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Review Article

BIODEGRADABLE MUCOADHESIVE NANOCARRIER SYSTEM FOR DELIVERY OF DENTAL DRUGS: A VITAL REQUIREMENT FOR CURING DENTAL DISEASE.

Mukul Singh *, Kaushal K Chandrul
Department of Pharmacy, Mewar University, Chittorgarh, Rajasthan, India.

Biodegradable polymer and particulate carriers have been shown to be of considerable potential for the delivery of peptides, proteins and DNA in animal models. In the context of vaccine delivery to the upper and lower respiratory tracts, the use of mucoadhesive agents offers a strategy for the facilitation of increased residence time and increased vaccine efficacy. Additional concerns addressed here include the potential of uptake of vaccine formulations by the primary olfactory nerves in the nasal cavity, effective delivery to the lung, strategies to maximize the immune-potentiation of candidate vaccine formulations, as well as the evaluation of animal models and interpretation of engendered immune responses in terms of antigen-specific antibody production. Experimental data are presented that demonstrate the potential of muco- and bio-adhesive agents in combination with liposomes for intranasal (i.n.) delivery of tetanus toxoid in mice. A delivery system utilising chitosan for the formulation of microspheres by the spray-drying method is described and assessed for intranasal vaccine delivery, and porous particles with potential for pulmonary administration are also outlined. Nanocarriers discovered thus far include polymer conjugates, polymeric nano-particles, lipid-based carriers, dendrimers, carbon nano-tubes, and gold nano-particles. Lipid-based carriers include both liposomes and micelles. Examples of gold nano-particles are gold nano-shells and nano-cages. Different types of nano-material being used in nano-carriers allows for hydro phobic and hydrophilic drugs to be delivered throughout the body. Since the human body contains mostly water, the ability to deliver hydrophobic drugs effectively in humans is a major therapeutic benefit of nano-carriers. Micelles are able to contain either hydrophilic or hydro phobic drugs depending on the orientation of the phospho-lipid molecules. Some nano-carriers contain nanotube arrays allowing them to contain both hydrophobic and hydrophilic drugs. Nano carriers range from sizes of diameter 1–1000 nm, however due to the width of micro capillaries being 200 nm, nano-medicine often refers to devices <200 nm. Because of their small size, nano -carriers can deliver drugs to otherwise inaccessible sites around the body. Since nano-carriers are so small, it is oftentimes difficult to provide large drug doses using them. The emulsion technique used to make nano-carriers also often result in low drug loading and drug capsulation, providing a difficulty for the clinical use. Dental caries is an infectious microbiological disease of the teeth that results in localized dissolution and destruction of the calcified tissues. It is the second most common cause of tooth loss and is found universally, irrespective of age, sex, caste, creed or geographic location. It is considered to be a disease of civilized society, related to lifestyle factors, but heredity also plays a role. In the late stages, it causes severe pain, is expensive to treat and leads to loss of precious man-hours. However, it is preventable to a certain extent. The prevalence of dental caries in India is 50%–60%.

Key words: Biodegradable, Mucoadhesive, Bio-adhesive, Nanocarriers, Liposomes .

INTRODUCTION

Periodontal disease is a collective term ascribed to a number of pathological conditions characterized by degeneration and inflammation of gums, periodontal ligaments, alveolar bone and dental cementum. Although bacteria are the primary cause of periodontal disease, the expression of microbial pathogenic factors alone may not be sufficient to cause periodontitis. Periodontal pathogens produce harmful by product and enzyme that break extracellular matrices as well as host cell membrane to produce nutrients for their

growth. In doing so ,they initiate damage directly or indirectly by triggering host mediated responses that lead to self injury. Periodontitis, a disease involving supportive structure of the teeth prevails in all groups, ethnicities, and both genders.

Nano medicine is the science and the technology of complex system of nano scale size that can be used for the prevention, diagnosis and treatment of disease. The complex system consists of a nano carrier and a drug. Nano carrier has important potential application for the administrations of therapeutic molecules. Nano particles have been used as a physical approach to alter and improve the pharmacokinetic and pharmaco-dynamic properties of various types of drug molecule. The advantages of using nano-partcles as a drug delivery system include the following:

- The particle size and surface characteristics of nano particles can be easily easily manipulated.
- They control and sustain release of the drug during the transportation and at the site of localization.
- Controlled release and particle degradation characteristics can be easily modulated by the choice matrix constituents.
- Drug loading is relatively high and drug can be incorporated into the system without any chemical reaction.
- Site specific targeting can be achieved by attaching targeting ligand to surface of particles.
- The system can be used for various route of administration including oral, nasal, parenteral, intra ocular etc.

Preparation of Nanoparticles: There are numerous preparation method available for producing nanoparticles. Depending on the physicochemical characteristics of a drug, it is now possible to choose the best method to achieve an efficient entrapment of drug.

- Dispersion of preformed polymers
- Polymerizations of monomers
- Ionic gelation or coacervation of hydropholic polymer.

Frequently used polymers are PLA, PLGA, ethyle cellulose (EC), cellulose acetate phthalate, poly (E-caprolactone) (PCL) and poly (h-hydroxybutyrate) (PHB). Different types of synthetic biodegradable polymers such as polyhydroxy butyric acid (PHBA) and ploy lactide co-glycolic acid (PLGA) have shown sustained delivery of tetracycline.

The term bioadhesive defined as material that is capable of being bound to a biological membrane and retained on the membrane for an extended period of time. The term bio-adhesion relates to the attatchment of a material to biological substances such as a biological membrane.

The term muco adhesive is defined as a in which an adhesive bonding is established between a material and the mucosa/mucus/mucin of a biological membrane.

The term mucoadhesive substance is in accordance with generally accepted terminology

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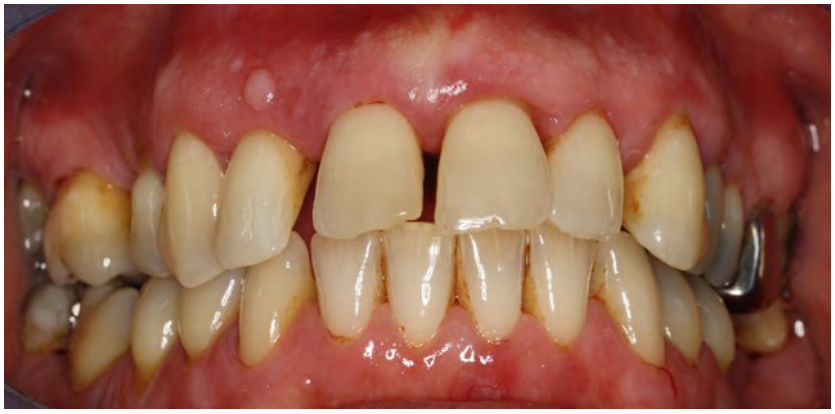
and is used synonymously with the term a "bioadhesive substance".

Prolonged retention can be achieved by making system bioadhesive or mucoadhesive by using natural or synthetic polymetric materials for localized periodontal therapy.

The potential advantages that bioadhesion can offer, include prolonged drug delivery, localization of drug therapy, targeting of specific tissues and intimate contact with the substrate.

Classification of Periodontal Diseases: The American dental association (ADA) and the American academy of periodontology (AAP) have developed system for classifying periodontal diseases. Ideally, each patient needs to be identified or categorized into an ADA and AAP periodontal classification. The classification system is primarily based on the severity of attachment lost. Using clinical and radiographic data, the patient classifies into one of the four case types.

1. **Gingivitis:** Plaque-induced inflammation of the gingivae characterised by red, swollen tissues which bleed on brushing or probing.
2. **Chronic periodontitis:** Characterised by the destruction of the junctional epithelium and connective tissue attachment of the tooth, together with bone destruction and formation of periodontal pockets. The disease progresses slowly and the amount of bone loss tends to reflect the age of the patient over time.
3. **Aggressive periodontitis:** A severe condition usually found in a younger cohort of patients, which may be associated with a familial history of aggressive periodontitis. Disease progression is rapid and the degree of destruction of the connective tissue attachment and bone is severe, considering the age of the patient. Plaque levels may be inconsistent with the level of disease seen
4. **Necrotising ulcerative gingivitis (NUG):** Painful ulceration of the tips of the interdental papillae. Grey necrotic tissue is visible and there is an associated halitosis. The condition is termed necrotising ulcerative periodontitis (NUP) in the presence of connective tissue attachment loss and bone destruction.
5. **Periodontal abscess:** Infection in a periodontal pocket which can be acute or



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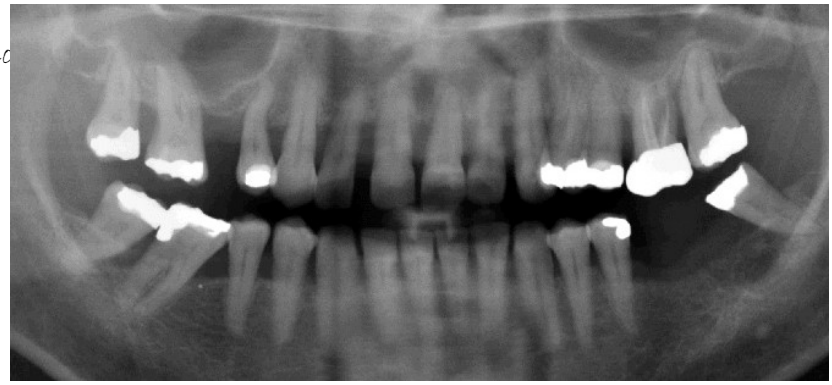

Figure 1 Generalised severe chronic periodontitis

chronic and asymptomatic if freely draining

6. **Perio-endo lesions:** Lesions may be independent or coalescing and the bacterial source originates either in the periodontium or the root canal systemGingival enlargement: Thickening of the gingivae which can occur as a response to irritation caused by plaque or calculus, repeated friction or trauma, fluctuations in hormone levels or the use of some medications

Pathopysiology of Periodontal Disorders: A healthy periodontum is characterized by gingival sulcus 1 to 3 mm in depth around the crown of the tooth. Healthy gingiva appears light pink in colour ,with a firm stippled surface that does not bleed. Gingivitis develops in subjects with healthy gingiva who,during a 2-3 weeks period,refrain from tooth cleaning and thereby allow microorganisms to colonize the supragingival part of the tooth. It is well established that bacterial irritation from the dento gingival plaque is essential for the development and maintenance of periodontal disease. Dental plaque is highly complex structured microbial mass in which more than 400 bacterial types have been identified. The microorganism recovered from infections generall reflect the host's indigenous oral flora. In the gingival cervice ,there are approximately $1.8x10^{11}$ anaeorobes /grams.

Treatment Approaches: The basic aims of overall treatment of regimens of periodontal disease

- Slowing the progression of the disease process.
- Elimination of periodontal pocket and improvement of attachment level.
- To reduce the nonpathogenic bacteria.

Oral mucoadhesive Nanocarrier Drug delivery System: Drug delivery through the oral mucosa has gained significant attention due to its convenient accessibility. The buccal and sublingual routes are considered as the most commonly used rotes. The nonkeratinized epithelium in the oral cavity, such as the soft palate, the mouth floor, the ventral side of the tongue, and the buccal mucosa, offers a relatively permeable barrier for drug transport. Hydrophilic compounds and large or highly polar molecules follow paracellular transport, whereas transcellular transport through the lipid bilayer is followed by lipophilic drugs. Drug delivery through the oral mucosa has proven particularly useful and offers several advantages over other drug delivery systems including bypassing hepatic

first-pass metabolism, increasing the bioavailability of drugs, improved patient compliance, excellent accessibility, unidirectional drug flux, and improved barrier permeability compared, for example, to intact skin. The oral cavity has been used as a site for local and systemic drug delivery. Local drug therapy is used to treat disease states like aphthous ulceration gingivitis, periodontal disease, and xerostoma. Different dosage designs include adhesive gels, tablets, films, patches, ointments, mouth washes, and pastes.

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 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.

Oral mucosal ulceration is a common condition with up to 50% of healthy adults suffering from recurrent minor mouth ulcers (aphthous stomatitis). Shermer evaluated the efficacy and tolerability of a mucoadhesive patch compared with a pain-relieving oral solution for the treatment of aphthous stomatitis. The mucoadhesive patch was found to be more effective than the oral solution in terms of healing time and pain intensity after 12 and 24 h. Local adverse effects 1 h after the treatment were significantly less frequent among the mucoadhesive patch patients compared with the oral solution patients.

Donnelly reported on a mucoadhesive patch containing TBO as a potential delivery system for use in photodynamic antimicrobial chemotherapy (PACT) of oropharyngeal candidiasis. Patches are prepared from aqueous blends of poly(methyl vinyl ether/maleic anhydride) and tripropyleneglycol methyl ether. The authors concluded that short application times of TBO-containing mucoadhesive patches should allow the treatment of recently acquired oropharyngeal candidiasis, caused solely by planktonic cells. Longer patch application times may be required for persistent disease where biofilms are implicated.

Periodontitis is an inflammatory disease of the oral cavity, which results in the destruction of the supporting structures of the teeth.Inflammatory periodontitis disease can be treated by the

combination of mechanical and intraperiondontal pocket chemotherapeutic agents. Jones and Andrews described the formulation and physicochemical characterization of syringeable semisolid, bioadhesive networks (containing tetracycline, metronidazole, or model protein drugs). Such systems may be formulated to exhibit requisitory flow properties (and hence may be easily administered into the periodontal pocket using a syringe), mucoadhesive properties (ensuring prolonged retention within the pocket), and sustained release of therapeutic agent within this environment.

Mucosal delivery of drugs *via* the buccal route is still very challenging in spite of extensive clinical studies. Here, we are underlining several formulations which are in clinical trials or commercial products. The 3M company has developed a buccal patch system which consists of a matrix patch containing drug, mucoadhesive polymers, and polymeric elastomers surrounded by a backing material. Their buprenorphine patch is capable of delivering the drug for a period up to 12 h, with good patient comfort reported.

Oralin, a novel liquid aerosol formulation (Generex Biotechnology), has been developed and it is now in clinical phase II trials. Oralin allows precise insulin dose delivery *via* a metered dose inhaler in the form of fine aerosolized droplets directed into the mouth. Levels of drug in the mouth are noticeably increased compared with conventional formulations. This oral aerosol formulation is rapidly absorbed through the buccal mucosal epithelium, and it provides the plasma insulin levels necessary to control postprandial glucose rise in diabetic patients. This novel, pain-free, oral insulin formulation has a number of advantages, including rapid absorption, user-friendly administration technique, precise dosing control (comparable to injection within one unit), and bolus delivery of drug.

CONCLUSION

The mucoadhesive dosage forms offer prolonged contact at the site of administration, low enzymatic activity, and patient compliance. The formulation of mucoadhesive drug delivery system depends on the selection of suitable polymer with excellent mucosal adhesive properties and biocompatibility. Now researchers are looking beyond traditional polymers, in particular next-generation mucoadhesive polymers (lectins, thiols, etc.); these polymers offer greater attachment and retention of dosage forms. However, these novel mucoadhesive formulations require much more work, to deliver clinically for the treatment of both topical and systemic diseases.

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