the teeth in the cavity. Periodontal disease is a term which includes a number of pathological conditions described by inflammation and degeneration of the gums (gingival) and the supporting structures of the teeth [27]. Typically periodontal diseases are gingivitis (inflammation of the gingival) and periodontitis (inflammation of the periodontal ligament).The periodontal diseases are generally degenerative or neoplastic in nature. Initially the disease is localized to the marginal gingival but later progresses to the marginal periodontitis[28]. The periodontal pocket provides diverse environment for the colonization of gram negative facultative or obligate anaerobes like *Porphyromonas gingivalis*, *Bacteroides spp.*, *Capnocytophaga spp.* and *Actinobacillus actionomycetemcomitns* The bacteria accumulate in the periodontal pocket that develops between the roots of affected teeth and soft tissues. Periodontal disease, bleeding gums and oral infections are at increased risk of dysphasia and leads to patient noncompliance. Oral bleeding results in bacterial infection (bacteremia) which leads to serious and fetal health problem known as infective endocarditis. Oral inflammation and swelling of gums makes drug difficult to reach at the site of action, so it is necessary to give large dose to get desired pharmacological action. To take care of oral-dental infection, gingival bleeding, pus and local ulceration, it is necessary to give drug which act quickly and achieves highest concentration at site of action. [29].

Dental caries

Bacteria can itself colonize the supporting structures of the tooth specially the enamel, with time the bacterial acids leach the enamel and tooth decay starts, termed as dental caries. Often this progresses to the inner pulp of the teeth containing the nervous and vasculature supply of the teeth. The diseases affecting the inner portion are referred to as endodontics diseases. The infection to this part is accompanied by pus production which leads to necrosis of the pulp tissue. Conventional treatment for endodontics includes root canal treatment and pulpotomy [31].

Apthous stomatitis

Apthous ulcers or recurrent aphthous stomatitis (RAS), commonly referred to as canker sores, are inflammatory lesions of the mucous lining of the mouth which may involve the cheeks, gums, tongue, lips, and roof or floor of the mouth. It is usually painful and associated with redness, swelling, and occasional bleeding from the affected area(s). Manifestation of the disease can range from mild to severe and, in extreme cases, even hinder a person's ability to ingest foods, thereby making the person susceptible to malnutrition. The cause of RAS is unknown, although several factors are suspected including genetics, Stress, nutritional deficiencies, diet, hormonal changes, infectious agents(both bacterial and viral) and immunological disorders. Due to the indeterminate etiology of the disease, it is difficult to find a definitive cure and current treatments are aimed towards ameliorating the symptoms. There are 3 clinical presentations of RAS: aphthous minor, aphthous major and herpetiform ulcers. Herpetiform ulcers appear on both non-

keratinized and keratinized mucosa unlike aphthae minor and major which are limited to non-keratinized mucosa[32].

Alveolar osteitis

Alveolar osteitis or dry socket, is a complication of wound healing following extraction of a tooth. The term alveolar refers to the alveolus, which is the part of the jawbone that surrounds the teeth, and osteitis means simply "bone inflammation". Alveolar osteitis remains one of the most common postoperative complications after dental extractions [33]. Various factors are considered important in causation of dry socket like: Insufficient blood supply to the alveolus, Preexisting infection. (Granuloma, periodontal or pericoronal infection), use of large amounts of local Anesthetic, leading to vasoconstriction. Post operative bleeding, Trauma to alveolus during extraction, Infection during or after extraction, Root/bone fragments or foreign bodies left in the socket, Excessive irrigation and curettage, Fibrolytic or proteolytic activity in the clot, Loss of clot due to patient's negligence, Patient actions like sucking liquids, sneezing, coughing, rinsing water post extraction, Predisposing factors in patient, eg smoking, poor general health[34].

Dry socket is more often seen in the mandibular molars particularly the third molars. This condition is associated with excruciating pain, foul breath, unpleasant taste, empty socket and gingival inflammation and Lymphadenopathy. Complications and problems that dry socket may cause or be associated with include Pain, Delayed healing after tooth extraction, infection, interference with other needed dental procedures[35].

Xerostomia

Xerostomia is defined as dry mouth resulting from reduced or absent salivary flow. Xerostomia is a common complaint among older adults and according to a study 30 percent of population aged

65 and above experience this disorder. There are various reasons which may lead to xerostomia like Xerostomia is a common complaint associated with several conditions, which include side effects of wide variety of medications, therapeutic radiation to head and neck, systemic diseases and diseases involving the salivary glands. When salivary hypofunction and xerostomia occur, transient and permanent oral and extraoral disorders can develop. Individuals with Xerostomia complain of dry mouth and problems with eating, speaking and swallowing. There is oral burning or soreness and a sensation loss of or altered taste. Diseases which affect the salivary glands are Sjogren's syndrome, Sarcoidosis, Amyloidosis and hence cause Xerostomia. Systemic diseases like Diabetes, HIV infections, Chronic graft-vs-host disease after allogeneic bone marrow transplant, emotional Stress and mental depression cause Xerostomia. Use of medications like Antihistamines, Antidepressants and antipsychotics, Antihypertensive, Antianxiety agents, Diuretics, Antiparkinsonism drugs, Antiemetics, Bronchodilators, Sedatives[36].

Halitosis [18,19]

About 85% of patients suffer with persistent genuine halitosis, the odor originates from the mouth, mainly from microorganisms. It is likely that there is a complex interaction between several oral bacteria species (mainly gram-negative anaerobic flora) because no single specific bacterial infection has invariably been associated with halitosis. The bacterium *Solobacterium moorei* was found to be associated with halitosis. The odiferous products that cause halitosis arise from the interaction of microbes with specific substrates, namely the amino acids cysteine, methionine, tryptophan, arginine and lysine that are biotransformed into hydrogen sulfide, methylmercaptan, indole, putrescine and cadaverine, respectively[37].

Table 2: Different terminologies of Halitosis [37]

Terms used	Defination
1 Halitosis	Any disagreeable odor of expired air, regardless of origin
2 Bad breath	Lay term for halitosis
3 Genuine halitosis	Where breath malodor can be verified objectively. Physiologic halitosis, also termed transient halitosis or Pathologic halitosis e.g. morning breath: oral malodor and extra-oral
4 Pseudo-halitosis	No objective evidence of malodor, but patient think they have it.
5 Halitophobia	The patient persists in believing they have halitosis despite firm evidence for the absence of objective evidence.

Micro organisms associated with Halitosis:

Centipeda periodontii, *Eikenella corrodens*, *Enterobacteriaceae*, *Fusobacterium nucleatum subsp. Nucleatum*, *Fusobacterium nucleatum subsp. Polymorphum*, *Fusobacterium nucleatum subsp. Vincentii*, *Fusobacterium periodonticum*, *Porphyromonas endodontalis*, *Porphyromonas gingivalis*, *Prevotella (Bacteroides) melaninogenica*, *Prevotella intermedia*, *Bacteroides (Bacteroides) looschei*, *Solobacterium moorei*, *Tannerella forsythia (Bacteroides forsythus)*, *Treponema denticola*

Causes

- 1) Gingivitis, periodontitis, acute necrotizing ulcerative gingivitis, pericoronitis, abscesses
- 2) Systemic disease (inflammatory/infectious disorders, cutaneous, gastrointestinal and hematological disease), malignancy, local causes, aphthae.
- 3) Poor dental hygiene.
- 4) Increased microbial metabolic activity during sleep that is aggravated by a physiological reduction in salivary flow, lack of nocturnal physiologic oral cleansing (e.g. movement of the facial and oral muscles) and variable oral hygiene procedures prior to sleep.
- 5) Halitosis as a result of the ingestion of certain food and drinks, such as spices, garlic, onion, durian, cabbage, cauliflower and radish, or of habits such as smoking tobacco or drinking alcohol, is usually transient, often caused by sulfur-containing volatile agents and is

considered to arise both from intra-oral (food debris) and extra-oral (respiratory) origins[38].

Drug delivery for orodental diseases

The effectiveness of dental products is limited to the conventional drug delivery products which suffer from the disadvantage of a short duration of action due to the lack of a prolonged contact time at the site of action. Most dental disorders require a prolonged contact of the active agent at the site of action which can be achieved by the controlled drug delivery systems[39]. The novel oro-dental drug targeting systems work on this rationale of prolonging the contact at the site of action. The treatment of the dental disorders is based on the removal of the pathogenic bacteria from the periodontal pocket; such an action will ideally require an increased contact of the active agent at the site of action, hence the duration of action being the most critical in the effectiveness of the dental drug delivery products. Presently number of controlled release products for orodental targeting is limited, but increased research and development in this field shows promising future results[40].

The conventional therapy towards dental diseases includes the antimicrobial therapeutics which requires high oral doses necessary to achieve effective concentration in the gingival fluid. The obvious disadvantage being the development of resistant bacterial strains. These have led to the development of localized target oriented drug delivery to the periodontal pocket [41]. Dr. Arvind Venkatesh et. al. have discussed various antimicrobial agents and their formulations used for treatment of Periodontal diseases[42].

Novel drug delivery systems

Novel drug delivery systems to orodental region offer various advantages over conventional drug delivery

- Local/Topical and site specific drug delivery to affected area in oral cavity – Drug will neither be exposed to other region in oral cavity nor to systemic circulation, hence no adverse effects.
- Better therapeutic control of the diseased conditions through targeted delivery
- Less /No systemic side effects
- Localized drug action and prolonged duration of action through mucoadhesion
- Bacterial resistance would not be developed
- Rapid onset along with slow and gradual drug release for prolong period - decrease dose frequency
- Improved patient compliance as ease to administer the dosage form and or ease of termination of therapy if required.

Novel approaches for treatment of orodental diseases

A) Vesicular systems

Liposomes

The localized drug delivery to the intra-periodontal pocket is beneficial as it lowers the incidence of the undesirable side effects, results in improved therapeutic efficacy and increased patient compliance. Liposomes have been found to be the most promising in this approach as they mimic the bio-membrane in structure and behavior. The potential of liposomes as a drug delivery system for use in the oral cavity has been investigated specifically targeting for the teeth, the *in vitro* adsorption of charged liposomal formulations to hydroxyapatite (HA), a common model substance for the dental enamel, has been conducted by Sanko Nguyen et al. Various liposomal formulations have been used as carriers to deliver bactericides to inhibit the growth of biofilms [43], and *in vitro* experiments have proven that liposomes adsorb to hydroxyapatite (HA), a commonly accepted model substance for tooth enamel [44]. Liposomes can thus be designed to be bioadhesive, e.g. being retained on enamel surfaces to increase the contact time, thereby prolonging the residence time in the oral cavity. In addition to its encapsulating ability of active pharmaceutical ingredients, e.g. antibacterial or anti-plaque agents affecting the attachment of cariogenic microorganisms onto the enamel, liposomes may protect the enamel against deterioration by physically covering the enamel surfaces. The initial adsorption of bacteria to dental enamel is the basis for dental plaque formation which in later and mature stages can give rise to plaque-related diseases such as caries and periodontal diseases. Phosphatidylcholine based liposomes have been prepared for targeting to the bacterial bio-film. Succinylated Con A bearing liposomes have been prepared for delivery of triclosan to the bio-film of *Staphylococcus epidermidis* and *Proteus vulgaris*. Liposomal targeting systems loaded with chlorhexidine and dipalmitoyl phosphatidylcholine, stearic acid have also been reported [45]

Microparticles

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They are made of polymeric, waxy or other protective materials, that is biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes [46]. It consists of encapsulation of drug into a polymer, which dissolves gradually releasing the drug at the target site. It is highly stable system for delivering an optimum concentration in the pocket. Nakahara et al demonstrated regeneration of periodontal tissues in 4 weeks by using a sandwich membrane composed of a collagen sponge scaffold and gelatin microspheres containing basic fibroblast growth factor (bFGF) *in situ*. [47] Renvert et al. treated periimplantitis patients with arestin (minocycline microspheres) with sustainance of improved results for 12 months [48]. Biodegradable poly alpha hydroxy acids such as poly lactide (PLA) or poly (lactide – co-glycolide) PLGA containing drug dosages can be used to treat periodontal disease.

Nanoparticulate system

Nanosizing of drugs can lead to a dramatic increase in their absorption and subsequently bioavailability leading to a subsequent reduction in drug dose. Owing to its small size, it acquires high dispersibility in an aqueous medium and controlled release rate. Nanoparticles, owing to their small size, penetrate regions that may be inaccessible to other delivery systems, such as the periodontal pocket areas below the gum line. These systems reduce the frequency of administration and further provide a uniform distribution of the active agent over an extended period of time. Chitosan/oligonucleotide-TPP nanoparticles, which were prepared by adding TPP after the formation of chitosan/oligonucleotide complex, showed the sustained release of oligonucleotides and are suitable for the local therapeutic application in periodontal diseases [49].

B) Mucoadhesive systems

Denticaps/dental moulds

A soft moldable gummy material containing analgesic as well as antibiotic drugs is attached to an offending tooth and sustained drug release occurs from it, a prolonged local action of the drugs is achieved. The polymeric mold should have an appropriate adhesiveness so that it may be easily fixed on the affected tooth and can be removed easily whenever necessary. Two types of Denticaps were prepared, one with eudragit L 100-55, carbopol 971 P, gum karaya powder, ethyl cellulose and another with corn zein, carbopol 934 P, gum karaya powder, poloxamer 407 containing Lidocaine hydrochloride were prepared by Biswajit Mukherjee et al. The onset of anesthetic effect was 1-5 minutes and duration was 105-125 minutes Different physicochemical characterization studies such as tooth adhesive strength test, water absorption capacity, swelling index, weight loss, surface pH, content uniformity related to those formulations and *in vitro* drug release studies were carried out. "Denticap" is a novel approach to local drug delivery for a prolonged period by applying it on the affected tooth. More patient compliance over the conventional dosage forms is the expected outcome of such approach. In the future, in root canal treatment and in different gum therapy, this type of dosage form may be very effective. Therefore, denticap may open a new era in dentistry in near endeavor [50].

Mucoadhesive Tablets

They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, but coupling of mucoadhesive properties to tablet has additional advantages, for example, it offers efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio and facilitates a much more intimate contact with the mucus layer. Until now adhesive tablets have been the most commonly used dosage forms for buccal drug delivery. Tablets can be applied to different regions of oral cavity, such as cheeks, lips, gums, and palate. Unlike conventional tablets, buccal tablets allow drinking, eating, and speaking without any major discomfort. Perioli et al. studied the influence of compression force on tablet behavior and drug release rate for mucoadhesive buccal tablets. Tablets were prepared by using hydroxyethyl cellulose (HEC) and carbopol 940 in a 1:1 ratio as matrix-forming polymers at varying compression forces. Compression forces did not significantly affect the water penetration and polymer chain stretching; however, mucoadhesion performance and drug release were influenced by compression force. Increase in compression force resulted in a decreased *in vitro* and *in vivo* drug release while giving the best *in vivo* mucoadhesive and hydration time. Moreover, it was observed that tablets prepared with the lowest force gave the best results, in comparison with tablets prepared with highest forces causing pain during *in vivo* application, needing to be detached by human volunteers. The major drawback of mucoadhesive tablets is their lack of physical flexibility, leading to poor patient compliance for long-term and repeated use [51]

Fibers

Thread like devices placed in periodontal pocket and are secured with periodontal packing to have sustained release of drugs at the specific site. Hollow fibers contain drug reservoir surrounded by polymer through which drug diffuse out. Goodson's first delivery devices involved hollow fibers of cellulose acetate filled with tetracycline. Reduction in spirochete number and a reduction in clinical signs were produced by these fibers when placed into periodontal pocket. However the hollow fiber system released the drug very rapidly and was not very successful at sustaining the drug release. Further, monolithic fibres where drug is impregnated into molten polymers, spinning it on high temperature followed by quick cooling were developed for controlled drug release for several days. Several polymers such as poly(ϵ -caprolactone) (PCL), polyurethane, polypropylene, cellulose acetate propionate and ethyl vinyl acetate (EVA) have been investigated as matrices for the delivery of drug to the periodontal pocket. In this respect, monolithic EVA fibres were found to be effective in controlling the release of encapsulated drug, and the same has been demonstrated by several *in vitro* and *in vivo* studies[52]. Tonetti et al. reported that Ethylene Vinyl Acetate (EVA) fibres containing 25% tetracycline hydrochloride maintained a constant drug level in the GCF above 600 mg/ml throughout ten days, showing zero-order release characteristics of EVA fibers. Outcomes included depression of periodontal pathogens, reduction of bleeding on probing, decrease in probing pocket depths and increase in probing attachment levels [53]

Films

Films are implantable devices with encapsulation of drug, in a manner that it is distributed throughout the polymer with control release occurring through diffusion, dissolution or erosion. The release action depends on type of polymer used to manufacture the chip. Ease of insertion with minimal pain, control on dosage, dimension and shape of the films makes it an ideal device to be used in periodontal pocket. Thickness of film should not exceed 400 μ m as well as have sufficient adhesiveness. An ideal film should be flexible, elastic, and soft, yet adequately strong to withstand breakage due to stress from mouth movements. It must also possess good mucoadhesive strength in order to be retained in the mouth for the desired duration of action. Swelling of film, if it occurs, should not be too extensive in order to prevent discomfort. A film composed of cross-linked hydrolysed gelatin and glycerine for local delivery of chlorhexidine digluconate has been developed and commercialised under the tradename Periochip. The system showed an initial burst effect, whereby 40% of chlorhexidine was released in the first 24 hours, followed by a constant slower release over about seven days. In an *in vitro* study by Perugini *et al.* the composite micro matricial films, made of three layers of polymers (chitosan/ PLGA /chitosan), as compared to the monolayer films, represent a suitable dosage form to prolong ipriflavone release for 20 days[54]. G.L.Prabhushankar et al. prepared and evaluated dental films for site specific delivery of Levofloxacin for the treatment of periodontitis by solvent casting technique. These films had excellent activity against anaerobic bacteria and released drug 10 days. Ageing studies showed that the drug remained intact and films were stable throughout the period [55].

Strips and Compacts

Acrylic strips have been fabricated using a mixture of polymers, monomers and different concentrations of antimicrobial agents. Strips were fabricated either by solvent casting or pressure melt method. Strips containing tetracycline, Metronidazole or chlorhexidine demonstrated a decrease in number of motile rods, notably spirochetes. In a later development, the evaluation of amoxicillin-clavulanic acid loaded acrylic strips is reported. Highest level of antibacterial agent was released during the first 24 hours period followed by release of therapeutic level of drugs for a subsequent 9 days period. Effect persisted even after 3 week of removal of acrylic strips. Tissue adhesive implants were made using n-butyl-2-cyanoacrylate as a drug trapping material and slowly release drug when used in the structure of a biodegradable local drug delivery device [56]. Mohammed Gulzar Ahmed et al. developed polymeric strip of Chitosan embedded with Gatifloxacin, a

site-specific system aiming at delivering the therapeutic agent at sufficient levels inside the pocket and at the same time minimizing the side effects associated with systemic drug administration for treatment of periodontitis. These strips crosslinked with glutaraldehyde controlled the release of gatifloxacin for 19 days[57]. Parthasarathy V *et al.* developed biodegradable polymer (poly lactide co glycolide and poly vinyl pyrrolidone) based periodontal chip of Sparfloxacin by solvent casting method is a potential local drug delivery device for the treatment of periodontitis for 21 days [58].

Patches

Patches are laminates consisting of an impermeable backing layer, a drug-containing reservoir layer from which the drug is released in a controlled manner, and a mucoadhesive surface for mucosal attachment. Two methods used to prepare adhesive patches include solvent casting and direct milling. In the solvent casting method, the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymer(s) onto a backing layer sheet, and subsequently allowing the solvent(s) to evaporate. In the direct milling method, formulation constituents are homogeneously mixed and compressed to the desired thickness, and patches of predetermined size and shape are then cut or punched out. An impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during the application period. The OraDisc technology is a proprietary mucoadhesive patch which gradually erodes and releases an active ingredient when applied to the inside of the mouth. The approval of this new drug application provides for the use of the amlexanox mucoadhesive patch 2mg for the treatment of aphthous ulcers in adults and adolescents 12 years of age and older with a normal immune system. The OraDisc dosage form is designed to be more acceptable to the patient in terms of ease of application, retention over the affected site, taste and its aesthetic qualities. Utilizing the OraDisc dosage form with amlexanox, it is anticipated that higher concentrations will be achieved at the site of administration and thus, potentially increasing the effectiveness of the product[59].

C) Responsive systems

Hydrogels

Hydrogels are also a promising dosage form for buccal drug delivery. They are formed from polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion. The application of mucoadhesive gels provides an extended retention time in the oral cavity, adequate drug penetration, as well as high efficacy and patient acceptability. A major application of adhesive gels is the local delivery of medicinal agents for the treatment of periodontitis, which is an inflammatory and infectious disease that causes formation of pockets between the gum and the tooth, and can eventually cause loss of teeth. It has been suggested that mucoadhesive polymers might be useful for periodontitis therapy when incorporated in antimicrobial-containing formulations that are easily introduced into the periodontal pocket with a syringe. HPMC has been used as an adhesive ointment ingredient. Additionally, a highly viscous gel was developed from carbopol and hydroxypropylcellulose for ointment dosage forms that could be maintained on the tissue for up to 8 hours. In order to develop a muco-adhesive hydrogel for buccal drug delivery it is necessary to understand fully the properties determining adhesiveness as well as mechanisms involved. In this regard glass transition temperatures, water contact angles and the peel- and shear detachment forces from porcine oral mucosa, of acrylic acid and butyl acrylate copolymers were studied. The contact angle maximized at 50% butyl acrylate content. The glass transition temperature decreased from 0% to 100% butyl acrylate. There exist a certain combination of contact angle and glass transition temperature which is related to adhesiveness. This strongly suggested that, in order to obtain a muco-adhesive hydrogel, at least two properties have to be optimized the polarity of the polymer surface and the molecular mobility of the polymer groups. Korsen et al studied the application of collagen hydrogel/sponge scaffold to facilitate periodontal wound healing in beagle dogs. [60]

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Nanogel

Nanogel can be defined as a colloidal system of aggregates in the sub-micrometer range prepared from hydrophilic polymers with gel-like characteristics, with high potential in gene and protein delivery. Nanogels are submicron-sized hydrophilic structures engineered from biocompatible polymers possessing the characteristics of nanoparticles as well as hydrogels, with a wide array of potential applications in biotechnology and biomedicine, namely, drug and protein delivery. In this work, nanogels were obtained using the physical self-assembly technique or 'layer-by-layer' which is based on electrostatic interactions. Liposomal vesicles were coated with alternating layers of hyaluronic acid and chitosan yielding a more viscous hydrogel formulation that previously reported core-shell nanoparticulate suspension, via simply modifying the physico-chemical characteristics of the system. Structural features, size, surface charge, stability and swelling characteristics of the nanogel were studied using scanning electron microscopy and dynamic light scattering. With a specific cranio-maxillofacial application in mind, the hydrogel was loaded with recombinant human (rh) bone morphogenetic protein-7, also known as osteogenic protein-1 or rhOP-1 and release was monitored over an extended period of 60 days. This preliminary study reports promising results on the formulation of a novel *core-shell* polymeric nanogel[61].

In situ gelling systems

These can be classified as open or closed loop systems. Open loop systems are called as pulse or externally regulated systems. These are based on a magnetically triggered release system in which small magnetic spheres are embedded in drug containing polymers. These release the drug when exposed to an oscillating field. Closed loop or self regulated systems are based on the drug release in response to pH, temperature. These are prepared by using thermo-responsive polymers like N-isopropylacrylamide. Polyethylene glycol and polypropylene glycol copolymers have been used in Atridox in which the drug is initially dissolved in a liquid form of the polymer at room temperature which gets converted into a semisolid gel at the body temperature of 37 °C.

H.Gupta[62] developed a local anesthetic *in situ* gelling system suitable for administering in periodontal pocket, which would enable the patient to have painless treatment without distress of injection, stay at application site due to viscosity increase and give a fast onset of anesthesia lasting throughout the dental procedure and after that can be easily rinsed out with water causing a fast decline in anesthetic effect. For this a novel polymeric system, gel-forming solution by a simple phase transition (sol-gel transition), mediated by pH were formulated using chitosan and hydroxypropylmethylcellulose (HPMC).

Regulatory and clinical aspects

Products intended for the treatment of dental and periodontal disease must meet all regulatory requirements pertaining to safety and efficacy under the conditions of use. A basic set of pharmacological, toxicological, and biopharmaceutical testing should be conducted and documented on raw materials, active agents, and finished product formulations. Format and content of chemistry, manufacturing, and controls (CMC) for the dental and periodontal products are expected to be the same as those applicable to the other pharmaceutical dosage forms filed as a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA). There are regulatory guidelines available for different aspects of the products. For example, the U.S. Food and Drug Administration (FDA) has issued guidelines for clinical evaluation of drugs to prevent dental caries and clinical evaluation of drugs to prevent, control, and/or treat periodontal disease. These guidelines suggest basic concepts that should be considered when developing suitable clinical protocols. The active agents in the formulations administered for periodontal and dental diseases in most cases are old drugs. This will have an advantage over new chemical entities in that some of the preclinical testing such as carcinogenicity,

reproduction, mutagenicity, and ADME studies are not required. Relatively simple pharmacology and safety studies such as adverse reactions and effect studies pertaining to the therapeutic indications are a part of the basic requirements. Most of the formulations administered for dental and periodontal diseases except for injections are topical products. It is expected that some subchronic topical toxicological testing will be required by the regulatory agencies. The clinical pharmacology studies may have to document the concentrations of the active ingredient in the suitable tissues or sites being treated. The drug concentration in saliva and/or systemic circulation for the duration of treatment is relevant also. To the extent that controlled drug release and effectiveness of therapy are claimed, it would be required to demonstrate *in vitro* and *in vivo* the bioavailability of the active drug for the duration of product use. For products indicated for the treatment of periodontal diseases, investigation into the effects of the actives on the microorganisms is also required. It should be pointed out, however, that the clinical significance of the microbiological consequences due to the active agents has not been determined and is not known. In the design of clinical protocols, there are two key aspects that need to be defined clearly. The first is the relevant information for the active, excipients, packaging, dose, stability, oral clearance rate, and the bioavailability of the active agent. The second is the variables selected for measurement and rationale for their choice, which are discussed in detail in the FDA guidelines for clinical evaluation of drugs to prevent dental caries[63]

CONCLUSION

The formulation of controlled release products based on various polymers have decreased the occurrence of systemic side effects and produced an increase in the therapeutic responsiveness and an increase in the patient compliance. During the past decade, numerous investigations have been done in the field of controlled drug delivery to the periodontal pocket.

Controlled drug delivery offers a potential treatment to the major dental diseases, as new delivery systems are being proposed the control of dental diseases has been increasing considerable. Several clinical trials have been conducted with NSAIDs like furbiprofen, ketoprofen and naproxen Techniques such as bioadhesion based systems, vesicular systems becoming the choice of both the prescriber and the patient.

Future scope

A number of pharmaceutical products are being used, developed for the oro-dental delivery, but still many are in the pipeline. Recent advances in the controlled and targeted drug delivery systems offer a large scope and potential for alleviating dental disorders by use of novel techniques.

REFERENCES

1. Annual Report 2005-2006. Ministry of Health and Family Welfare, Govt. of India, New Delhi. 2006. New Delhi.
2. Parkash H, Shah N. National Oral Health Care Programme: Implementation Strategies, Directorate General of Health Services, Ministry of Health and Family Welfare, Govt. of India, New Delhi. 2000
3. Morrison HI, Ellison LF, Taylor GW *et al*. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. *J Cardiovasc Risk*.1999; 6: 7-11.
4. Lief S. *et al*. The oral conditions and pregnancy study: periodontal status of a cohort of pregnant women. *J Periodontol*. 2004; 75:116-26.
5. Genco RJ, Evans RT, Ellison SA *et al*. Review of dental research in microbiology with emphasis on periodontal research. *Journal of American Dental Association* 1969; 78: 1016-1023.
6. Becker W, Berg L, Becker BE *et al*. Untreated periodontal disease: a longitudinal study. *Journal of Periodontology* 1979; 50:234-244.
7. Lindhe J, Haffajee AJ, Socransky SS *et al*. Progression of periodontal disease in adult subjects in the absence of periodontal therapy. *Journal of Clinical Periodontology* 1983, 10: 433-442.

8. N.V.Satheesh Madhav, Ashok K.Shakya, Pragati Shakya, Kuldeep Singh *et al.* Orotransmucosal Drug Delivery System: A review. *Journal Of Controlled Release* 2009;2-11.
9. V.Sankar *et al.* Local Drug Delivery For Oral Mucosal Diseases: Challenges and Opportunities. *Oral Diseases* 2011; 17:73-84.
10. Kamlapreet Chinna, Rakhi Bhatnagar *et al.* Local Drug Delivery: A Review. *Indian Journal Of Dental Sciences* 2012; 4:66-69.
11. J.D. Smart *et al.* Buccal drug delivery, *Expert Opin. Drug Deliv.* 2005, 2:507-17.
12. T.K. Ghosh, W.R. Pfister. *Drug delivery to the oral cavity: Molecules to market*, BocaRaton, FL: CRC Press, 2005, pp. 41-66.
13. H. Sohi, A. Ahuja, F.J. Ahmad, R. K. Khar *et al.*, Critical evaluation of permeation enhancers for oral mucosal drug delivery. *Drug Dev. Ind. Pharm.* 2010; 36: 254-282.
14. C.A. Squier, D. Nanny *et al.* Measurement of blood flow in the oral mucosa and skin of the rhesus monkey using radiolabelled microspheres. *Arch. Oral Biol.* 1985; 30: 313-318.
15. M.E. de Vries, H.E. Bodde, J.C. Verhoef, H.E. Junginger *et al.* Developments in buccal drug delivery. *Crit. Rev. Ther. Drug Carrier Syst.* 1991; 8: 271-303.
16. C.A. Squier, R.A. Eady, R.M. Hopps *et al.* The permeability of epidermis lacking normal membrane-coating granules: an ultrastructural tracer study of Kyrle-Flegel disease. *J. Invest. Dermatol.* 1978;70 : 361-364.
17. D. Harris, J.R. Robinson, Drug delivery via the mucous membranes of the oral cavity. *J. Pharm. Sci.* 1992; 81:1-10.
18. M. Rathbone, B. Drummond, I. Tucker, Oral cavity as a site for systemic drug delivery. *Adv. Drug Del. Rev.* 1994; 13: 1-22.
19. Viralkumar F. Patel *et al.* Advances in oral transmucosal drug delivery. *Journal of Controlled Release.* 2011; 153: 106-116.
20. Amir H. Shojaei *et al.* Buccal Mucosa as a Route for Systemic Drug Delivery: A Review. *J Pharm Pharmaceut Sci.* 1991; 1 : 15-30.
21. M.R. Castellanos, H. Zia, C.T. Rhodes *et al.* Mucoadhesive drug delivery systems. *Drug Dev. Ind. Pharm.* 1993; 19: 143-194.
22. L.M.Collins, C. Dawes *et al.* The surface area of adult human mouth and thickness of salivary film covering the teeth and oral mucosa. *J. Dent. Res.* 1987; 66: 1300-1302.
23. C.A. Squier, M.J. Kremer *et al.* Biology of oral mucosa and esophagus. *J. Natl. Cancer Inst. Monogr.* 2001; 29 : 7-15.
24. Puratchikody, A. *et al.* Buccal Drug Delivery: Past, Present and Future - A Review. *International Journal of PharmTech Research.* 2011; 3 : 171-184.
25. Behra A. *et al.* An Exhaustive Review on Recent Advancement in Pharmaceutical Bioadhesive Used for Systemic Drug Delivery Through Oral Mucosa for Achieving Maximum Pharmacological Response and Effect. *International Journal of Pharmacology* 2012; 8: 283-305.
26. Raghad Fouad Ghali *et al.* The Potential Link Between Periodontitis and Systemic Diseases- An overview. *Journal of Advanced Medical Research* 2011; 1 : 24-35
27. Slots J *et al.* Subgingival microflora and periodontal disease. *Journal of Clinical Periodontology* 1979; 6 : 351-354.
28. Baker PJ, Evans RT, Slots J, Genco RJ *et al.*, Susceptibility of human oral anaerobic bacteria to antibiotics suitable for topical use. *Journal of Clinical Periodontology* 1985; 12: 201-204.
29. Williams RC *et al.*, Periodontal diseases, *New England Journal of Medicine*, 1990; 322 : 373-391.
30. Chen C, Slots J *et al.*, The current status and future prospects of altering the pathogenic microflora of periodontal disease. *Current Opinions in Periodontology* 1993; 71-77.
31. Crispian Scully *et al.* Aphthous Ulceration. *The New England Journal of Medicine*, 2006; 355(2):165-172.
32. Antonia Kolokythas, Eliza Olech *et al.*. Alveolar Osteitis: A comprehensive review of concepts and controversies. *International Journal of Dentistry* 2010:1-10.
33. Muhammad Azhar Sheikh *et al.*, Pathogenesis and Management Of Dry Socket (Alveolar osteitis). *Pakistan Oral & Dental Journal* 2012; 30(2):323-326.
34. Dr. Denise C. Bowe *et al.* The management of dry socket. *Journal of Irish Dental Association* 2011; 57(6):305-310.
35. Ramandeep Dugal *et al.* Xerostomia: Dental Implications and Management. *Annals and Essences of Dentistry* 2010; 2: 37-140.
36. Ken Yaegaki, Jeffrey Coil *et al.* Examination, Classification, and Treatment of Halitosis; Clinical Perspectives. *Journal of Cannadian Dental Association* 2000; 66(5):257-261.
37. Crispian Scully & John Greenman *et al.* Halitosis (breath odor). *Periodontology* 2008; 48: 66-75.
38. Addy M, Renton HP *et al.* Local and systemic chemotherapy in the management of periodontal disease: an opinion and review of concept. *Journal of Oral Rehabilitation* 1996; 23: 219-231.
39. Higashi K, Matsushi M, Morisaki K, Hayashi S, Mayui T *et al.* Local drug delivery systems for treatment of periodontal disease. *Journal of Pharmacobio- Dynamics* 1991; 14: 72-81.
40. Greenstein G, Polson A *et al.* The role of local drug delivery in the management of periodontal diseases: a comprehensive review. *Journal of Periodontology* 1998; 69: 507-520.
41. A.M. Robinson, M. Bannister, J.E. Creeth, M.N. Jones *et al.*, The interaction of phospholipid liposomes with mixed bacterial biofilms and their use in the delivery of bactericide. *Colloids Surf. A Physicochem. Eng. Asp.* 2001; 186:43- 53.
42. Dr Arvind Venkatesh *et al.*, Dr Jaiganesh Ramamurthy. Local drug delivery systems in the treatment of periodontitis - An Overview. *International Journal of Pharmacy and Pharmaceutical Sciences* 2012; 4 : 30-37
43. M.N. Jones, M. Kaszuba, M.D. Reboiras, I.G. Lyle, K.J. Hill, Y.-H. Song *et al.*, The targeting of phospholipid liposomes to bacteria. *Biochim. Biophys. Acta.* 1994; 1196: 57-64.
44. Jones MN, Kaszuba M, Hill KJ, Song YH, Creeth JE *et al.*, The use of phospholipid liposomes for targeting to oral and skin-associated bacteria. *Journal of Drug Targeting* 1994; 2: 381-389.
45. Saravana Kumar K *et al.* A Review on Microspheres for Novel Drug Delivery System. *Journal of Pharmacy research* 2012; 5(1): 420-424.
46. Nakahara T, Nakamura T, Kobayashi E, Inoue M, Shigeno K *et al.* Novel Approach to Regeneration of Periodontal Tissues Based on *in Situ* Tissue Engineering: Effects of Controlled Release of Basic Fibroblast Growth Factor from a Sandwich Membrane. *Tissue Engineering* 2003; 9: 153-62.
47. Renvert S, Lessem J, Dahle NG, Lindahl C, Svensson M *et al.* Topical minocycline microspheres versus topical chlorhexidine gel as an adjunct to mechanical debridement of incipient periimplant: a randomized clinical trial. *J Clin Periodontol.* 2006;33 : 362-69
48. Patravale VB, Date AA, Kulkarni RM *et al.*. Nanosuspensions: a promising drug delivery strategy. *J pharma and pharmacology* 2004; 56: 827-40.
49. Dung TH. *et al.* Chitosan -TPP nanoparticle as a release system of antisense oligonucleotide in the oral environment. *J. Nanosci. Nanotechnol* 2007; 7: 3695-3699.
50. Soma Ghosh, Gopa Roy and Biswajit Mukherjee *et al.* Dental Mold: A Novel Formulation to Treat Common Dental Disorder's AAPS PharmSciTech 2009; 10 : 692-702
51. Luana Perioli *et al.*, Valeria Ambrogi, Stefano Giovagnoli, Paolo Blasi, Alessandra Mancini, Maurizio Ricci. Influence of Compression Force on The Behavior of Mucoadhesive Buccal Tablets. *AAPS PharmSciTech.* 2008; 9(1): 274-281.
52. Goodson JM *et al.* Monolithic tetracycline-containing fibres for controlled delivery to periodontal pockets. *J. Periodontol.* 1983; 54: 575-579.
53. Maurizio S. Tonetti *et al.* Local delivery of tetracycline: from concept to clinical application. *Journal of Clinical Periodontology* 1998; 25 : 969-977.
54. Perugini P *et al.*, Genta I, Conti B, Modena T, Pavanetto F. Periodontal delivery of ipriflavone: new chitosan/PLGA film delivery system for a lipophilic drug. *Int J Pharm* 2003; 18 : 1-9
55. G.L. Prabhushankar *et al.*, B.Gopalkrishna, Manjunatha K.M. Formulation and evaluation of levofloxacin dental films for periodontitis. *International Journal of Pharmacy and Pharmaceutical Sciences* 2010; 2:162-168.
56. Larsen T *et al.* In vitro release of doxycycline from bioabsorbable materials and acrylic strips. *J Periodontol.* 1990; 61:30-34

57. Mohammed Gulzar Ahmed *et al*, Narayana Charyulu. R, Kanthraj.K. Preparation and evaluation of periodontal strips of gatifloxacin for periodontal diseases. International Journal of Pharma and Bio Sciences 2010; 1: 1-8
58. Parthasarathy V *et al*, Manavalan R, Mythili R, Siby CT, Jeya M. Ethyl cellulose and polyethylene glycol-based sustained-release sparfloxacin chip: an alternative therapy for advanced periodontitis. Drug Dev Ind Pharm. 2002; 28:849-62
59. Murray B *et al*, Biagioni PA, Lamey PJ. The efficacy of amlexanox OraDisc on the prevention of recurrent minor aphthous ulceration. J Oral Pathol Med. 2006; 35 :117-22
60. Kosen Yet *al*, Miyaji H, Kato A, Sugaya T, Kawanami M. Application of collagen hydrogel/sponge scaffold facilitates periodontal wound healing in class II furcation defects in beagle dogs. J Periodontal Res. 2012; 47 :626-634.
61. Koen Raemdonck, Joseph Demeester and Stefaan De Smedt *et al*. Advanced nanogel engineering for drug delivery. Soft Matter 2009; 5: 707–715.
62. H Gupta *et al*, RM Singh, GN Singh, D Kaushik, A Sharma. pH-Induced *in situ* gel for periodontal anesthesia. Indian Journal of Pharmaceutical sciences 2008; 70 (6) : 776-778.
63. Pranshu Tangri *et al*. Controlled and Targeted Delivery to the Dental Cavity. Journal of Pharmacy Research 2011; 4: 437-439.