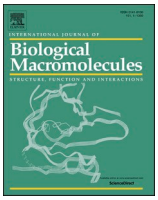
International Journal of Biological Macromolecules 247 (2023) 125808

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: www.elsevier.com/locate/ijbiomac



Dental delivery systems of antimicrobial drugs using chitosan, alginate, dextran, cellulose and other polysaccharides: A review

Mousumi Paul [a], Siddhartha Das Pramanik [b], Rudra Narayan Sahoo [c], Yadu Nandan Dey [a,*], Amit Kumar Nayak [c,*]

[a] Department of Pharmacology, Dr. B.C. Roy College of Pharmacy and Allied Health Sciences, Durgapur 713206, West Bengal, India
[b] Department of Biosciences and Bioengineering, Indian Institute Technology-Roorkee, Roorkee 247667, Uttarakhand, India
[c] Department of Pharmaceutics, School of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar 751003, Odisha, India

ARTICLE INFO

Keywords:
Dental diseases
Periodontitis
Drug release
Natural polysaccharides

ABSTRACT

Dental caries, periodontal disease, and endodontic disease are major public health concerns worldwide due to their impact on individuals' quality of life. The present problem of dental disorders is the removal of the infection caused by numerous microbes, particularly, bacteria (both aerobes and anaerobes). The most effective method for treating and managing dental diseases appears to be the use of antibiotics or other antimicrobials, which are incorporated in some drug delivery systems. However, due to their insufficient bioavailability, poor availability for gastrointestinal absorption, and pharmacokinetics after administration *via* the oral route, many pharmaceutical medicines or natural bioactive substances have limited efficacy. During past few decades, a range of polysaccharide-based systems have been widely investigated for dental dug delivery. The polysaccharide-based carrier materials made of chitosan, alginate, dextran, cellulose and other polysaccharides have recently been spotlighted on the recent advancements in preventing, treating and managing dental diseases. The objective of the current review article is to present a brief comprehensive overview of the recent advancements in polysaccharide-based dental drug delivery systems for the delivery of different antimicrobial drugs.

1. Introduction

The commonly occurring dental conditions in human are periodontal disorders including gingivitis and periodontitis, which are caused by caries [1]. Dental caries is a widespread issue that affects people of all ages, and natural polysaccharides may be able to help in repairing cavities caused by microbial colonization and demineralization [2]. Periodontitis is a typical diseased dental condition by bacterial pathogens and immune system reactions, which results in toxin releasing [1]. Immune cells become engaged during the chronic stage, producing the various cytokines and reactive oxygen species (ROSs), which cause the breakdown of bone and periodontal fibers. Similarly, the application of nanotechnology may be able to overcome the difficulties associated with the treatment of oral candidiasis, a *Candida albicans* infection, which currently relies on expensive, unpleasant, and potentially hazardous medications [3]. For the localized treatment of dental disorders affecting the oral cavity including mouth, numerous pharmaceutical dosage forms have been designed and investigated [4]. The shorter retention duration in the oral cavity caused by several issues (like salivation, intermittent swallowing, consumption of foods, abrasion by the movement of soft tissue, *etc.*), is a drawback of these conventional systems. The available conventional therapy includes the procedures of mechanical plaque control, which take more time, demand highly skilled technicians, and cause patients to experience varied degrees of discomfort [5]. However, the systemic antibiotic-therapy can be crucial in the control of periodontal pathogens present in other areas of the mouth from where they may translocate to the periodontal site as well as in the eradication of pathogenic bacteria that infiltrate gingival tissue. Numerous systemic dosages of antibiotics have revealed a number of negative effects, such as insufficient concentrations of antibiotics at the location of the periodontal pocket [6]. Due to the drug's thousand-fold dilution, an adequate concentration of antibiotics at the action site is not attained, which results in a lower benefit-to-risk ratio, a quick drop in plasma of antibiotics concentrations to sub-therapeutic levels, the microbial resistance development, and peak plasma concentration of antibiotics [7].

* Corresponding authors.
E-mail addresses: yadunandandey@gmail.com (Y.N. Dey), amitkrnayak@yahoo.co.in (A.K. Nayak).

https://doi.org/10.1016/j.ijbiomac.2023.125808
Received 10 May 2023; Received in revised form 20 June 2023; Accepted 1 July 2023
Available online 17 July 2023

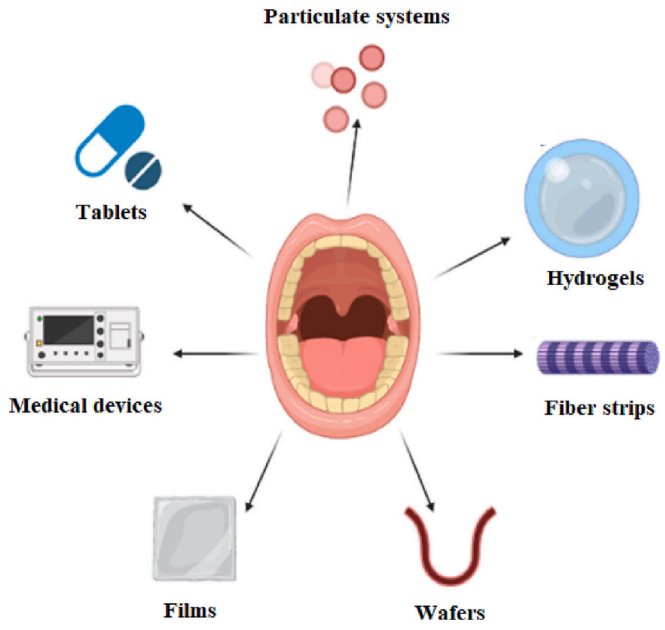


Fig. 1. Drug delivery for the management of dental disorders.

Due to the problems with systemic administration, a huge concentration has been focused to how the antimicrobial drugs can be given locally to treat dental diseases (Fig. 1). Several researchers have attempted to treat tooth infections by administering antibiotics locally to the affected area [8,9]. Conventional formulations for the uses in oral cavity, including toothpaste and mouthwash, have a relatively low penetration rate into the affected area and a very limited duration of action. Recently, nanotechnology has been used in dentistry to facilitate restorations and regenerate new tissues within diseased or damaged teeth that closely resemble natural teeth [2,3,10,11]. It has been demonstrated that adding nanoparticles can increase the mechanical toughness of dental implants. Additionally, nanoparticles with antimicrobial activity are frequently employed to prevent dental cavities [12]. Recent years, many antimicrobial biomaterials are being researched and developed for the uses in many healthcare applications [13].

At present the whole world is turning towards the uses of different naturally-derived materials including biopolymers in almost all possible applications [14–17]. Natural polysaccharides are responsible for a variety of important functions in microbes, plants, and animals [18]. They are composed of lengthy monomers of the same kind or mixtures of different monomer chains [19]. Because of their advantageous character, such as biocompatibility, large-scale accessibility, relative affordability, and biodegradability, different natural polysaccharides are acknowledged as safe biomaterial category for many biomedical applications including for targeting distribution. Due to their multiple biological roles, polysaccharides are employed in a variety of biomedical sectors including bone tissue regeneration, therapeutic delivery, biosensors, wound healing, dentistry, *etc.* [20]. Natural polysaccharides have grown in prominence in the nanotechnological field for controlled drug administration to improve safety, longer retention period, enhanced permeability bioavailability and biocompatibility in order to address such constraints [21,22]. Pectin, amylose, alginate, dextran, *etc.*, are some of the examples of polysaccharide-based nanoparticles that have already been used in preparation of nanoparticles for encapsulation of therapeutic agents to be used in medicinal applications. However, there aren't many research reports on the preparation and uses of antimicrobial drugs-loaded polysaccharide-based nanoparticles for

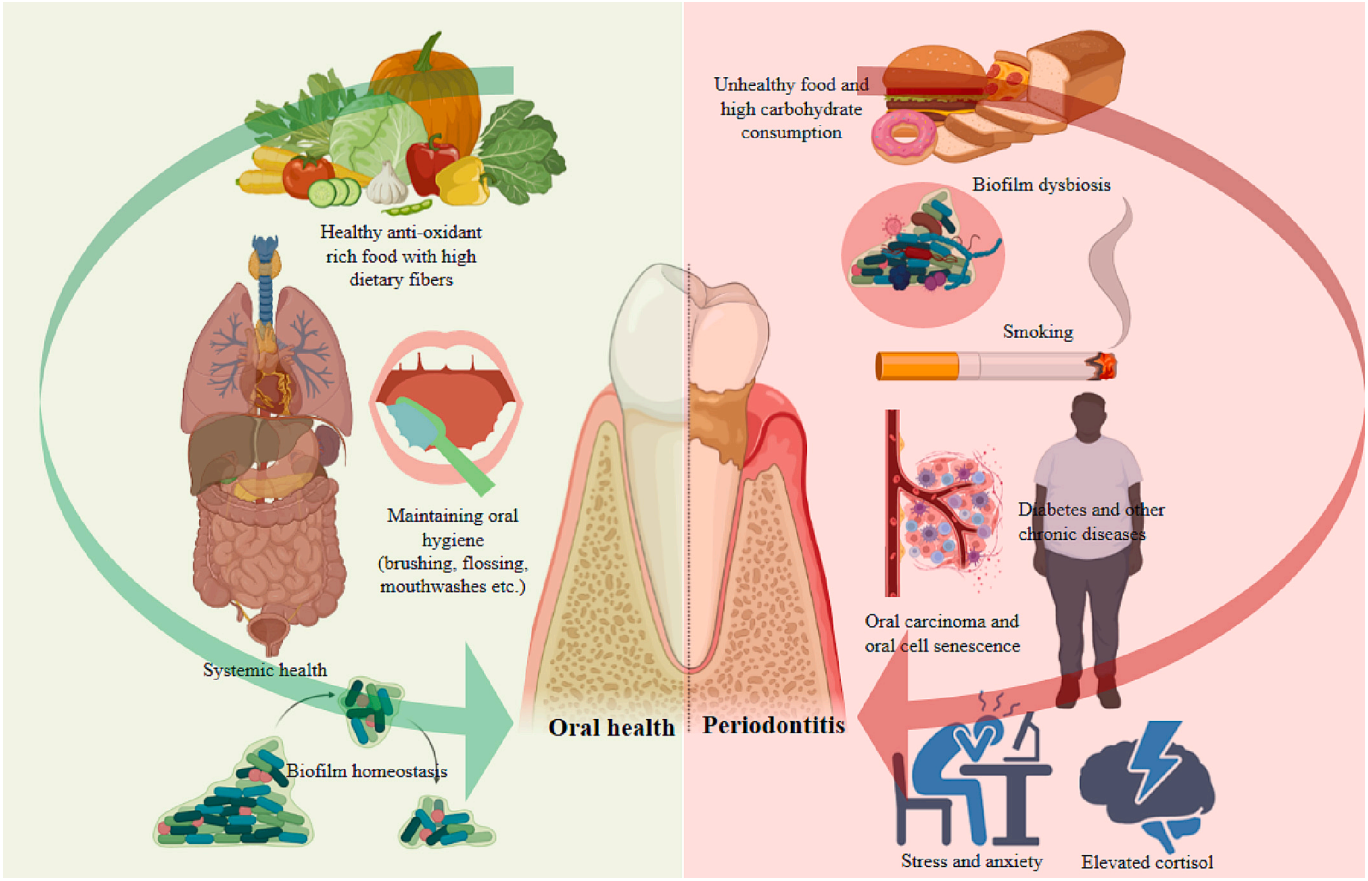


Fig. 2. Factors contributing to oral health and maintaining healthy oral biome *vs.* factors contributing to dysbiosis of oral microflora and periodontitis.

Table 1
Composition of biofilm.

Key pathogens responsible for dental plaques	Organic constituents	Inorganic constituents
Aggregatibacter actinomycetemcomitans	Polysaccharides	Phosphorus
Porphyromonas intermedia	Lipids	Calcium
Tannerella forsythia	Glycoproteins	Fluoride
Peptostreptococcus micros	Proteins	Sodium
Campylobacter rectus		
Fusobacterium nucleatum		

many dental applications [23–28]. The polysaccharide-based carrier materials made of chitosan, alginate, dextran, cellulose and other polysaccharides have recently been spotlighted on the recent advancements in preventing, treating and managing dental diseases. The objective of the current review article is to present a brief comprehensive overview of the recent advancements in polysaccharide-based dental drug delivery systems for the delivery of different antimicrobial drugs. In addition, pathogenesis of perodontitis and available current management of periodontitis, and antimicrobial drug releasing formulations in dentistry have also been addressed for better understanding of the current topic.

2. Methodology of review

The searching of reported literature for the current review was carried out using different popular scientific databases like Science Direct, Scopus, Web of Science, Google Scholar, and PubMed. The keywords employed for searching the literature sources comprise of dental diseases, periodontitis, antimicrobial drugs in dentistry, polysaccharide-based dental drug delivery, and use of antimicrobial drugs in dentistry. This review covers all published researches on the current topic till date.

3. Periodontitis

Approximately 10 % of all dental diseases in the global adult population are directly contributed to periodontitis, which is a widespread pathology of the human oral cavity [29]. Its high prevalence makes it a significant health issue, which might result in compromised tooth health and may cause impairment of dental tissues as well as loss of teeth. Not only does periodontitis impair the quality of life, but it also significantly accounts for edentulism and masticatory dysfunction, which incurs significant costs for dental care, and has a detrimental effect on overall health [30]. However, other factors, including anatomical features like the short trunk, cervical enamel projections, developmental grooves, dental plaque, calculus, protruding restorations, systemic factors, genetic makeup, tobacco, and anxiety, act as secondary causal factors speeding up the propagation and advancement of periodontal diseases. Factors contributing to oral health and maintaining healthy oral biome *vs.* factors contributing to dysbiosis of oral microflora and periodontitis are presented in Fig. 2.

3.1. Pathogenesis of periodontitis

The pathogenesis of periodontitis can be comprehended by understanding the intricate formation of dental biofilm along with the immune response associated with it [31]. The formation of dental plaque is a key symptom which is observed in the progression of periodontitis. This dental plaque is nothing but a complex biofilm, which is made up of microbial colonies (mainly gram-positive) and their protective matrix

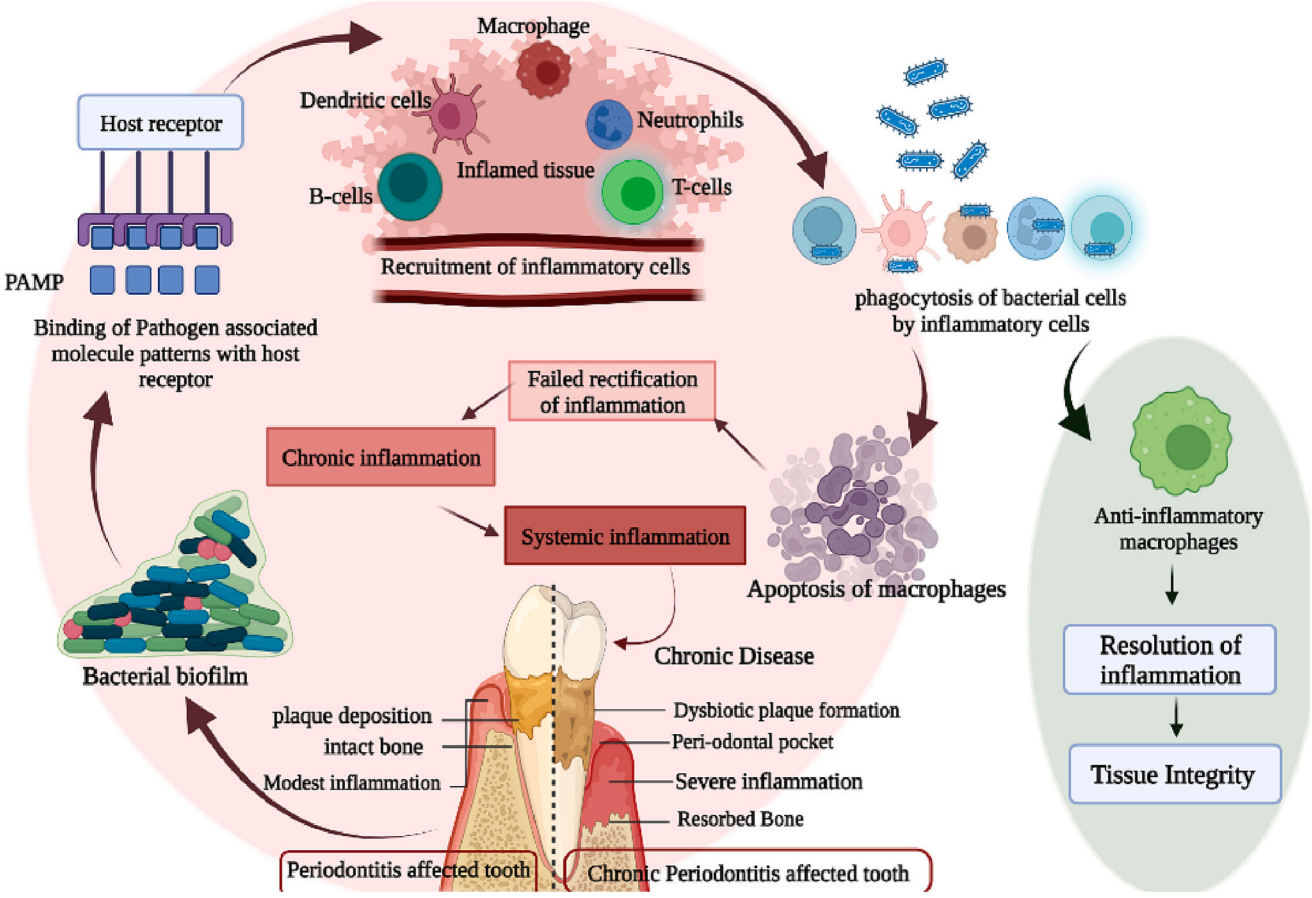


Fig. 3. Periodontitis pathogenesis and progression.

made up of glycocalyx and polysaccharides [32–34]. Key pathogens responsible as well as the organic and inorganic constituents of a biofilm are given in Table 1.

In bacteria, cell density-mediated gene expression or quorum sensing controls the expression of particular genes by the buildup of signaling molecules, which facilitate inter-cellular communications. These signaling compounds are also called auto-inducers. The first layer of dental plaque that is deposited on the teeth surface is called 'acquired pellicle'. The proline-rich proteins of the capsule are bound by the 'adhesin receptors' on the surface of initial colonizers. This binding causes the 'cryptitope' receptor sites to become exposed, which in turn causes coaggregation. In this way, there is a layer by layer deposition of dental plaque leading to compromised oxygen availability in the bacterial colonies and these results in the spurge of anaerobic bacterial colonies. Fusobacterium species serve as the linking microbe between primary and secondary colonizers. Oral bacteria like *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* also contain fimbriae, which helps in bridging. This gradual shift from aerobic to anaerobic microbial colonies results in accelerating gingivitis to periodontitis [35,36]. When bacterial virulence factors (like *P. gingivalisgingipains*) and chronic inflammation, which manifest as gingival bleeding and modifications in soft tissue shape and color overwhelm this intricate and well-adapted defense mechanism, the junctional epithelium relocates superficially on the root surface and stimulates collagen destruction, which then eventually results in the formation of periodontal pockets [36].

In response to this chronic progression of infection, the host exhibits innate immune response. As a result, signs of acute inflammation like red and bleeding gums, reddening and swelling of gingiva and neutrophil migration to the site of inflammation. The primary immune response also activates host cells to trigger the adaptive response, which in turn results in the boosting of prostaglandins, tumor necrosis factor, and other pro-inflammatory mediators like interleukin-1 β. The cascade is thus activated, which is followed by the B-cell and T-cell activations. The pathogenesis and progression of periodontitis affected tooth is presented in Fig. 3. A severe case of periodontitis can loosen the teeth. Periodontitis can generally be treated in a systematic approach to slow down the disease's progression. If there are gum pockets that have become at least 3.5 mm deep, treatment is required.

3.2. Current management of periodontitis

Even if periodontitis has already caused bone or tooth loss, maintaining routine oral hygiene can assist to preserve the remaining teeth. Sometimes, as per need dentures can be fixed with healthy alternative of the supportive tissue [37]. Improved behavioral patterns like quitting smoking can help in reliving symptoms and progression of periodontitis along with minimizing chances of relapse. Once proper at-home treatment or management of biofilms is established, scaling and root planning (SRP) should be done in those areas where the periodontal probings have reached depths of 5 mm or more [37]. Tartar (calculus) is removed and this process is known as scaling. This is achieved with the help of unique instruments called scalers or gingival curettes. Sometimes, they can also be ultrasound devices or piezoelectric or rotating instruments. Treatment during this phase should also include treating active carious lesions, extracting teeth that are beyond saving, and addressing any local contributory factors. To enhance patient comfort during scaling and root planing, a suitable amount of local anaesthesia should be given before initiating the procedure. Automated devices may be more efficient than curettes for clearing subgingival biofilm and calculus in sites where access is challenging. To reduce fremitus and extreme mobility, occlusal modification should be taken into consideration [38]. In order to fix enamel deformities, Chen et al. designed HAp-based films directly on the enamel utilizing the pulsed laser deposition (PLD) technique employing a chairside erbium-doped yttrium aluminum garnet laser [39]. Future clinical uses of erbium-doped yttrium aluminum garnet laser utilizing the PLD to repair enamel defects have tremendous potential. For treating periodontal pockets, antimicrobial chemical substances (antiseptics) are employed for nonsurgical periodontitis treatments. The most important advantage was seen with metronidazole and amoxicillin. Delivery of a locally administered minocycline (a tetracycline-derivative antibiotic) *via* microspheres or chlorhexidine (an antimicrobial) containing chip may be used for the localized site with deep periodontal probing depth. Due to the limitations of traditional surgical techniques, bone grafts (BGs) have become increasingly important in periodontal regeneration. HAp has been used in the synthetic bones for a long time. It has been employed in bone regeneration because it resembles mineralized bone. BGs made from HA improve bone bonding by forming a chemical-nature bonding with the bone matrix. A nanohydroxyapatite (nHAp)-based hard tissue bone replacement technology has effectively been used for the management of space-maintaining bone defects [40,41]. Many herbal plants like Japanese herbal medicine like rokumigan [42], flavonoids (*Epimedium* spp. Plant) [43], curcumin [44], cardamom [45], eugenia, *etc.*, have been observed to impart therapeutic action against different causal factors leading to periodontitis.

In dentistry, the most commonly used antiseptic is chlorhexidine. It contains broad-spectrum properties as antimicrobial that help reduce bleeding, gingival irritation, and plaque development. It may have additional supplementary actions on dental hygiene maintenance (brushing as well as flossing). Additionally, H_2O_2 can be used to peroxidize the lipidic materials in the cell-walls of bacteria and has chemotactic effects on leukocytes. Quaternary ammonium drugs may be used to kill bacteria by attaching to some bacteria *via* their cell membranes [46]. It was shown that 4-dihydroxyphenyl alanine (DOPA)-linked polychlorinated biphenyls (PCB) coating (DOPA-PCB); pCB-(DOPA) 4-coated materials dramatically reduced the adhesion of *S. aureus*, *P. aeruginosa*, and *S. mutans* [47].

4. Antimicrobial drug releasing formulations in dentistry

Numerous microorganisms occurred in the oral cavity cause biofilms to develop, which then triggers the formation of dental plaque and this in turn causes tooth decay [32]. In general, dental caries is one of the very common non-communicable diseases, which develop when bacteria are found in the dental plaque produce acid and this often damages the tooth tissue [48]. Combating active dental caries has recently been the important most top priorities in enhancing oral health worldwide since it causes irreversible damage to teeth that even finally results in their death. Despite major efforts that vary from preventive to restorative measures being made, these diseases affect around a third of the global population [49]. For the repair of damaged tissues, among others, naturally-occurring biopolymers like chitosan, peptides, and various bio-based polyesters exhibit significant promise, particularly when infections hinder their regenerative processes [50].

Low-molecular-weight proteins called antimicrobial peptides (AMPs) have a broad range of antibacterial action [51]. The majority of AMPs are cationic and amphiphilic in nature. Their effectiveness is dependent upon their level of cationic and amphipathic properties [52]. Several models have been employed to elucidate the mechanism of action. AMPs have the ability to adhere to the anionic bacterial cell membrane, resulting in bacterial cell-lysis. The effectiveness of AMPs is dependent on their amphipathicity [53]. It has been demonstrated that a number of AMPs, both natural and synthetic, have bactericidal effects on a number of bacterial species found in the oral cavity [54,55]. Moussa et al. previously revealed long-acting amphipathic-natured AMPs that target the dental plaque microbiota and are applied as coatings on dentine-restoration interfaces [56]. *Ex vivo* experiments revealed possible protection against recurrent caries, and the study demonstrated the effectiveness of specific antimicrobials.

Dental adhesive systems that possess intrinsic antibacterial properties operate either *via* contact killing, such as quaternary ammonium

salts, or the existence of charged species, and do not rely on the discharge of any antibacterial agents [57,58]. One strategy that has demonstrated potential involves the use of methacrylate derivatives of molecules such as eugenol or *N*,*N*-dimethylammonium derivatives. These molecules possess established bactericidal properties and have been employed as polymer therapeutics in dental applications. However, this approach is presently limited to laboratory assessment [59]. Antibacterial medicines should have a low cytotoxic effect on mammalian cells while still limiting bacterial growth. As is well known, modest quantities of eugenol have actions on the tooth pulp that are both anti-inflammatory and local anaesthetic; nevertheless, excessive concentrations can have some cytotoxic consequences [59,60]. Due to their higher affinity for plasma membranes and lipid solubility, eugenol and similar chemicals have been linked to cellular damage [61]. However, when examined *in vitro* using human fibroblast cell line, it was found that both eugenol-methacrylate and poly(eugenol-methacrylate) were cytocompatible in nature [62].

The number of units determines how hydrophobic the molecule is, and quaternary ammonium compounds (QACs) are a class of cationic-natured antimicrobial agents with positively charged heads and hydrophobic tails that are typically chains of alkyl groups [63]. The exact mechanism responsible for the antibacterial properties of these molecules remains uncertain, it is generally believed to involve their ability to bind to and then penetrate the bacterial cell wall. This disruption of the internal organization of cells eventually results in cell disorganization [64].

Dentists frequently prescribe antibiotics to treat or prevent infections, which add to the problem of antibiotic resistance. Tetracyclines, a group of cationic chelating broad-spectrum antibiotics, have demonstrated collagenase and gelatinase inhibitory effects [65,66]. Because of its higher affinity for di-valent zinc cations than the other tetracyclines and their semisynthetic equivalents, doxycycline, is well-recognized as the most effective and therefore, is widely used in restorative materials in dentistry [67].

Methacryloxylethylcetyl dimethyl ammonium chloride, 12-methacryloyloxy dodecylpyridinium bromide and poly(2-methyloxazoline), are some of the examples are monomeric methacrylates with pendant quaternary ammonium salts, which have been used in different dental systems designed for dental uses dental composite restorations intrinsic antibacterial properties [68]. Additionally, connecting the antimicrobial-natured monomers through two polymerizable groups and in combination with two quaternary ammonium groups with one polymerizable group have also been shown to boost antibacterial effectiveness [69]. Since then, QACs have been included in various dental biomaterials including composite resins [70], adhesive systems [71], acrylic resins [72], and bone cements [73], which have proven already effective antibacterial qualities.

A cationic-natured substance having a broad-spectrum type antibacterial action is chlorhexidine [74]. It usually disrupts the cellular membranes and has successfully been employed in dental applications for the management of dental biofilms as an antibacterial agent. It is a crucial ingredient in oral formulations that can be applied topically to treat oral biofilms, such as mouthwashes and oral gels. In a research, Barbour and co-investigators reported that chlorhexidine hexametaphosphate displayed decreased solubility [75]. The possibility of releasing this substance from elastomeric ligatures employed in the management of orthodontic treatments was also investigated [76].

5. Polysaccharide-based dental delivery systems for releasing of antimicrobial drugs

A polymeric carrier should be completely inert in nature as well as free of leachable contaminants, which can be employed effectively in controlled drug releasing formulations. In other words, the polymeric carrier systems should have a suitable physical structure, minimum unwanted degradation, and be easily processed. The uses of different biodegradable polymers also eliminate the necessity of returning to the dentist to have the device removed or second surgical operation for device removal. In-depth research has been done on different natural polymers including cellulose, alginate, and chitosan as well as synthetic polymer-candidates like poly(vinylpyrrolidone) [PVP], poly(vinyl-alcohol) [PVA], poly(d,L-lactide) [PLA], poly(d,L-lactide)-co-glycolic acid [PLGA], poly(Ɛ-caprolactone) [PCL], *etc.* [24,77,78]. The most critical requisites for a drug delivery device in periodontitis management by a drug delivery system are the administration of antimicrobial agents in those places, where the mechanical scaling devices cannot reach and antimicrobial drug release at a required level over the total treatment period while simultaneously demonstrating cytocompatibility and biocompatibility [13]. Through different mechanisms, such as solute diffusion, aqueous swelling of the polymer matrices, degradation, as well as erosion of the polymeric-matrices, the drug can leak out of the devices and into the pocket. Zwitterionic polymers (ZPs) exhibit special properties that limit biofilm formation, inhibit protein adhesion, and preserve biocompatibility [79].

A hydrogel is a three-dimensional matrix of cross-linked, aqueous soluble biopolymers, which includes hydrophilic groups like hydroxyl groups or amide group(s) [80,81]. Cross-linking allows for the formation of polymer networks. For controlled drug release, hydrogels have the capability to swelling (absorbing a significant amount of water) and subsequently contract. Thermosensitive injectable hydrogels are gaining momentum in the advanced management of periodontal pockets, which are seemingly difficult to access [82]. Injectable and thermosensitive hydrogels containing aspirin and erythropoietin were studied, respectively, to impart anti-inflammation and tissue regeneration effects, by Xu et al. [83]. The best candidates for mimicking soft tissues are bilayer hydrogels, which have intelligent functionalities [84]. Liposome-based systems with submicron dimensions were studied to infiltrate into the dentinal tubule [85].

There are a strong linkage in-between dental disorders and common chronic illnesses. Numerous investigations have found linking among periodontal diseases, heart diseases, and diabetes mellitus, *etc.* [86–88]. Additionally, a number of general medical conditions, such as diabetes mellitus, anaemia, Crohn's disease, Addison's disease, thrombocytopenia, leukaemia, lupus erythematosus, lichen planus, human immuno virus (HIV)-associated periodontal diseases, *etc.*, which increase the risk of oral diseases, such as hemorrhagic, ulceration, mucosal bleeding, petechiae, bullae, *etc.* [89]. According to recent studies, the polysaccharide-based systems for dental delivery field are experiencing significant growth through a variety of techniques for the improvement of drugs' bioavailability. In this regard, polysaccharides are being modified/functionalized chemically as well as physically using various pH modifiers, enzyme inhibitors, permeability enhancers, *etc*.

5.1. Chitosan-based systems

Chitosan is a natural biopolymer that has antimicrobial as well as antioxidant properties against a variety of microorganisms, including yeast, filamentous fungus, and Gram-positive and Gram-negative bacteria [90]. Chitin is partially alkaline deacetylated using sodium hydroxide to produce chitosan, a cationic polysaccharide, comprising of α-1, 4-linked 2-amino-2-deoxy-α-D-glucose (*N*-acetyl glucosamine) [91,92]. Because of its cationic nature (contributed by the occurrence of amino groups in its chemical formula) as compared to other polysaccharides in recent decades, chitosan has attracted significant attention to design many dosage forms [93,94]. Chitosan has lately been investigated for its osteoconductive qualities as bone substitute polymeric biomaterial in dentistry and orthopaedic applications [90]. It also imparts significant characteristics of drug delivery excipients like: controlled drug release and mucoadhesion [94].

For the administration of hydrophilic-natured antimicrobial drugs (like chlorhexidine gluconate), the applications of chitosan as a film-based matrix is extensively established, while there are very few

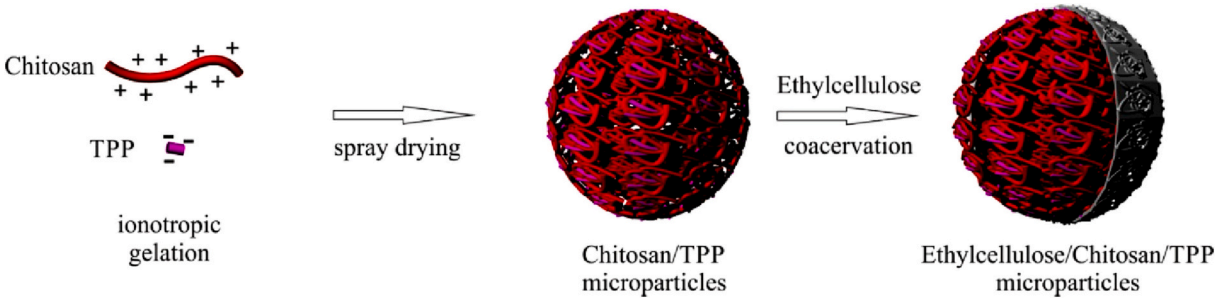


Fig. 4. Schematic presentation of the preparation procedure of the microparticles; stage 1–ionotropic gelation of chitosan and sodium tripolyphosphate (TPP), stage 2–ethylcellulose coating of the ionotropically-gelled chitosan matrix using coacervation technique [97].

reports on the delivery of lipophilic drugs using chitosan films. Perugini et al. designed a PLGA/chitosan composite film by emulsification/casting/evaporation process for ipriflavone delivery in the periodontal site [95]. All of these prepared chitosan-based films were found flexibility with elastic nature because of glycerin incorporation as plasticizer. The presence of citrate ions was observed to significantly affect the swelling, degradation, and drug release of the polymeric film. The result demonstrated a sustained *in vitro* ipriflavone releasing pattern from these PLGA-chitosan monolayer films for a period of 20 days. The research findings suggested that the release of ipriflavone was contingent upon not only the process of diffusion through PLGA micromatrices but also the process of diffusion through the chitosan matrix, which exhibited a more compacted structure when comprised of chitosan citrate. Another research group reported the preparation of buccal tablets using chitosan microspheres that contained chlorhexidine diacetate and these buccal tablets were produced by compressing the chlorhexidine diacetate-containing microparticles directly with either sodium alginate or mannitol [96]. The ability of these buccal tablets to provide a longer releasing of the medication (chlorhexidine diacetate) in the buccal region was demonstrated by the *in vivo* results of this investigation, which involved measuring the presence of chlorhexidine in saliva. The results of the experiment indicated that the activity of microparticles having a chlorhexidine-to-chitosan ratio of 1:4 was higher as compared to microparticles having a ratio of 1:2. The reason for this result can be attributed to the inherent antimicrobial properties of chitosan.

For the localized treatment of periodontitis, Gjoseva and associates carried out a study wherein they utilized an ionotropic gelation/spray drying technique to prepare microparticles containing doxycycline hyclate-loaded chitosan (medium and low molecular weight) using sodium tripolyphosphate as a crosslinker [97]. These doxycycline hyclate-loaded chitosan microparticles were subjected to an additional coating process utilizing the coacervation/solvent displacement approach with ethylcellulose. Fig. 4 depicts a schematic illustration of ionotropic gelation/spray drying technique utilized for the production of doxycycline hyclate-containing chitosan microparticles, followed by a subsequent polymer coating with ethylcellulose. The loading of doxycycline hyclate within the chitosan microparticles resulted in a reduction in porosity, while the microparticle surface retained a highly wrinkled appearance. The surface area of doxycycline hyclate-loaded microparticles composed of low- and medium-molecular-weight chitosan was found to be 25.8 m^2/g and 24.6 m^2/g, respectively. Additionally, the pore volumes of these microparticles were determined to be 0.063 cm^3/g and 0.059 cm^3/g, respectively. The surface area of the microparticles loaded with doxycycline hyclate and coated with ethylcellulose (EC N45) was observed to reduce to 19.3 m^2/g and 15.5 m^2/g for low and medium molecular weight chitosan, respectively. Additionally, the pore volume of these microparticles was also observed to reduce to 0.036 cm^3/g and 0.022 cm^3/g for the respective chitosan formulations. The rate of *in vitro* drug release was found to be dependent upon both the concentration (5 %, 7.5 %, and 10 %) and type of ethylcellulose (EC N10 or EC N45) for coacervation and the interaction among ethylcellulose type and concentration. Overall, it was observed that the utilization of EC N45 as a coating material resulted in a decreased drug release rate, with the most gradual release rate being observed at a 7.5 % EC N45 concentration. The drug release rate was observed to be much faster for both types of ethylcellulose when the concentration of chitosan was increased to 10 %. This effect can be attributed to the suppression of coacervation procedures in highly viscous and concentrated chitosan solutions. The mucoadhesive potential of both coated and uncoated chitosan microparticles was observed to be high without any significant impact on the viability of the examined epithelial cells. The study found that the RAW 264.7 cells (murine macrophage cell line), exhibited a gradual and delayed apoptotic response when exposed to microparticles. The observed effect was found to be dependent on the type of formulation and concentration of doxycycline hyclate-loaded microparticles composed of chitosan. The results of our experiments indicated a synergistic relationship between the biological response of the doxycycline hyclate-loaded microparticles composed of chitosan (medium and low molecular weight) and the anti-inflammatory properties of doxycycline hyclate.

Dos Santos et al. performed a recent study wherein they created innovative core-sheath structured chitosan-based nonwovens intended for delivering drugs in management of periodontitis [98]. The present study involved the preparation of nanofibers using a coaxial electrospinning technique, wherein chitosan was employed to form the shell layer and polyvinyl alcohol (PVA) containing tetracycline HCl was used to form the core layer. The present study involved the cross-linking of chitosan with genipin prior to the electrospinning procedure. The nanofibers acquired exhibited consistent geometric properties, with a diameter spanning from 100 to 300 nm. The core-sheath structural features were observed through transmission electron microscopy (TEM) even following genipin-induced cross-linking. The cross-linking induced by genipin was observed to significantly enhance the mechanical properties and stability of the nonwovens in an aqueous environment. The sustained release of tetracycline HCl over 2 weeks was found in the core-sheath chitosan-based nonwovens as a result of genipin-caused cross-linking. Furthermore, the findings of the drug release study, specifically regarding tetracycline HCl, indicate that the presence of lysozyme had an impact on its release, which was observed to be influenced by the composition of the shell layer. It was observed that the reduction in the degree of deacetylation of the chitosan used resulted in an increase in the tetracycline HCl discharge rate. The findings from the antimicrobial analysis indicate that the nonwoven materials composed of tetracycline HCl cross-linked with genipin-caused chitosan demonstrated enhanced efficacy against bacterial strains responsible for periodontal disease. Furthermore, it was observed that the nonwovens composed of core-sheath chitosan exhibited no cytotoxicity when subjected to fibroblast cell culture.

Dias et al. designed a novel injectable formulation of *in situ* gel

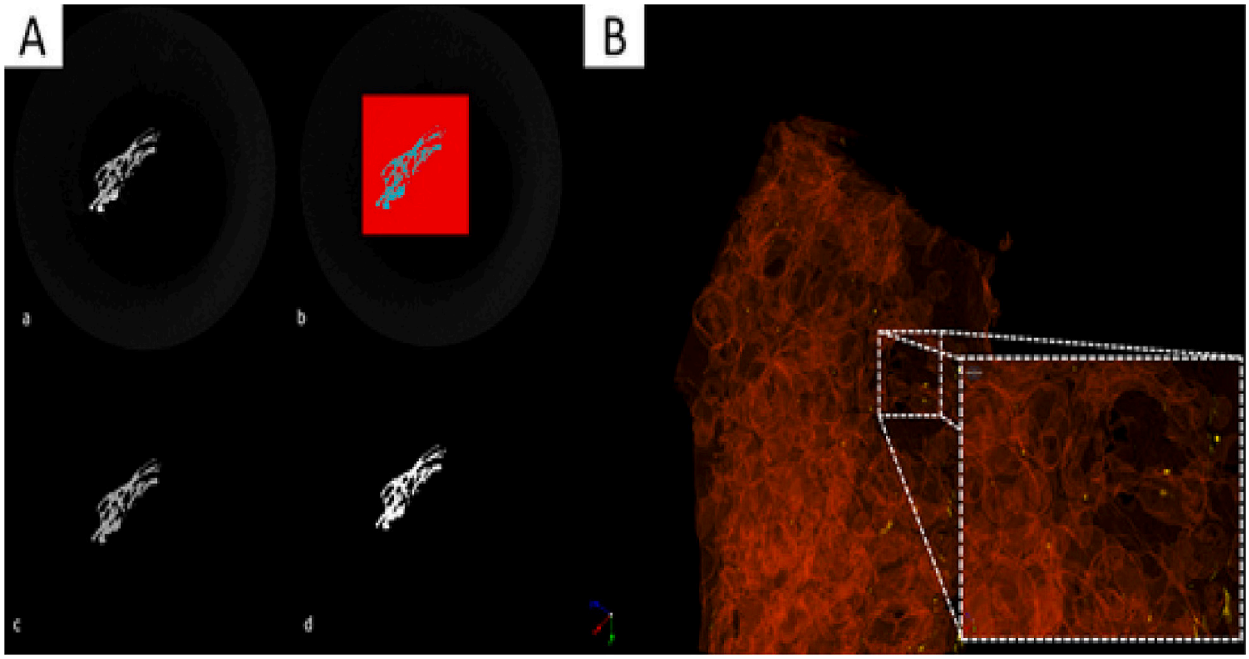


Fig. 5. Micro-CT images of the clindamycin-loaded chitosan/alginate polyelectrolyte complex dental film showing (A): axial slice of film specimen (a), selection of ROI including all specimen (b), binarization of the image by the gray-level histogram (c), thresholding for analysis Micro-CT image (d) and (B): 3D Micro-CT images after all adjustments [101].

containing ornidazole-loaded chitosan microparticles was designed for periodontitis treatment [99]. An *in vitro* adhesion test was conducted on sheep cheek mucosa, and the results demonstrated that the formulated ornidazole-loaded chitosan particles displayed excellent bioadhesion. In this research, an improvement in adhesion was noticed as the concentration of polymers increased, which contributed to the increased accessibility of polymeric chains for interaction with the mucus. The ornidazole-loaded microspheres demonstrated sustained ornidazole release *via* diffusion for up to 5 days. In another research, chitosan-based bioadhesive microspheres of tetracycline were formulated for use in localized periodontal therapy, and the drug-releasing potential was investigated [100]. A formulation consisted of chitosan (3 % *w*/w), tripolyphosphate (9 % *w/v*), and tetracycline HCl (10 % w/w) was acknowledged for maximizing bioadhesivity and obtaining controlled release of tetracycline, which was selected as an optimized formulation. The findings pertaining to bioadhesion indicated that the formulation of chitosan-based bioadhesive microspheres containing tetracycline with the optimal maximum detachment force (MDF) demonstrated a greater value (469 ± 20.25 mN) in comparison to the optimal mean dissolution time (MDT) of the formulation (293 ± 17.03 mN). The bioadhesion outcomes indicated that the optimal MDF formulation demonstrated a greater propensity to extend the retention duration on the mucosa in comparison to the optimal MDT formulation. The outcomes of tetracycline release suggested that the optimal MDT formulation exhibited a greater release of tetracycline in comparison to the optimal MDF formulation. Specifically, at the initial 1 h, the optimal MDT formulation demonstrated a tetracycline release of 18.19 %, while the optimal MDF formulation exhibited a tetracycline release of 13.23 %. Upon completion of the 8 h testing time frame, it was observed that the optimal MDT formulation exhibited 46.93 % tetracycline release, whereas the optimal MDF formulation exhibited 36.65 % tetracycline release. The findings of the study indicated that the release of loaded tetracycline from chitosan-based microspheres was observed to follow the Fickian diffusion mechanism. Additionally, the textural assessment demonstrated that there was minimal hydration throughout the course of the experiment. This research aimed to assess the antimicrobial efficacy of chitosan-based bioadhesive microspheres of tetracycline against *Staphylococcus aureus* (a bacterial strain commonly isolated from the periodontal pockets among individuals suffering from periodontal disease). The *in vitro* analysis was conducted in PBS, pH 6.8. The results of antimicrobial investigations suggested that the levels of tetracycline present in the *in vitro*-releasing samples exceeded the minimum threshold concentration of tetracycline necessary to impede the growth of *Staphylococcus aureus*. The results of thermal analyses suggested the potential for an interaction to occur between the loaded tetracycline and the polymer used (here, chitosan). The integrity of these chitosan-based bioadhesive microspheres of tetracycline was confirmed, and the morphological alterations that occurred after tetracycline release became apparent through the use of scanning electron microscopy.

Kilicarslan and associates developed biopolymeric dental films made from chitosan- and alginate-based polyelectrolyte complexes loaded with clindamycin [101]. The present study employed the solvent cast methodology to fabricate chitosan/alginate films loaded with clindamycin. The films were prepared by varying the proportions of excipient polymers (chitosan and alginate) with varying molecular weights. The thickness measurements of the developed chitosan/alginate films were found to be within 445.00 ± 33.91 to 1903.00 ± 254.90 μm. The polysaccharidic films that were manufactured employing chitosan of medium and low molecular weights exhibited a granular texture and surface roughness, as evidenced by the microscopically analysis by scanning electron microscopy (SEM). The 3-dimensional (3-D) structure of the developed biopolymeric films composed of polyelectrolyte complex-based polysaccharides loaded with clindamycin was analyzed using Micro-CT imaging, as depicted in Fig. 5. The study revealed that the concentration of chitosan as well as alginate had a positive correlation with the increase in clindamycin content in the developed films. The films loaded with clindamycin exhibited effective disintegration within a 2-h period. The study determined that the dental films containing clindamycin and 5 ml of alginate exhibited the smallest swelling rate. By comparison, the dental films containing clindamycin exhibited the greatest degree of swelling when formulated with alginate-to-chitosan concentration and volume ratio of 3:1 and 2:1, respectively.

Table 2
Antimicrobial drugs releasing chitosan-based systems for dental drug delivery.

Chitosan-based systems	Antimicrobial drugs	Important features	References
Chitosan films	Metronidazole and levofloxacin	• Prepared *via* solvent-casting method using propylene glycol and glutaraldehyde. • Sustained release of loaded drugs up to 7 days. • Concentrations of chitosan and glutaraldehyde affected the *in vitro* drug releasing and T_{90} (time for 90 % drug releasing). • Good antibacterial efficacy against *Escherichia coli* and *Staphylococcus aureus*. • Trials on patients demonstrated the therapeutic efficacy by a significant ($p < 0.05$) decline in the clinical markers of periodontitis (*i.e.*, pocket depth, plaque index and gingival index).	[102]
Chitosan-pectin and chitosan-alginate polyelectrolyte complex (PEC) films	Tetracycline HCl	• PEC films containing tetracycline HCl (maintaining tetracycline to PEC as 1:1) were formulated using chitosan to sodium alginate. • An initial burst release of loaded tetracycline, *in vitro*, subsequently a prolonged release pattern for 70 h. • Prolonged *in vitro* antibacterial action against *Staphylococcus aureus* over 21 days. • Clinical study results demonstrated a significant decrease in periodontal pocket depth to their standard ranges.	[103]
Chitosan-based nanostructured particles-incorporated films	Doxycycline	• Nanostructured doxycycline/chitosan particles were formulated by spray drying method and the formed particles were then incorporated in polyvinyl alcohol-based films. • The prepared nanostructured particles had 52.86 nm particle size, +13.8 mV zeta potential and 0.946 polydispersity index. • *In vitro* doxycycline release was found to be sustained for a week, approximately; the nanostructured particles-incorporated films showed 23 % doxycycline releasing as compared those of 44 % from doxycycline-containing films. • Clinical results designated a significant outcome of both nanostructured doxycycline/chitosan particles-incorporated films as compared to both placebo and control groups, when clinically investigated on 150 periodontal pockets from moderate chronic periodontitis patients.	[104]
Spray-dried chitosan microparticles	Clindamycin phosphate	• Formulated by spray drying method and using glutaraldehyde as cross-linker. • The drug incorporation efficiencies in these chitosan microparticles were found >80 %. • A delayed release for more than one week was observed.	[105]
Chitosan inserts	Metronidazole	• Formulated *via* the casting technique. • Initial burst releasing of metronidazole at 24 h and further metronidazole releasing was found sustained over the next 6 days.	[106]
Thermosensitive and mucoadhesive *in situ* gels	Moxifloxacin	• Formulated using cold method. • *In situ* gels were found clear and pH ranged within 7.01–7.40. • *In situ* gels made of chitosan (2 %) and β-glycerophosphate (70 %) exhibited sustained moxifloxacin releasing for 8 h, *in vitro*, • Good antimicrobial efficacy against *Streptococcus mutans* and *Aggregatibacter actinomycetemcomitans*.	[107]
Cross-linked chitosan microparticles-containing mucoadhesive hydrogel and film	Metronidazole	• Formulated by emulsion cross-linking. • The formula of optimized formulation of metronidazole-loaded chitosan microparticles were Span 80 (1 %) in soybean oil and glutaraldehyde (5 %, as cross-linker) with cross-linking period of 30 min, metronidazole to chitosan ratio of 1:1, metronidazole addition in form of ethanol solution and use of hexane for washing. • Metronidazole-loaded cross-linked chitosan microparticles were formulated using the optimal formulation *via* incorporation in mucoadhesive hydrogel and film.	[108]

(*continued on next page*)

Table 2 (*continued*)

Chitosan-based systems	Antimicrobial drugs	Important features	References
		• The metronidazole-loaded cross-linked chitosan microparticles incorporated hydrogels demonstrated preferable profile of drug than the films.	
PLGA-chitosan nanoparticles	Tetracycline and lovastatin	• Sequential releasing of tetracycline and lovastatin. • Good antibacterial action against periodontal pathogens. • Good biocompatibility as well as improved alkaline phosphatase activity, when tested using osteoblast cell cultures. • The results of the volumetric analysis conducted through micro-CT indicated a noteworthy augmentation in the formation of new bone in defects that were filled with nanoparticles in three-walled defects in beagle dogs.	[109]
Composite membrane made of thiolated chitosan-hyaluronic acid	Doxycycline	• Prepared *via* solvent casting technique. • Good swelling capacity, excellent mucoadhesive behavior and higher mechanical strength than those of unmodified chitosan-based membrane. • About >80 % release of doxycycline within 7 days, *in vitro*. • Effective against *Porphyromonas gingivalis* cells. • 90 % of the thiolated chitosan-hyaluronic acid composite membrane was found biodegradable, *ex vivo*.	[110]
Hydroxyapatite/ chitosan composite	Minocycline	• Prepared *via* the co-precipitation technique. • Minocycline-loaded hydroxyapatite/ chitosan composite material demonstrated better results in promoting periodontal bone regeneration, *in vivo*, as tested in rabbit model of mandible bone defect.	[111]
Double-layer nanofiber mat comprising of a chitosan/ polyethylene oxide layer containing ciprofloxacin (30 %) and a poly (ε-caprolactone) layer containing metronidazole (5 %)	Ciprofloxacin and metronidazole	• Prepared *via* the co-precipitation technique. • Slower release of loaded ciprofloxacin and metronidazole • Good antibacterial action against *Aggregatibacter actinomycetemcomitans* and *Escherichia coli*.	[112]
Chitosan/ polyethylene oxide nanofibers	Metronidazole	• Prepared using electrospinning of aqueous solutions of chitosan and polyethylene oxide • Drug releasing (*in vitro*) from chitosan/ polyethylene oxide nanofibers containing metronidazole was found to be strongly dependent on the drug release method tested.	[113]

The dental films containing clindamycin that were formulated using high concentrations of sodium alginate and chitosan exhibited superior adhesion properties. The study determined that the release rates and kinetics of clindamycin from dental films were controlled by the polyelectrolyte complexation in-between alginate and chitosan. The study reported that the clindamycin-loaded dental films, which were formulated with lower alginate content and a combination of high molecular weight chitosan as well as low molecular weight chitosan, exhibited a rapid releasing of clindamycin. The dental films containing clindamycin were formulated with an increased alginate concentration and either high- or low-molecular-weight chitosan. These films demonstrated a sustained and regulated release of clindamycin. The dental films containing clindamycin that were manufactured from a polyelectrolyte complex-based polysaccharidic material with an increased alginate content displayed a slower rate of clindamycin release for up to 10 h, as well as outstanding swelling and excellent adhesion. The utilization of chitosan/alginate polyelectrolyte complex-based dental films loaded with clindamycin presents a promising approach for the targeted management of periodontitis through localized application within the periodontal pocket [97]. Some other antimicrobial drugs-releasing chitosan-based systems for dental drug delivery are described in Table 2.

5.2. Cellulose-based systems

In general, cellulose is a group of hundreds to millions of individual sugar molecules known as anhydrous-D-glucopyranose units (AGUs) that are connected by glucosidic connections. It is an essential component of plant cell walls and is frequently consumed as fibre by humans [114]. The biomedical field, including dentistry, cellulose and its derivatives has enormous potential uses for both bacterial and plant cellulose [115].

A research group designed porous matrices containing metronidazole and applied them topically to the periodontal pocket [116]. These metronidazole containing porous matrices were prepared using the cellulose derivatives like carboxymethyl cellulose sodium (NaCMC) and hydroxyethyl cellulose (HEC) in combination with gelatin (a protein biopolymer). In another research, Fini and co-researchers designed mucoadhesive-natured aqueous gels containing chlorhexidine that comprise the cellulose derivatives like hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) and carboxymethyl cellulose (CMC), either alone or in binary combinations [117]. The combination of HPC and CMC in the 2/3 weight ratio enabled the development of mucoadhesive aqueous gels, which maintained the releasing of chlorhexidine. Thus, the overall results indicated their potential to interact with the mucin. For the treatment of periodontitis, a mucoadhesive polymeric-gel were prepared using propolis extract (as natural antimicrobial), HPMC K4M, Carbopol 940, and NaCMC has been designed [118]. The gel made of NaCMC (3 %) and Carbopol 940 (1 %) was found to be the optimal formulation in terms of *in vitro* drug releasing, viscosity and mucoadhesion investigations. The authors of this study came to the conclusion that these formulations effectively inhibited the growth of *P. gingivalis*, and they advise clinical testing of these products.

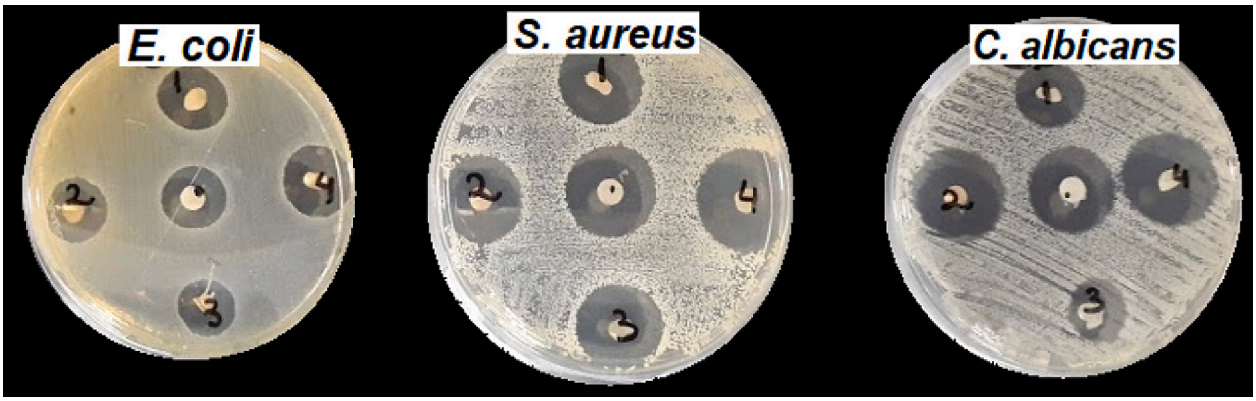


Fig. 6. Antimicrobial activity of chlorhexidine-releasing polymeric membrane made of chlorhexidine/β-cyclodextrin inclusion complexes and oxidized bacterial 2,3-dialdehyde cellulose against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* [120].

Recently, Hirun and coworkers designed polysaccharide-based hydrogels using methylcellulose and tamarind seed xyloglucan for *in-situ* metronidazole delivery [119]. A crucial property is that both methylcellulose and tamarind seed xyloglucan are biodegradable and biocompatible biopolysaccharides. The methylcellulose-tamarind seed xyloglucan hydrogels underwent a sol-gel transition. Furthermore, it has been found that the viscosity exhibited an upward trend as the concentration of methylcellulose increased. The incorporation of tamarind seed xyloglucan was found to result in an increase in viscosity in the samples. In addition, favourable mucoadhesivity and injectabile characteristics of these prepared hydrogels were found. The obtained results of this investigation revealed that the hydrogels composed of 7 % *w/v* methylcellulose and 1.5 % w/v tamarind seed xyloglucan exhibited a prolonged release pattern for loaded metronidazole, which was comparable to the commercially available gel. In a research, Inoue and *co*-researchers designed a chlorhexidine-releasing polymeric membrane composed of oxidized bacterial 2,3-dialdehyde cellulose [120]. In order to monitor the release and effectiveness of chlorhexidine, the synthesis of inclusion complexes of chlorhexidine with β-cyclodextrin was carried out. Chlorhexidine interacts chemically strongly with the cellulosic structure, which significantly aids in its retention. Comparing oxidized bacterial cellulose to its natural form, the combination of membrane-oxidation and the development of the inclusion-complex with cyclodextrin resulted in a 10-fold rise in rate of chlorhexidine release. The chlorhexidine-releasing polymeric membrane made of chlorhexidine/β-cyclodextrin inclusion complexes and oxidized bacterial 2, 3-dialdehyde cellulose exhibited greater inhibition against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* (Fig. 6).

Some other antimicrobial drugs-releasing cellulose-based systems for dental drug delivery are described in Table 3.

5.3. Alginate-based systems

Alginate is a naturally occurring algal biopolysaccharide isolated from seaweeds [131]. During past few years, alginate has been investigated for numerous uses in medicine, dentistry, tissue engineering, enzyme immobilization, cell encapsulation, *etc.* [22,132]. Alginates are well-known as nonimmunogenic, nonallergic, nontoxic, and biodegradable. They are used in dentistry as dental impression biomaterials to capture the intra-oral structure prior to the construction of dental restorations [22]. Gypsum casts made from alginate can be used for a variety of purposes, including removable dental prostheses, sports mouth guards, provisional bridges and crowns, orthodontic modeling, and diagnostic casts [133].

For application in periodontal therapies, Scholz et al. designed and assessed chlorhexidine release from alginate-based microbeads [134]. The dripping technique and internal gelation procedure were used for producing these chlorhexidine-releasing alginate-based microbeads. In the fabrication of these chlorhexidine-releasing alginate-based microbeads, calcium chloride was used as a cross-linker (ionic-type). The chlorhexidine releases from several microbeads revealed chlorhexidine-releasing properties equivalent to clinically recognized systems, *in vitro*. The present study demonstrated that the release profiles of alginate beads could be customized for individual patients and adjusted according to their inflammation status by manipulating various factors such as particle size, loading duration, concentration of chlorhexidine, and particle combinations. The potential for implementation within clinical settings appears promising, owing to its advantageous features such as adaptability, low production costs, and ease of handling. Alginate-based dental implantable rings combined with PCL were developed and investigated by Lan and associates for the controlled release delivery of metronidazole. This metronidazole-containing composite-material can be used as a customized ring system for dental implantation to prevent bacterial growth [135]. Fig. 7 illustrates the diagrammatic representation of the arrangement of PCL/alginate composite dental implantable rings that comprise metronidazole. The process of fabricating PCL-alginate dental implantable rings was carried out utilizing the solvent cast technique, employing polydimethyl siloxane (PDMS) moulds. Three different kinds of medicated rings, specifically alginate rings, PCL rings, and PCL-alginate composite rings, were formulated and investigated. In this study, PCL-alginate composite dental implantable rings were developed using varying ratios of PCL and alginate. Specifically, three distinct proportions were utilized, namely the total quantity of metronidazole in PCL to the total amount of metronidazole in alginate at ratios of 5:1, 10:1, and 50:1. Fig. 8 depicts the structural morphology of PCL/alginate dental implantable rings. The study revealed that the morphology of the inner alginate ring was effectively obstructed by a relatively rigid and less permeable polymer material, namely PCL, which formed a barrier that could potentially reduce the chance of rapid and unexpected burst release of metronidazole, as observed in the case of the alginate ring. The metronidazole release into phosphate buffered saline could be protected by this layer. Moreover, PCL has the potential to provide the necessary level of rigidity to the composite ring, thereby promoting smooth integration with the bodily structure of dental implants. The findings of the *in vitro* investigations indicate that the metronidazole release kinetics of the alginate rings exhibited a rapid initial release within a period of 120 min, rendering them unsuitable for prolonged therapeutic efficacy. Conversely, the metronidazole release profile of the PCL rings was observed to be comparatively slower, while the metronidazole release kinetics of the PCL/alginate composite dental implantable rings varied depending on the specific ratios of the two polymers utilized. The PCL/alginate composite dental implantable rings that were produced and incorporated with metronidazole exhibited an

Table 3
Antimicrobial drugs releasing cellulose-based systems for dental drug delivery.

Cellulose-based systems	Antimicrobial drugs	Important features	References
In situ gels made of ethylcellulose and *N*-methyl pyrrolidone	Metronidazole, benzyl peroxide and doxycycline hyclate	• Transformed into formation into *in situ* gels after injection to simulated gingival crevicular fluid. • Increasing ethylcellulose amount in the *in situ* gels augmented the viscosity but, decreased the drug releasing. • Good antibacterial actions against Porphyrommonas gingivalis, *Staphylococcus aureus*, *Streptococcus mutans*, *Escherichia coli*, and *Candida albicans*.	[121]
Polysaccharidic hydrogels composed of κ-carrageenan oligosaccharides nanoparticles and cellulose nanofibers	Herbmedotcin and surfactin	• Surfactin concentrations were increased for the production of composite hydrogels. • Good antibacterial action against Porphyrommonas gingivalis, Staphylococcus mutans, *Pseudomonas aeruginosa* and *Fusobacterium nucleatum*. • The composite hydrogel comprising herbmedotcin and surfactin was observed to cause a reduction in both the formation of biofilm and the metabolic activity of the bacteria. • Reduced production of transcription factor, cytokines and reactive oxygen species in human gingival fibroblast cells.	[122]
κ-Carrageenan oligosaccharides entangled cellulose nanofibers	Surfactin	• Chemo-mechanical technique was employed to extract cellulose nanofibers and the modification was done by means of κ-carrageenan oligosaccharides. • After sonication, the size of the nanofibers was measured as 330 nm. • The surfactin loading capacity and surfactin entrapment efficiency were 36.72 ± 1.24 % and 53.15 ± 2.36 %, respectively. • Controlled surfactin releasing. • Antioxidant action and inhibited the growth of *Porphyromonas gingivalis* and *Streptococcus mutans*.	[123]
Films made of hydroxypropyl methylcellulose, and Carbopol 934	Metronidazole and pentoxifylline	• Good physical characteristics as well as mechanical properties. • *In vitro* burst release for both metronidazole and pentoxifylline during the earliest 2 h and subsequently, the drug releasing rate was noticeably declined. • The outcome of clinical trials on patients indicated the beneficial application of metronidazole and pentoxifylline as an adjunct therapy.	[124]
Cellulose-based hydrogel films	Chlorhexidine	• Formulated using microcrystalline cellulose, sodium carboxymethylcellulose, and epichlorohydrin (cross-linker). • Increment in the sodium carboxymethylcellulose ratio influenced the drug release, *in vitro*. • Inhibited the growth of *Streptococcus oralis* and *Candida albicans*.	[125]
Mucoadhesive gel	Mertronidazole	• Prepared using glycerylmonooleate, ethylcellulose and propylene glycol. • Prolonged sustained releasing of metronidazole, *in vitro*. • Gel contained metronidazole (20 %), glycerylmonooleate (65 %), ethylcellulose (7 %), propylene glycol (10 %) and water (5 %) was found to be mucoadhesive in nature.	[126]
Injectable smart gels	Azithromycin dihydrate	• Prepared using Pluronic® F-127 and hydroxy ethylcellulose (as copolymer). • Azithromycin dihydrate-containing smart gels were injectable, transparent, and thermoresponsive in nature. • Controlled azithromycin releasing, *in vitro*, which was found to be significantly, affected by Pluronic® F-127 and hydroxy ethylcellulose concentrations. • *In vivo* results demonstrated a significant enhancement in clinical factors of periodontitis.	[127]
Ethylcellulose-based chip	Sparfloxacin	• Formulated using sparfloxacin, ethylcellulose (10 cps), polyethylene glycol 4000, and diethylphthalate. • The chip dimension was 10 × 2 × 0.5 mm^3. • Short-term clinical results indicated the efficacy of sparfloxacin-releasing ethylcellulose-based chip can eradicate the pathogenic bacteria in the periodontal pockets.	[128]
pH-dependent nanofibers made of cellulose acetate phthalate	Chlorhexidine	• Chlorhexidine-loaded cellulose acetate phthalate nanofibers formulated with acetone-ethanol at the polymer content (12 % *w/v*) presented uniform morphology, 934 nm diameter, 42 % chlorhexidine entrapment efficiency, and 55 % process efficiency. • Chlorhexidine-loaded cellulose acetate phthalate nanofibers formulated with acetone-methanol at the polymer content (11 % *w/v*) presented discontinuous morphology, 257 nm diameter, 32 % chlorhexidine entrapment efficiency, and 40 % process efficiency. • The chlorhexidine releasing was found to follow Fickian diffusion mechanism.	[129]
pH-dependent cellulose acetate phthalate nanospheres and nanocapsules	Chlorhexidine	• Prepared using the emulsion-diffusion method. • The *in vitro* chlorhexidine releasing results indicated that the chlorhexidine release from chlorhexidine-loaded cellulose acetate phthalate nanospheres followed Fickian diffusion mechanism involving diffusion-erosion. • Chlorhexidine-loaded cellulose acetate phthalate nanocapsules exhibited a slower *in vitro* release than the nanospheres and followed non-Fickian diffusion (anomalous transport).	[130]

in vitro release pattern of 50 % metronidazole during the first 48 h. Nonetheless, the remaining amount of metronidazole was gradually discharged during the period of inactivity. The study observed an initial burst release of metronidazole from the PCL-alginate composite dental implantable rings, which was followed by a controlled release over a period of 303 days. The observed phenomenon could potentially be attributed to the comparatively rigid and less permeable characteristics of PCL, which impeded the potential swelling of alginate. The present study investigated the impact of varying ratios of PCL and alginate on the controlled release of metronidazole, with the aim of achieving the

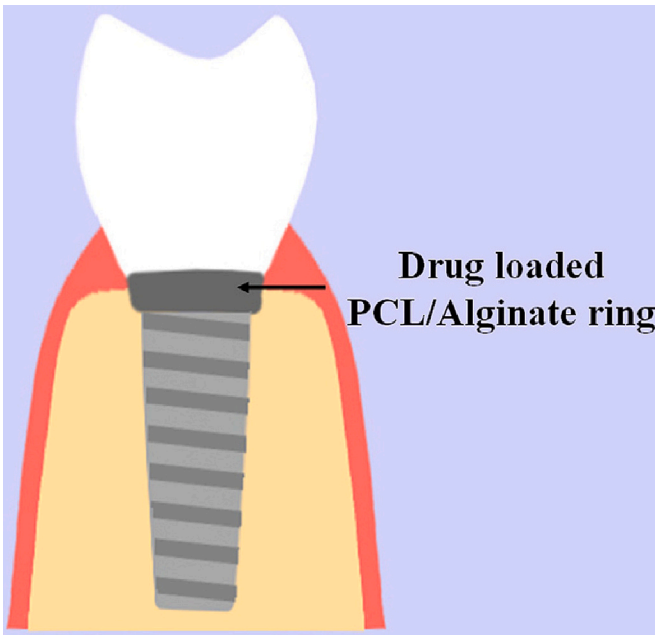


Fig. 7. Diagrammatic representation of the arrangement of PCL/alginate composite dental implantable rings contained metronidazole [135].
(Copyright © 2013 Academy of Dental Materials. Published by Elsevier Ltd.)

MIC necessary for effective protection against the pathogen. The study found that the PCL/alginate composite dental implantable rings developed for *in vitro* metronidazole release followed the Ritger-Peppas model, indicating a diffusion mechanism for drug release. Composite PCL/alginate dental implantable rings that release metronidazole can be customized to accommodate dental implants of varying diameters, dimensions, and designs, fitting perfectly around the dental root.

Park et al. carried out a study wherein they utilized the ionotropic gelation technique in order to formulate alginate-chitosan microspheres that contained minocycline (10 %) [136]. These minocycline-loaded alginate-chitosan microspheres were designed to serve as a polymeric implantable drug delivery system for insertion into the periodontal pocket, thereby facilitating the sustained release of minocycline into the gingival fluid over 7 days. These developed formulations of minocycline-loaded alginate-chitosan microspheres exhibited significant efficacy against pathogenic bacteria, including *Prevotella intermedia*, which is known to cause periodontitis. In a research, Prakash et al. designed amoxicillin-releasing in polyvinyl alcohol/sodium alginate/hydroxyapatite films. To prepare these films, hydroxyapatite-nanoparticles and amoxicillin incorporated in polyvinyl alcohol/sodium alginate films. Fig. 9 presents the schematic diagram of the preparation of amoxicillin-releasing in polyvinyl alcohol/sodium alginate/hydroxyapatite films. These polymeric-ceramic composite-based films containing amoxicillin exhibited good tensile strength, good swelling, nonhaemolytic nature, antibacterial activity, and biocompatibility, *in vitro*. The results of *in vitro* drug release exhibited a sustained drug release over 10 days. The overall results of the study clearly

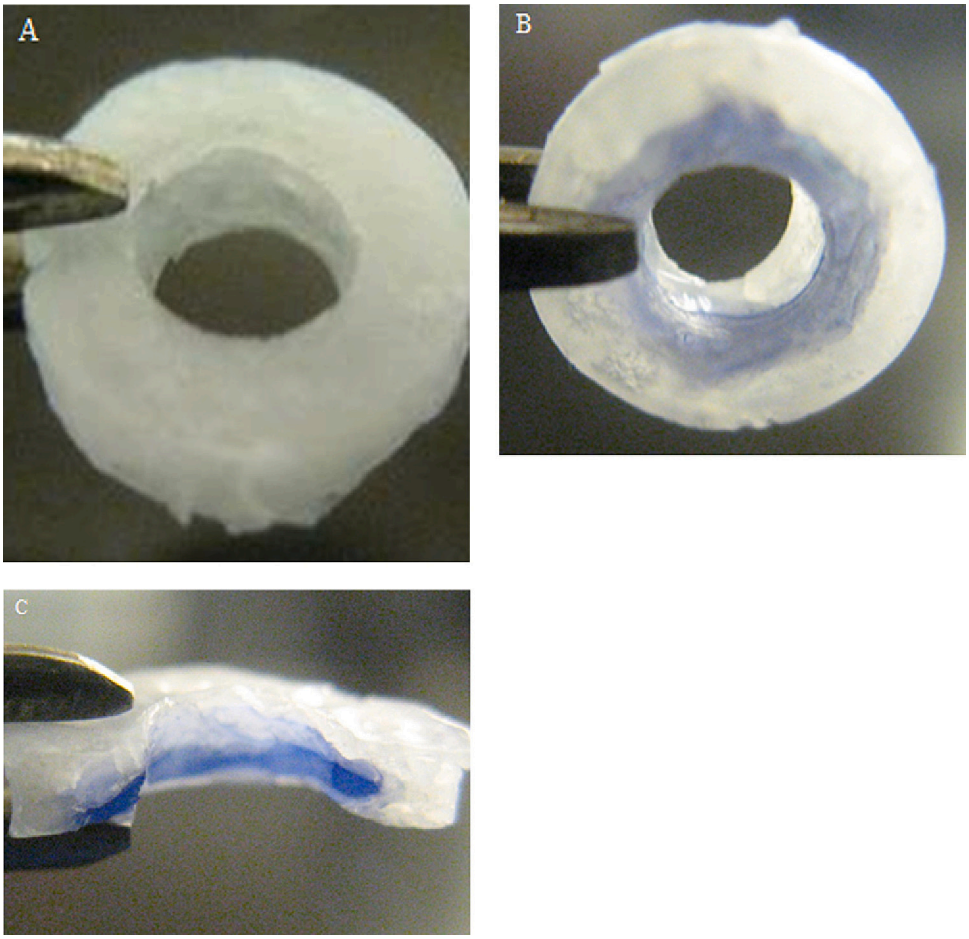


Fig. 8. The structural morphology of PCL/alginate dental implantable rings containing metronidazole (A) PCL ring. (B) PCL/alginate ring (5:1). Alginate was colored with trypan blue for visual clarity. (C) PCL/alginate ring (5:1) with a central sectional cut. Dyed alginate was covered with PCL [135].
(Copyright © 2013 Academy of Dental Materials. Published by Elsevier Ltd.)

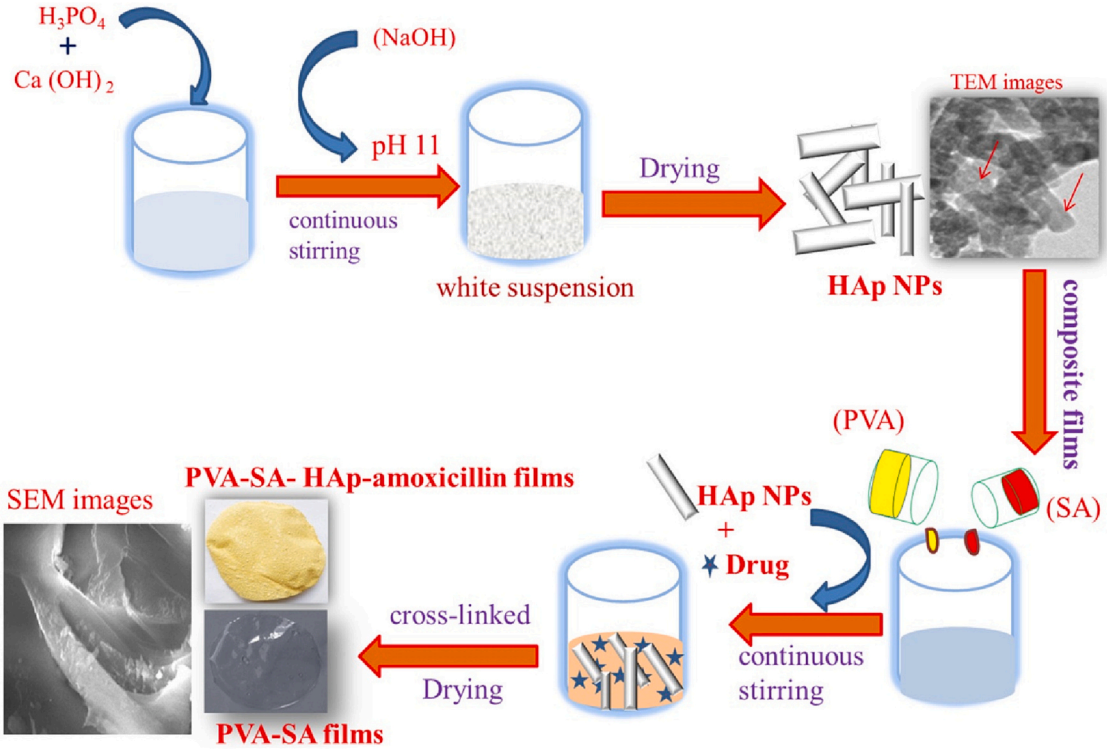


Fig. 9. The schematic diagram of the preparation of amoxicillin-releasing in polyvinyl alcohol/sodium alginate/hydroxyapatite films [Key: PA: Polyvinyl alcohol, SA: sodium alginate, HAp: hydroxyapatite] [137].

demonstrated that these developed amoxicillin-releasing in polyvinyl alcohol/sodium alginate/hydroxyapatite films for periodontitis treatment as amoxicillin could help in healing bacterial infection and hydroxyapatite-nanoparticles could help in periodontal tissue regeneration in the infected periodontal site.

Some other antimicrobial drugs-releasing alginate-based systems for dental drug delivery are described in Table 4.

5.4. Dextran-based systems

Because of its significant hydrophilic nature and biocompatibility, dextran (a hydrophilic natural polysaccharide of hydrophilic nature) has received great interest for the uses in different controlled release systems [146,147]. It is capable of being broken down by enzymatic degradation. Each anhydroglucose residue in dextran also contains 3-hydroxyl groups and these may be employed in a variety of ways for chemical modification and building networks. Glycidyl methacrylated dextran, potentially synthesized *via* coupling glycidyl methacrylates to those hydroxyl groups of dextran and the synthesized modified dextran material was tested to design-co-gelatin microspheres for localized controlled release of insulin-like growth factor-I to enhance the periodontal tissue regeneration [148].

In a research Wu et al. fabricated calcium-dextran sulfate complex microparticles for localized minocycline delivery to treat periodontitis [149]. These microparticles exhibited 96.98 ± 0.12 % loading efficiency of minocycline, 44.69 ± 0.03 % minocycline loading, sustained *in vitro* minocycline releasing (for at least 9 days at pH 7.40 and 18 days at pH 6.40, correspondingly), and antimicrobial actions against *Aggregatibacter actinomycetemcomitans* and *Streptococcus mutans*. The observed research findings indicated that the interaction between minocycline, Ca^{2+}, and polymers containing sulfonate/sulfate functionality through ion pairing/complexation could be utilized for the development of complex microparticles as localized therapeutic delivery carrier matrices for the management of periodontitis. Zhao et al. designed an injectable drug delivery system for metformin and doxycycline utilizing oxidized dextran and phenylboronic acid functionalized poly(ethylene imine) [150]. This injectable system demonstrated proper adhesiveness to gingival mucosal tissue, excellent biocompatibility, and significant antibacterial effect against *Staphylococcus aureus*, *Escherichia coli* and *Porphyromonas gingivalis*. Additionally, the beneficial synergistic impact of the combination of metformin and doxycycline was confirmed in an *in vivo* study utilizing a rat model of chronic periodontitis with diabetes mellitus. This was achieved *via* the utilization of morphometric and histological assessments of alveolar bone, immuno-histochemical staining, and the measurement of immune-inflammatory mediator expression levels in gingival tissue. Thus, the ROS-triggered localized drug releasing suggested the potential of chronic periodontitis therapy in diabetic rats.

5.5. Other polysaccharides-based systems

In addition to chitosan, cellulose, alginate and dextran, some other polysaccharides like gellan gum, gum tragacanth, xanthan gum, pectin, *etc.*, have been used for releasing of antimicrobial drugs in dental drug delivery. Some other antimicrobial drugs-releasing some other polysaccharides-based systems for dental drug delivery are described in Table 5.

6. Limitations

Antimicrobial treatments, which require high oral doses to obtain efficient concentration in the gingival fluid, are a part of conventional therapy for dental disorders. The rise of resistant bacterial strains is the obvious drawback. As a result, the periodontal pocket now receives localized, target-oriented medicament administration [158]. Dental medications can only distribute drugs conventionally, which has the drawback of having a brief duration of action because there isn't a longer contact period at the action site. The controlled medication delivery

Table 4
Antimicrobial drugs releasing alginate-based systems for dental drug delivery.

Alginate-based systems	Antimicrobial drugs	Important features	References
Injectable gelatin-alginate hydrogels	Metronidazole	• A dual network hydrogel was prepared using alginate and gelatin with carbodiimide (as a cross-linker). • The metronidazole-loaded hydrogels exhibited a sustained release pattern, wherever most of the loaded metronidazole eluted within 24 h. • *In vitro* fibroblast viability (when tested using human fibroblasts) of at least 75 % after 24 h and 48 h, indicating well biocompatibility.	[138]
Alginate films	Clindamycin	• Prepared by solvent casting technique using Sodium alginate, sodium carboxymethylcellulose, and glycerine. • Maximum clindamycin content was found 98.49 % and showed 98.16 % clindamycin release	[139]
Alginate gels	Metronidazole	• Prepared using 0.5 and 1 % Carbopol addition to sodium *alginate base*. • A sustained metronidazole release pattern. • High inhibition to *Staphylococcus aureus*.	[140]
Alginate-based *in situ* gels	*Doxycycline HCl*	• Prepared using sodium alginate and hydroxypropyl methylcellulose. • A sustained *doxycycline* release pattern for an extended period of >12 days.	[141]
PCL/alginic acid-based polymeric film	Metronidazole	• Prepared by solvent casting method. • An initial burst release of metronidazole and subsequently, a gradual release with first-order model kinetic. • Metronidazole (3 % wt)-containing formulation displayed good biocompatibility using L929 cells.	[142]
Alginate-coated poly(D,L-lactic-*co*-glycolic acid) microspheres	Tetracycline	• Prepared by double emulsion solvent evaporation • Enhanced tetracycline encapsulation efficiency 17.9 ± 0.5 % and prolonged tetracycline release. • Higher swelling than uncoated microspheres.	[143]
Gelatin-alginate/calcium deficient hydroxyapatite nanocomposite films	Tetracycline	• Prepared by solvent casting technique, where calcium deficient hydroxyapatite nanoparticles were incorporated into gelatin-sodium alginate films. • High tetracycline loading and sustained *in vitro* tetracycline release for 10 days.	[144]
Chitosan-calcium phosphate microflowers and drug-loaded calcium alginate sponges	Metronidazole	• The designed chitosan-calcium phosphate micro-flowers particles displayed 3-D and relatively homo-geneous architectures. • The chitosan-calcium phosphate microflowers/metronidazole sponges were shaped into the tooth root. • Inter-connected porous and lamellar structures with good swelling, and hemostatic action. • Satisfactory cytocompatibility, *in vitro*, and promoted cellular osteogenic differentiation • Suppressed the growth of *Staphylococcus aureus*, and *Escherichia coli*.	[145]

systems can be used to achieve the prolonged interaction with the active agent at the site of action that is necessary for the majority of dental ailments [159]. According to the extending contact at the action site, the innovative orodental medication targeting systems operate. Natural polysaccharides provide benefits in dentistry, but they have drawbacks in biological applications. For example, they have weak mechanical qualities. The therapeutic effectiveness of natural polysaccharides is constrained by their poor adhesiveness and transient *in vivo* durability [160]. Polysaccharides can only be as good as their starting source. The extraction and purification process has an impact on how reliable the goods are [161]. The sensitivity of natural polysaccharides to moisture is very great. They hydrolyze during processing and become unstable in the mouth [162].

7. Conclusion

In addition to increasing treatment responsiveness and patient compliance, the designing and development of controlled releasing systems based on different polysaccharides has reduced the incidence of systemic side effects. Numerous investigations in the area of controlled drug release to the periodontal pocket have been conducted during the last ten years. The principal dental illnesses may be treated with controlled drug delivery; as novel delivery methods are suggested, the control of dental diseases has grown significantly. The many dental drug delivery systems including films, fibers, gels, nanoparticulate systems, micro-particle systems, and injectable systems, made of chitosan, alginate, dextran, cellulose and other polysaccharides have recently been spotlighted on the recent advancements in preventing, treating and managing dental diseases and covered in detail in the current review. The development of biocompatible systems for sustained release of antimicrobials, the reduction of dose frequency, and the consequent reduction in the likelihood of bacterial resistance have all been made possible by the switch from non-biodegradable polymers like polysaccharides to a range of biodegradable polymers. It must be prepared to aid in the systemic elimination of antimicrobials-related adverse effects.

CRediT authorship contribution statement

Mousumi Paul, Siddhartha Das Pramanik and Rudra Narayan Sahoo contributed significantly and equally in the preparation of the manuscript and the literature review. Yadu Nandan Dey and Amit Kumar Nayak contributed in the generation of concept, literature search and

Table 5
Antimicrobial drugs releasing other polysaccharides-based systems for dental drug delivery.

Other polysaccharides-based systems	Antimicrobial drugs	Important features	References
Gellan gum-based mucoadhesive bilayer films	Moxifloxacin	• The process of synthesizing films involved the use of the double solvent casting method. The primary layer of the polysaccharide-based films was composed of gellan gum and contained moxifloxacin, while the secondary layer was composed of hydroxyethyl cellulose and contained clove oil. • Flexible, transparent, and high antimicrobial action against both Gram negative and positive bacteria. • An initial burst release and subsequently, sustained releasing of moxifloxacin for up to 48 h.	[151]
In situ gels made of gellan gum-based	Moxifloxacin HCl	• Formulated using gellan gum, poloxamer 407, and Carbopol 934P. • Augmented release of moxifloxacin from 7 to 12 h, *in vitro*, and the moxifloxacin release were found to be dependent on polymer used. • Antimicrobial activity against *Staphylococcus aureus*, and *Escherichia coli*.	[152]
Smart gel made of gellan gum	Ornidazole	• Prepared using ornidazole, lutrol F127, and gellan gum. • Sustained release of ornidazole with best-fitting of Korsemeyer-Peppas model. • *In vitro* ornidazole releasing was found to be significantly reduced as the polymer concentrations were increased in the gel formula.	[153]
Temperature-sensitive gellan gum-based *in situ* gel	Chlorhexidine HCl	• Formulated using gellan gum, Poloxamer 407, Poloxamer 188, and Carbopol 934P. • Sustained release of chlorhexidine HCl for 6 h period.	[154]
Low and high methoxyl pectin films	Metronidazole	• Prepared using 5 % metronidazole, 3 % pectin and 40 % glycerin. • Low methoxyl pectin films containing metronidazole exhibited an initial burst releasing and subsequently, a slower releasing pattern. • High methoxyl pectin films containing metronidazole exhibited an immediate release pattern. • Both the pectin-based films demonstrated the antibacterial activity against *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*.	[155]
PLGA/gum tragacanth nanofibers	Tetracycline HCl	• Prepared using gum tragacanth, PLGA, and tetracycline HCl by electrospinning. • A smooth morphology • Nanofiber was ranged in-between 180 and 460 nm. • Sustained tetracycline release for 75 days.	[156]
Xanthan gum-based gel	Chlorhexidine	• Better improvements as compared to the scaling and root planing group for probing depths and clinical attachment level at 3 and 6 months. • Greater reductions in the sites positive for 8 putative periodontopathic bacteria were generally noticed for the chlorhexidine-releasing xanthan gum-based gel treatment group compared to scaling and root planing alone.	[157]

revision of the manuscript. All authors of this manuscript have read and approved the manuscript for submission.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

I don't have problem in sharing data as it is a review article.

Acknowledgment

The authors are thankful to the Science and Engineering Research Board (SERB), and the Department of Science and Technology (Grant No. SRG/2021/001631) for providing the facilities for the completion of the research work. The authors are also thankful to the Director and Principal, Dr. B. C. Roy College of Pharmacy and Allied Health Sciences, Durgapur and President, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar 751030, Odisha, India for their encouragement of this work.

References

[1] G.N. Belibasakis, D. Belstrøm, S. Eick, U.K. Gursoy, A. Johansson, E. Könönen, Periodontal microbiology and microbial etiology of periodontal diseases: historical concepts and contemporary perspectives, Periodontol. (2023), https://doi.org/10.1111/prd.12473.
[2] A.K. Nayak, S. Mazumder, T.J. Ara, M.T. Ansari, M.S. Hasnain, Calcium fluoride-based dental nanocomposites, in: Inamuddin, A.M. Asiri, A. Mohammad (Eds.), Applications of Nanocomposite Materials in Dentistry, Woodhead Publishing Series in Biomaterials, Elsevier Inc., United States, 2019, pp. 27–45.

[3] S. Mazumder, A.K. Nayak, T.J. Ara, M.S. Hasnain, Hydroxyapatite composites for dentistry, in: Inamuddin, A.M. Asiri, A. Mohammad (Eds.), Applications of Nanocomposite Materials in Dentistry, Woodhead Publishing Series in Biomaterials, Elsevier Inc., United States, 2019, pp. 108–121.

[4] T. Higino, R. França, Drug-delivery nanoparticles for bone-tissue and dental applications, Biomed. Phys. Eng. Express 8 (4) (2022), https://doi.org/10.1088/2057-1976/ac682c.

[5] S. Nguyen, M. Hiorth, Advanced drug delivery systems for local treatment of the oral cavity, Ther. Deliv. 6 (5) (2015) 595–608, https://doi.org/10.4155/tde.15.5.

[6] P.K. Suresh, M.K. Dewangan, Development and *in vitro* characterization of metronidazole loaded chitosan microspheres for delivery to periodontal pocket, J. Appl. Pharm. Sci. (2011) 165–169.

[7] N. Jain, G.K. Jain, S. Javed, Z. Iqbal, S. Talegaonkar, F.J. Ahmad, R.K. Khar, Recent approaches for the treatment of periodontitis, Drug Discov. Today 13 (21−22) (2008) 932–943, https://doi.org/10.1016/j.drudis.2008.07.010.

[8] A. Ahuja, J. Ali, R. Sarkar, A. Shareef, R.K. Khar, Targeted retentive device for oro-dental infections: formulation and development, Int. J. Pharm. 259 (1–2) (2003) 47–55, https://doi.org/10.1016/s0378-5173(03)00204-7.

[9] M. Szulc, A. Zakrzewska, J. Zborowski, Local drug delivery in periodontitis treatment: a review of contemporary literature, Dent. Med. Probl. 55 (3) (2018) 333–342, https://doi.org/10.17219/dmp/94890.

[10] N. Li, L. Jiang, H. Jin, Y. Wu, Y. Liu, W. Huang, L. Wei, Q. Zhou, F. Chen, Y. Gao, B. Zhu, X. Zhang, An enzyme-responsive membrane for antibiotic drug release and local periodontal treatment, Colloids Surf. B: Biointerfaces 183 (2019), 110454, https://doi.org/10.1016/j.colsurfb.2019.110454.

[11] M. Chieruzzi, S. Pagano, S. Moretti, R. Pinna, E. Milia, L. Torre, S. Eramo, Nanomaterials for tissue engineering in dentistry, Nanomaterials (Basel). 6 (7) (2016) 134, https://doi.org/10.3390/nano6070134.

[12] P. Zhang, S. Wu, J. Li, X. Bu, X. Dong, N. Chen, F. Li, J. Zhu, L. Sang, Y. Zeng, S. Liang, Z. Yu, Z. Liu, Dual-sensitive antibacterial peptide nanoparticles prevent dental caries, Theranostics. 12 (10) (2022) 4818–4833, https://doi.org/10.7150/thno.73181.

[13] A. Manzoor, S. Khan, A.H. Dar, V.K. Pandey, R. Shams, S. Ahmad, G. Jeevarathinam, M. Kumar, P. Singh, R. Pandiselvam, Recent insights into green antimicrobial packaging towards food safety reinforcement: a review, J. Food Saf. (2023), e13046, https://doi.org/10.1111/jfs.13046.

[14] T. Majeed, A.H. Dar, V.K. Pandey, K.K. Dash, S. Srivastava, R. Shams, G. Jeevarathinam, P. Singh, N. Echegaray, R. Pandiselvam, Role of additives in starch-based edible films and coating: a review with current knowledge, Prog. Org. Coat. 181 (2023), 107597, https://doi.org/10.1016/j.porgcoat.2023.107597.

[15] A. Yadav, N. Kumar, A. Upadhyay, A. Singh, R.K. Anurag, R. Pandiselvam, Effect of mango kernel seed starch-based active edible coating functionalized with lemongrass essential oil on the shelf-life of guava fruit, Qual. Assur. Saf. Crop. Food. 14 (2022) 103–105, https://doi.org/10.15586/qas.v14i3.1094.

[16] K. Sharma, M. Kumar, R. Waghmare, R. Suhag, O.P. Gupta, J.M. Lorenzo, S. Prakash, Rais N. Radha, V. Sampathrajan, C. Thappa, T. Anitha, A.A.S. Sayed, B.A. Abdel-Wahab, M. Senapathy, R. Pandiselvam, A. Dey, S. Dhumal, R. Amarowicz, J.F. Kennedy, Moringa (*Moringa oleifera* Lam.) polysaccharides: extraction, characterization, bioactivities, and industrial application, Int. J. Biol. Macromol. 209 (2022) 763–778, https://doi.org/10.1016/j.ijbiomac.2022.04.047.

[17] U. Neog, P. Dhar, T. Kumari, C. Nickhil, S.C. Deka, R. Pandiselvam, Optimization of microwave-assisted process for extraction of phytochemicals from norabogori fruit (*Prunus persica* L. Batsch) and its application as fruit leather, Biomass Convers. Biorefin. 2023 (2023) 1–15, https://doi.org/10.1007/s13399-023-04035-w.

[18] M. Hamidi, O.V. Okoro, P.B. Milan, M.R. Khalili, H. Samadian, L. Nie, A. Shavandi, Fungal exopolysaccharides: Properties, sources, modifications, and biomedical applications, Carbohydr. Polym. 284 (2022), 119152, https://doi.org/10.1016/j.carbpol.2022.119152.

[19] P. Allawadhi, V. Singh, K. Govindaraj, I. Khurana, L.P. Sarode, U. Navik, A. K. Banothu, R. Weiskirchen, K.K. Bharani, A. Khurana, Biomedical applications of polysaccharide nanoparticles for chronic inflammatory disorders: Focus on rheumatoid arthritis, diabetes and organ fibrosis, Carbohydr. Polym. 281 (2022), 118923, https://doi.org/10.1016/j.carbpol.2021.118923.

[20] L. Bai, S. Huan, J. Gu, D.J. McClements, Fabrication of oil-in-water nanoemulsions by dual-channel microfluidization using natural emulsifiers: saponins, phospholipids, proteins, and polysaccharides, Food Hydrocoll. 61 (Dec 1 2016) 703–711, https://doi.org/10.1016/j.foodhyd.2016.06.035.

[21] A.K. Nayak, M.S. Hasnain, M. Tabis, T.M. Aminabhavi, Use of tailored polysaccharides in dentistry, in: A.K. Nayak, M.S. Hasnain, T.M. Aminabhavi (Eds.), Tailor-made Polysaccharides in Biomedical Applications, Academic Press, Elsevier Inc., USA, 2021, pp. 287–304.

[22] M.S. Hasnain, V. Kiran, M. Kurakula, G.S.N.K. Rao, M. Tabish, A.K. Nayak, Use of alginates for drug delivery in dentistry, in: A.K. Nayak, M.S. Hasnain (Eds.), Alginates in Drug Delivery, Academic Press, Elsevier Inc., United States, 2020, pp. 387–404.

[23] P. Katsarov, M. Shindova, P. Lukova, A. Belcheva, C. Delattre, B. Pilicheva, Polysaccharide-based micro- and nanosized drug delivery systems for potential application in the pediatric dentistry, Polymers (Basel). 13 (19) (2021) 3342, https://doi.org/10.3390/polym13193342.

[24] N. Baranov, M. Popa, L.I. Atanase, D.L. Ichim, Polysaccharide-based drug delivery systems for the treatment of periodontitis, Molecules. 26 (9) (2021) 2735, https://doi.org/10.3390/molecules26092735.

[25] S.P. Pilipchuk, A.B. Plonka, A. Monje, A.D. Taut, A. Lanis, B. Kang, W. V. Giannobile, Tissue engineering for bone regeneration and osseointegration in the oral cavity, Dent. Mater. 31 (4) (2015) 317–338, https://doi.org/10.1016/j.dental.2015.01.006.

[26] R. Eftekhar Ashtiani, M. Alam, S. Tavakolizadeh, K. Abbasi, The role of biomaterials and biocompatible materials in implant-supported dental prosthesis, Evid. Based Complement. Alternat. Med. 2021 (2021) 3349433, https://doi.org/10.1155/2021/3349433.

[27] V.P. Mathur, J.K. Dhillon, Dental caries: a disease which needs attention, Indian J. Pediatr. 85 (3) (2018) 202–206, https://doi.org/10.1007/s12098-017-2381-6.

[28] A. Elbourne, R.J. Crawford, E.P. Ivanova, Nano-structured antimicrobial surfaces: from nature to synthetic analogues, J. Colloid Interface Sci. 508 (2017) 603–616, https://doi.org/10.1016/j.jcis.2017.07.021.

[29] M.A. Nazir, Prevalence of periodontal disease, its association with systemic diseases and prevention, Int. J. Health Sci. (Qassim) 11 (2) (2017) 72–80.

[30] N. Arora, A. Mishra, S. Chugh, Microbial role in periodontitis: have we reached the top? Some unsung bacteria other than red complex, J. Indian Soc. Periodontol. 18 (1) (2014) 9–13, https://doi.org/10.4103/0972-124X.128192.

[31] M.A. Listgarten, Pathogenesis of periodontitis, J. Clin. Periodontol. 13 (5) (1986) 418–430.

[32] C.J. Seneviratne, C.F. Zhang, L.P. Samaranayake, Dental plaque biofilm in oral health and disease, Chin. J. Dent. Res. 14 (2) (2011) 87–94.

[33] Mehrotra N, Singh S. Periodontitis. StatPearls. Treasure Island (FL): StatPearls Publishing LLC.

[34] R. Saini, S. Saini, S. Sharma, Biofilm: a dental microbial infection, J. Nat. Sci. Biol. Med. 2 (1) (2011) 71–75, https://doi.org/10.4103/0976-9668.82317.

[35] G. Hajishengallis, T. Chavakis, J.D. Lambris, Current understanding of periodontal disease pathogenesis and targets for host-modulation therapy, Periodontol. 84 (1) (2020) 14–34, https://doi.org/10.1111/prd.12331.

[36] A. Cekici, A. Kantarci, H. Hasturk, T.E. Van Dyke, Inflammatory and immune pathways in the pathogenesis of periodontal disease, Periodontol. 64 (1) (2014) 57–80, https://doi.org/10.1111/prd.12002.

[37] T. Kwon, I.B. Lamster, L. Levin, Current concepts in the management of periodontitis, Int. Dent. J. 71 (6) (2021) 462–476, https://doi.org/10.1111/idj.12630.

[38] Pef Barzegar, R. Ranjbar, M. Yazdanian, E. Tahmasebi, M. Alam, K. Abbasi, H. Tebyaniyan, K. Esmaeili Fard Barzegar, The current natural/chemical materials and innovative technologies in periodontal diseases therapy and regeneration: a narrative review, Mater. Today Comm. 32 (2022), 104099.

[39] L. Chen, S. Hontsu, S. Komasa, E. Yamamoto, Y. Hashimoto, N. Matsumoto, Hydroxyapatite film coating by Er:YAG pulsed laser deposition method for the repair of enamel defects, Materials (Basel) 14 (23) (2021) 7475, https://doi.org/10.3390/ma14237475.

[40] A.K. Nayak, M.S. Hasnain, S.S. Nanda, D.K. Yi, Hydroxyapatite-alginate based matrices for drug delivery, Curr. Pharm. Des. 25 (31) (2019) 3406–3416, https://doi.org/10.2174/1381612825666190906164003.

[41] A.K. Nayak, M. Maity, H. Barik, S.S. Nanda, M.S. Hasnain, D.K. Yi, Hydroxyapatite-based composites for orthopedic drug delivery and tissue engineering, in: S. Ahamed (Ed.), Applications of Advanced Green Materials, Woodhead Publishing, Elsevier Inc., United States, 2021, pp. 293–361.

[42] J. Liao, J. Azelmat, L. Zhao, M. Yoshioka, D. Hinode, D. Grenier, The Kampo medicine Rokumigan possesses antibiofilm, anti-inflammatory, and wound healing properties, Biomed. Res. Int. 2014 (2014), 436206, https://doi.org/10.1155/2014/436206.

[43] M. Shahzad, E. Millhouse, S. Culshaw, C.A. Edwards, G. Ramage, E. Combet, Selected dietary (poly)phenols inhibit periodontal pathogen growth and biofilm formation, Food Funct. 6 (3) (2015) 719–729, https://doi.org/10.1039/c4fo01087f.

[44] J. Yang, Z. Zhou, Y. Wu, M. Nie, Study on the mechanism of curcumin in the treatment of periodontitis through network pharmacology and mole-cular docking, Hua Xi Kou Qiang Yi Xue Za Zhi 41 (2) (2023) 157–164, https://doi.org/10.7518/hxkq.2023.2022370 (English, Chinese).

[45] M. Souissi, J. Azelmat, K. Chaieb, D. Grenier, Antibacterial and anti-inflammatory activities of cardamom (Elettaria cardamomum) extracts: potential therapeutic benefits for periodontal infections, Anaerobe. 61 (2020), 102089, https://doi.org/10.1016/j.anaerobe.2019.102089.

[46] I. Borges, M. Faveri, L.C. Figueiredo, P.M. Duarte, B. Retamal-Valdes, S.C. L. Montenegro, M. Feres, Different antibiotic protocols in the treatment of severe chronic periodontitis: a 1-year randomized trial, J. Clin. Periodontol. 44 (8) (2017) 822–832, https://doi.org/10.1111/jcpe.12721.

[47] S.A. Mahuli, A.M. Zorair, M.A. Jafer, A. Sultan, G. Sarode, H.A. Baeshen, A.T. Raj, S. Sarode, S. Patil, Antibiotics for periodontal infections: biological and clinical perspectives, J. Contemp. Dent. Pract. 21 (4) (2020) 372–376.

[48] E. Haznedaroglu, E. Polat, Dental caries, dental erosion and periodontal disease in children with inflammatory bowel disease, Int. J. Med. Sci. 20 (5) (2023) 682–688, https://doi.org/10.7150/ijms.83075.

[49] W. Marcenes, N.J. Kassebaum, E. Bernabé, A. Flaxman, M. Naghavi, A. Lopez, C. J. Murray, Global burden of oral conditions in 1990-2010: a systematic analysis, J. Dent. Res. 92 (7) (2013) 592–597, https://doi.org/10.1177/0022034513490168.

[50] M. Martín-del-Campo, D. Fernández-Villa, G. Cabrera-Rueda, L. Rojo, Antibacterial bio-based polymers for cranio-maxillofacial regeneration applications, Appl. Sci. 10 (23) (2020) 8371.

[51] M. Erdem Büyükkiraz, Z. Kesmen, Antimicrobial peptides (AMPs): a promising class of antimicrobial compounds, J. Appl. Microbiol. 132 (3) (2022) 1573–1596, https://doi.org/10.1111/jam.15314.

[52] G. Wang, Y. Cui, H. Liu, Y. Tian, S. Li, Y. Fan, S. Sun, D. Wu, C. Peng, Antibacterial peptides-loaded bioactive materials for the treatment of bone infection, Colloids Surf. B: Biointerfaces 225 (2023), 113255, https://doi.org/10.1016/j.colsurfb.2023.113255.
[53] J. Lei, L. Sun, S. Huang, C. Zhu, P. Li, J. He, V. Mackey, D.H. Coy, Q. He, The antimicrobial peptides and their potential clinical applications, Am. J. Transl. Res. 11 (7) (2019) 3919–3931.
[54] A.D. Luong, A. Buzid, J.H.T. Luong, Important roles and potential uses of natural and synthetic antimicrobial peptides (AMPs) in oral diseases: cavity, periodontal disease, and thrush, J. Funct. Biomater. 13 (4) (2022) 175, https://doi.org/10.3390/jfb13040175.
[55] J.Y. Niu, I.X. Yin, W.K.K. Wu, Q.L. Li, M.L. Mei, C.H. Chu, Antimicrobial peptides for the prevention and treatment of dental caries: a concise review, Arch. Oral Biol. 122 (2021), 105022, https://doi.org/10.1016/j.archoralbio.2020.105022.
[56] D.G. Moussa, C. Aparicio, Targeting the oral plaque microbiome with immobilized anti-biofilm peptides at tooth-restoration interfaces, PLoS One 15 (7) (2020), e0235283, https://doi.org/10.1371/journal.pone.0235283.
[57] J. He, E. Söderling, M. Österblad, P.K. Vallittu, L.V. Lassila, Synthesis of methacrylate monomers with antibacterial effects against *S. mutans*, Molecules 16 (11) (2011) 9755–9763, https://doi.org/10.3390/molecules16119755.
[58] A. Abbaszadegan, Y. Ghahramani, A. Gholami, B. Hemmateenejad, S. Dorostkar, M. Nabavizadeh, H. Sharghi, The effect of charge at the surface of silver nanoparticles on antimicrobial activity against gram-positive and gram-negative bacteria: a preliminary study, J. Nanomater. 2015 (2015), 720654.
[59] L. Rojo, S. Deb, Polymer therapeutics in relation to dentistry, Front. Oral Biol. 17 (2015) 13–21, https://doi.org/10.1159/000381688.
[60] K. Markowitz, M. Moynihan, M. Liu, S. Kim, Biologic properties of eugenol and zinc oxide-eugenol. A clinically oriented review, Oral Surg. Oral Med. Oral Pathol. 73 (6) (1992) 729–737, https://doi.org/10.1016/0030-4220(92)90020-q.
[61] A. Manabe, S. Nakayama, K. Sakamoto, Effects of essential oils on erythrocytes and hepatocytes from rats and dipalmitoyl phosphatidylcholine-liposomes, Jpn. J. Pharmacol. 44 (1) (1987) 77–84, https://doi.org/10.1254/jjp.44.77.
[62] L. Rojo, A. Borzacchiello, J. Parra, S. Deb, B. Vázquez, Román J. San, The preparation of high conversion polymeric systems containing eugenol residues and their rheological characterization, J. Mater. Sci. Mater. Med. 19 (4) (2008) 1467–1477, https://doi.org/10.1007/s10856-007-3317-x.
[63] F. Li, M.D. Weir, H.H. Xu, Effects of quaternary ammonium chain length on antibacterial bonding agents, J. Dent. Res. 92 (10) (2013) 932–938, https://doi.org/10.1177/0022034513502053.
[64] D. Kwaśniewska, Y.L. Chen, D. Wieczorek, Biological activity of quaternary ammonium salts and their derivatives, Pathogens. 9 (6) (2020) 459, https://doi.org/10.3390/pathogens9060459.
[65] A. Frassetto, L. Breschi, G. Turco, G. Marchesi, R. Di Lenarda, F.R. Tay, D. H. Pashley, M. Cadenaro, Mechanisms of degradation of the hybrid layer in adhesive dentistry and therapeutic agents to improve bond durability—a literature review, Dent. Mater. 32 (2) (2016) e41–e53, https://doi.org/10.1016/j.dental.2015.11.007.
[66] G.J. Boelen, L. Boute, J. d'Hoop, M. EzEldeen, I. Lambrichts, G. Opdenakker, Matrix metalloproteinases and inhibitors in dentistry, Clin. Oral Investig. 23 (7) (2019) 2823–2835, https://doi.org/10.1007/s00784-019-02915-y.
[67] A.R.F. Castilho, C. Duque, P.F. Kreling, J.A. Pereira, A.B. Paula, M.A.C. Sinhoreti, R.M. Puppin-Rontani, Doxycycline-containing glass ionomer cement for arresting residual caries: an *in vitro* study and a pilot trial, J. Appl. Oral Sci. 26 (2018), e20170116, https://doi.org/10.1590/1678-7757-2017-0116.
[68] C.P. Fik, S. Konieczny, D.H. Pashley, C.J. Waschinski, R.S. Ladisch, U. Salz, T. Bock, J.C. Tiller, Telechelic poly(2-oxazoline)s with a biocidal and a polymerizable terminal as collagenase inhibiting additive for long-term active antimicrobial dental materials, Macromol. Biosci. 14 (11) (2014) 1569–1579, https://doi.org/10.1002/mabi.201400220.
[69] J.M. Antonucci, D.N. Zeiger, K. Tang, S. Lin-Gibson, B.O. Fowler, N.J. Lin, Synthesis and characterization of dimethacrylates containing quaternary ammonium functionalities for dental applications, Dent. Mater. 28 (2) (2012) 219–228, https://doi.org/10.1016/j.dental.2011.10.004.
[70] L. Huang, F. Yu, X. Sun, Y. Dong, P.T. Lin, H.H. Yu, Y.H. Xiao, Z.G. Chai, X. D. Xing, J.H. Chen, Antibacterial activity of a modified unfilled resin containing a novel polymerizable quaternary ammonium salt MAE-HB, Sci. Rep. 6 (2016) 33858, https://doi.org/10.1038/srep33858.
[71] K. Zhang, S. Wang, X. Zhou, H.H. Xu, M.D. Weir, Y. Ge, M. Li, S. Wang, Y. Li, X. Xu, L. Zheng, L. Cheng, Effect of antibacterial dental adhesive on multispecies biofilms formation, J. Dent. Res. 94 (4) (2015) 622–629, https://doi.org/10.1177/0022034515571416.
[72] C. Pesci-Bardon, T. Fosse, D. Serre, I. Madinier, In vitro antiseptic properties of an ammonium compound combined with denture base acrylic resin, Gerodontology. 23 (2) (2006) 111–116, https://doi.org/10.1111/j.1741-2358.2006.00088.x.
[73] S. Deb, R. Doiron, L. Disilvio, S. Punyani, H. Singh, PMMA bone cement containing a quaternary amine comonomer with potential antibacterial properties, J Biomed Mater Res B Appl Biomater 85 (1) (2008) 130–139, https://doi.org/10.1002/jbm.b.30925.
[74] M. Casarin, R.S. de Matos, Nolasco W. da Silva, F.Q. Pirih, F.W.M.G. Muniz, Effect of mouthwashes on gingival healing after surgical procedures: a systematic review, Eur. J. Oral Sci. (2023), e12931, https://doi.org/10.1111/eos.12931.
[75] C.A. Bellis, A.H. Nobbs, D.J. O'Sullivan, J.A. Holder, M.E. Barbour, Glass ionomer cements functionalised with a concentrated paste of chlorhexidine hexametaphosphate provides dose-dependent chlorhexidine release over at least 14 months, J. Dent. 45 (2016) 53–58, https://doi.org/10.1016/j.jdent.2015.12.009.
[76] Y. Kamarudin, M.K. Skeats, A.J. Ireland, M.E. Barbour, Chlorhexidine hexametaphosphate as a coating for elastomeric ligatures with sustained antimicrobial properties: a laboratory study, Am. J. Orthod. Dentofac. Orthop. 158 (5) (2020) e73–e82, https://doi.org/10.1016/j.ajodo.2020.07.027.
[77] D.M. Dos Santos, P.A.M. Chagas, I.S. Leite, N.M. Inada, S.R. de Annunzio, C. R. Fontana, S.P. Campana-Filho, D.S. Correa, Core-sheath nanostructured chitosan-based nonwovens as a potential drug delivery system for periodontitis treatment, Int. J. Biol. Macromol. 142 (2020) 521–534, https://doi.org/10.1016/j.ijbiomac.2019.09.124.
[78] H. Gao, N. Wu, N. Wang, J. Li, J. Sun, Q. Peng, Chitosan-based therapeutic systems and their potentials in treatment of oral diseases, Int. J. Biol. Macromol. 222 (Pt B) (2022) 3178–3194, https://doi.org/10.1016/j.ijbiomac.2022.10.090.
[79] D. Zhang, Y. Tang, J. Yang, Y. Gao, C. Ma, L. Che, J. Wang, J. Wu, J. Zheng, *De novo* design of allochroic zwitterions, Mater. Today 60 (2022) 17–30, https://doi.org/10.1016/j.mattod.2022.09.001.
[80] Y. Yang, J. Yuan, Y. Ni, Y. Gu, J. Zhou, W. Yuan, S. Xu, L. Che, S.Y. Zheng, W. Sun, D. Zhang, J. Yang, Spatiotemporal self-strengthening hydrogels for oral tissue regeneration, Compos. B Eng. 243 (2022), 110119, https://doi.org/10.1016/j.compositesb.2022.110119.
[81] M. Samiei, E. Dalir Abdollahinia, N. Amiryaghoubi, M. Fathi, J. Barar, Y. Omidi, Injectable thermosensitive chitosan/gelatin hydrogel for dental pulp stem cells proliferation and differentiation, Bioimpacts. 13 (1) (2023) 63–72, https://doi.org/10.34172/bi.2022.23904.
[82] W. Talaat, S. Aryal Ac, S. Al Kawas, A.B.R. Samsudin, N.G. Kandile, D.R. K. Harding, M.M. Ghoneim, W. Zeiada, J. Jagal, A. Aboelnaga, M. Haider, Nanoscale thermosensitive hydrogel scaffolds promote the chondrogenic differentiation of dental pulp stem and progenitor cells: a minimally invasive approach for cartilage regeneration, Int. J. Nanomedicine 15 (2020) 7775–7789, https://doi.org/10.2147/IJN.S274418.
[83] X. Xu, Z. Gu, X. Chen, C. Shi, C. Liu, M. Liu, L. Wang, M. Sun, K. Zhang, Q. Liu, Y. Shen, C. Lin, B. Yang, H. Sun, An injectable and thermosensitive hydrogel: promoting periodontal regeneration by controlled-release of aspirin and erythropoietin, Acta Biomater. 86 (2019) 235–246, https://doi.org/10.1016/j.actbio.2019.01.001.
[84] D. Zhang, Y. Tang, K. Zhang, Y. Xue, S.Y. Zheng, B. Wu, J. Zheng, Multiscale bilayer hydrogels enabled by macrophase separation, Matter. 6 (2023) 1484–1502, https://doi.org/10.1016/j.matt.2023.02.011.
[85] G. Di Turi, C. Riggio, O. Vittorio, S. Marconcini, F. Briguglio, N. Funel, D. Campani, A. Barone, V. Raffa, U. Covani, Sub-micrometric liposomes as drug delivery systems in the treatment of periodontitis, Int. J. Immunopathol. Pharmacol. 25 (3) (2012) 657–670, https://doi.org/10.1177/039463201202500312.
[86] Y. Leng, Q. Hu, Q. Ling, X. Yao, M. Liu, J. Chen, Z. Yan, Q. Dai, Periodontal disease is associated with the risk of cardiovascular disease independent of sex: a meta-analysis, Front. Cardiovasc. Med. 10 (2023) 1114927, https://doi.org/10.3389/fcvm.2023.1114927.
[87] X. Xiong, P. Buekens, W.D. Fraser, J. Beck, S. Offenbacher, Periodontal disease and adverse pregnancy outcomes: a systematic review, BJOG. 113 (2) (2006) 135–143, https://doi.org/10.1111/j.1471-0528.2005.00827.x.
[88] R.T. Demmer, D.R. Jacobs Jr., M. Desvarieux, Periodontal disease and incident type 2 diabetes: results from the first national health and nutrition examination survey and its epidemiologic follow-up study, Diabetes Care 31 (7) (2008) 1373–1379, https://doi.org/10.2337/dc08-0026.
[89] A.C. Chi, B.W. Neville, J.W. Krayer, W.C. Gonsalves, Oral manifestations of systemic disease, Am. Fam. Physician 82 (2010) 1382–1388.
[90] S. Jagga, M.S. Hasnain, A.K. Nayak, Chitosan-based scaffolds in tissue engineering and regenerative medicine, in: M.S. Hasnain, S. Beg, A.K. Nayak (Eds.), Chitosan in Biomedical Application, Academic Press, Elsevier Inc., United States, 2022, pp. 329–354.
[91] S. Roy, T. Chakraborty, J. Begum, M.S. Hasnain, A.K. Nayak, Chitosan: a versatile biopolymer, in: M.S. Hasnain, S. Beg, A.K. Nayak (Eds.), Chitosan in Biomedical Applications, Academic Press, Elsevier Inc., United States, 2022, pp. 1–11.
[92] A.K. Azad, T. Bhattacharya, M.S. Hasnain, G. Tripathi, A.K. Nayak, Chitin- and chitosan-based nanomaterials for therapeutic applications, in: M.S. Hasnain, A. K. Nayak, T.M. Aminabhavi (Eds.), Polymeric Nanosystems, Theranostic Nanosystems, Academic Press, Vol. 1, Elsevier Inc., United States, 2023, pp. 173–205.
[93] A. Bernkop-Schnürch, S. Dünnhaupt, Chitosan-based drug delivery systems, Eur. J. Pharm. Biopharm. 81 (3) (2012) 463–469.
[94] S. Padhi, A. Behera, M.S. Hasnain, A.K. Nayak, Uses of chitosan in drug delivery, in: M.S. Hasnain, S. Beg, A.K. Nayak (Eds.), Chitosan in Biomedical Applications, Academic Press, Elsevier Inc., United States, 2022, pp. 139–162.
[95] P. Perugini, I. Genta, B. Conti, T. Modena, F. Pavanetto, Periodontal delivery of ipriflavone: new chitosan/PLGA film delivery system for a lipophilic drug, Int. J. Pharm. 252 (1–2) (2003) 1–9, https://doi.org/10.1016/s0378-5173(02)00602-6.
[96] P. Giunchedi, C. Juliano, E. Gavini, M. Cossu, M. Sorrenti, Formulation and in vivo evaluation of chlorhexidine buccal tablets prepared using drug-loaded chitosan microspheres, Eur. J. Pharm. Biopharm. 53 (2) (2002) 233–239, https://doi.org/10.1016/s0939-6411(01)00237-5.
[97] S. Gjoseva, N. Geskovski, S.D. Sazdovska, R. Popeski-Dimovski, G. Petruševski, K. Mladenovska, K. Goracinova, Design and biological response of doxycycline loaded chitosan microparticles for periodontal disease treatment, Carbohydr. Polym. 186 (2018) 260–272, https://doi.org/10.1016/j.carbpol.2018.01.043.
[98] D.M. Dos Santos, P.A.M. Chagas, I.S. Leite, N.M. Inada, S.R. de Annunzio, C. R. Fontana, S.P. Campana-Filho, D.S. Correa, Core-sheath nanostructured chitosan-based nonwovens as a potential drug delivery system for periodontitis

treatment, Int. J. Biol. Macromol. 142 (2020) 521–534, https://doi.org/10.1016/j.ijbiomac.2019.09.124.
[99] R.J. Dias, V.D. Havaldar, V.S. Ghorpade, K.K. Mali, V.K. Gaikwad, D.M. Kumbhar, Development and evaluation of *in-situ* gel containing ornidazole loaded microspheres for treatment of periodontitis, J. Appl. Pharm. Sci. 6 (2016) 200–209.
[100] S. Govender, V. Pillay, D.J. Chetty, S.Y. Essack, C.M. Dangor, T. Govender, Optimisation and characterisation of bioadhesive controlled release tetracycline microspheres, Int. J. Pharm. 306 (1–2) (2005) 24–40, https://doi.org/10.1016/j.ijpharm.2005.07.026.
[101] M. Kilicarslan, M. Ilhan, O. Inal, K. Orhan, Preparation and evaluation of clindamycin phosphate loaded chitosan/alginate polyelectrolyte complex film as mucoadhesive drug delivery system for periodontal therapy, Eur. J. Pharm. Sci. 123 (2018) 441–451, https://doi.org/10.1016/j.ejps.2018.08.007.
[102] G. Khan, S.K. Yadav, R.R. Patel, G. Nath, M. Bansal, B. Mishra, Development and evaluation of biodegradable chitosan films of metronidazole and levofloxacin for the management of periodontitis, AAPS PharmSciTech 17 (6) (2016) 1312–1325, https://doi.org/10.1208/s12249-015-0466-y.
[103] A.A. Kassem, F.A. Ismail, V.F. Naggar, E. Aboulmagd, Preparation and evaluation of periodontal films based on polyelectrolyte complex formation, Pharm. Dev. Technol. 20 (3) (2015) 297–305, https://doi.org/10.3109/10837450.2013.862262.
[104] M.M. Mahmoud, W.M. Samy, Enhanced periodontal regeneration by novel single application sustained release nano-structured doxycycline films, Curr. Drug Deliv. 13 (6) (2016) 899–908, https://doi.org/10.2174/1567201813666151113122752.
[105] M. Kilicarslan, M. Gumustas, S. Yildiz, T. Baykara, Preparation and characterization of chitosan-based spray-dried microparticles for the delivery of clindamycin phosphate to periodontal pockets, Curr Drug Deliv. 11 (1) (2014) 98–111, https://doi.org/10.2174/15672018113109990055.
[106] R. Barat, A. Srinatha, J.K. Pandit, S. Anupurba, N. Mittal, Chitosan inserts for periodontitis: influence of drug loading, plasticizer and crosslinking on *in vitro* metronidazole release, Acta Pharma. 57 (4) (2007) 469–477, https://doi.org/10.2478/v10007-007-0037-1.
[107] R. Sheshala, S.Y. Quah, G.C. Tan, V.S. Meka, N. Jnanendrappa, P.S. Sahu, Investigation on solution-to-gel characteristic of thermosensitive and mucoadhesive biopolymers for the development of moxifloxacin-loaded sustained release periodontal *in situ* gels, Drug Deliv. Transl. Res. 9 (2) (2019) 434–443, https://doi.org/10.1007/s13346-018-0488-6.
[108] W. Pichayakorn, P. Boonme, Evaluation of cross-linked chitosan microparticles containing metronidazole for periodontitis treatment, Mater. Sci. Eng. C Mater. Biol. Appl. 33 (3) (2013) 1197–1202, https://doi.org/10.1016/j.msec.2012.12.010.
[109] B.S. Lee, C.C. Lee, Y.P. Wang, H.J. Chen, C.H. Lai, W.L. Hsieh, Y.W. Chen, Controlled-release of tetracycline and lovastatin by poly(D,L-lactide-co-glycolide acid)-chitosan nanoparticles enhances periodontal regeneration in dogs, Int. J. Nanomedicine 11 (2016) 285–297.
[110] A. Kanwal, A. Iqbal, R. Arshad, S. Akhtar, S. Razzaq, N.M. Ahmad, H. Naz, G. Shahnaz, Formulation and evaluation of novel thiolated intra pocket periodontal composite membrane of doxycycline, AAPS PharmSciTech 20 (8) (2019) 325, https://doi.org/10.1208/s12249-019-1536-3.
[111] H. Gao, K. Ge, Y. Xu, Y. Wang, M. Lu, Y. Wei, Q. Zhu, X. Han, Q. Huang, Z. Cao, Controlled release of minocycline in hydroxyapatite/chitosan composite for periodontal bone defect repair, Dent. Mater. J. 41 (3) (2022) 346–352, https://doi.org/10.4012/dmj.2021-217.
[112] Š. Zupančič, L. Casula, T. Rijavec, A. Lapanje, M. Luštrik, A.M. Fadda, P. Kocbek, J. Kristl, Sustained release of antimicrobials from double-layer nanofiber mats for local treatment of periodontal disease, evaluated using a new micro flow-through apparatus, J. Control. Release 316 (2019) 223–235, https://doi.org/10.1016/j.jconrel.2019.10.008.
[113] Š. Zupančič, T. Potrč, S. Baumgartner, P. Kocbek, J. Kristl, Formulation and evaluation of chitosan/polyethylene oxide nanofibers loaded with metronidazole for local infections, Eur. J. Pharm. Sci. 95 (2016) 152–160, https://doi.org/10.1016/j.ejps.2016.10.030.
[114] R. Ganpisetti, A. Lalatsa, Cellulose bio–ink on 3D printing applications, J. Young Pharm. 13 (1) (2021) 1.
[115] K.B.R. Teodoro, R.C. Sanfelice, F.L. Migliorini, A. Pavinatto, M.H.M. Facure, D. S. Correa, A review on the role and performance of cellulose nanomaterials in sensors, ACS Sens. 6 (7) (2021) 2473–2496, https://doi.org/10.1021/acssensors.1c00473.
[116] G.S. Labib, H.M. Aldawsari, S.M. Badr-Eldin, Metronidazole and Pentoxifylline films for the local treatment of chronic periodontal pockets: preparation, *in vitro* evaluation and clinical assessment, Expert. Opin. Drug Deliv. 11 (6) (2014) 855–865, https://doi.org/10.1517/17425247.2014.897325.
[117] A. Fini, V. Bergamante, G.C. Ceschel, Mucoadhesive gels designed for the controlled release of chlorhexidine in the oral cavity, Pharmaceutics. 3 (4) (2011) 665–679, https://doi.org/10.3390/pharmaceutics3040665.
[118] A. Aslani, N. Malekpour, Design, formulation, and physicochemical evaluation of periodontal propolis mucoadhesive gel, Dent. Res. J. (Isfahan) 13 (6) (2016) 484–493, https://doi.org/10.4103/1735-3327.197037.
[119] N. Hirun, V. Tantishaiyakul, T. Sangfai, P. Ouiyangkul, L. Li, *In situ* mucoadhesive hydrogel based on methylcellulose/xyloglucan for periodontitis, J. Sol-Gel Sci. Tech. 89 (2020) 531–542.
[120] B.S. Inoue, S. Streit, A.L. Dos Santos Schneider, M.M. Meier, Bioactive bacterial cellulose membrane with prolonged release of chlorhexidine for dental medical application, Int. J. Biol. Macromol. 148 (2020) 1098–1108, https://doi.org/10.1016/j.ijbiomac.2020.01.036.
[121] T. Phaechamud, J. Mahadlek, Solvent exchange-induced *in situ* forming gel comprising ethyl cellulose-antimicrobial drugs, Int. J. Pharm. 494 (1) (2015) 381–392, https://doi.org/10.1016/j.ijpharm.2015.08.047.
[122] A. Johnson, F. Kong, S. Miao, H.V. Lin, S. Thomas, Y.C. Huang, Z.L. Kong, Therapeutic effects of antibiotics loaded cellulose nanofiber and κ-carrageenan oligosaccharide composite hydrogels for periodontitis treatment, Sci. Rep. 10 (1) (2020) 18037, https://doi.org/10.1038/s41598-020-74845-9.
[123] A. Johnson, J.L. He, F. Kong, Y.C. Huang, S. Thomas, H.V. Lin, Z.L. Kong, Surfactin-loaded κ-carrageenan oligosaccharides entangled cellulose nanofibers as a versatile vehicle against periodontal pathogens, Int. J. Nanomedicine 15 (2020) 4021–4047, https://doi.org/10.2147/IJN.S238476.
[124] G.S. Labib, H.M. Aldawsari, S.M. Badr-Eldin, Metronidazole and pentoxifylline films for the local treatment of chronic periodontal pockets: preparation, *in vitro* evaluation and clinical assessment, Expert. Opin. Drug Deliv. 11 (6) (2014) 855–865, https://doi.org/10.1517/17425247.2014.897325.
[125] O. Tarawneh, I. Hamadneh, R. Huwaitat, A.R. Al-Assi, A. El Madani, Characterization of chlorhexidine-impregnated cellulose-based hydrogel films intended for the treatment of periodontitis, Biomed. Res. Int. 2021 (2021) 9853977, https://doi.org/10.1155/2021/9853977.
[126] A.S. Sallam, F.F. Hamudi, E.A. Khalil, Effect of ethylcellulose and propylene glycol on the controlled-release performance of glyceryl monooleate-mertronidazole periodontal gel, Pharm. Dev. Technol. 20 (2) (2015) 159–168, https://doi.org/10.3109/10837450.2013.852573.
[127] M.P. Venkatesh, T.M. Kumar, B.S. Avinash, G.S. Kumar, Development, *in vitro* and *in vivo* evaluation of novel injectable smart gels of azithromycin for chronic periodontitis, Curr. Drug Deliv. 10 (2) (2013) 188–197, https://doi.org/10.2174/1567201811310020005.
[128] V. Parthasarathy, R. Manavalan, R. Mythili, C.T. Siby, M. Jeya, Ethyl cellulose and polyethylene glycol-based sustained-release sparfloxacin chip: an alternative therapy for advanced periodontitis, Drug Dev. Ind. Pharm. 28 (7) (2002) 849–862, https://doi.org/10.1081/ddc-120005631.
[129] G. Vidal-Romero, V. Rocha-Pérez, M.L. Zambrano-Zaragoza, A. Del Real, L. Martínez-Acevedo, M.J. Galindo-Pérez, D. Quintanar-Guerrero, Development and characterization of pH-dependent cellulose acetate phthalate nanofibers by electrospinning technique, Nanomaterials (Basel) 11 (12) (2021) 3202, https://doi.org/10.3390/nano11123202.
[130] G. Vidal-Romero, M.L. Zambrano-Zaragoza, L. Martínez-Acevedo, G. Leyva-Gómez, S.E. Mendoza-Elvira, D. Quintanar-Guerrero, Design and evaluation of pH-dependent nanosystems based on cellulose acetate phthalate, nanoparticles loaded with chlorhexidine for periodontal treatment, Pharmaceutics. 11 (11) (2019) 604, https://doi.org/10.3390/pharmaceutics11110604.
[131] M.S. Hasnain, E. Jameel, B. Mohanta, A.K. Dhara, S. Alkahtani, A.K. Nayak, Alginates: sources, structure, and properties, in: A.K. Nayak, M.S. Hasnain (Eds.), Alginates in Drug Delivery, Academic Press, Elsevier Inc., United States, 2020, pp. 1–17.
[132] A.K. Nayak, B.C. Mohanta, M.S. Hasnain, M.N. Hoda, G. Tripathi, Alginate-based scaffolds for drug delivery in tissue engineering, in: A.K. Nayak, M.S. Hasnain (Eds.), Alginates in Drug Delivery, Academic Press, Elsevier Inc., United States, 2020, pp. 359–386.
[133] R.A. Sharif, K.M. Abdelaziz, N.M. Alshahrani, F.S. Almutairi, M.A. Alaseri, H. L. Abouzeid, M.F.A. Elagib, The accuracy of gypsum casts obtained from the disinfected extended-pour alginate impressions through prolonged storage times, BMC Oral Health. 21 (1) (2021) 296, https://doi.org/10.1186/s12903-021-01649-2.
[134] M. Scholz, T. Reske, F. Böhmer, A. Hornung, N. Grabow, H. Lang, In vitro chlorhexidine release from alginate based microbeads for periodontal therapy, PLoS One 12 (10) (2017), e0185562, https://doi.org/10.1371/journal.pone.0185562.
[135] S.F. Lan, T. Kehinde, X. Zhang, S. Khajotia, D.W. Schmidtke, B. Starly, Controlled release of metronidazole from composite poly-ε-caprolactone/alginate (PCL/alginate) rings for dental implants, Dent. Mater. 29 (6) (2013) 656–665, https://doi.org/10.1016/j.dental.2013.03.014.
[136] Y.J. Park, J.Y. Lee, H.R. Yeom, K.H. Kim, S.C. Lee, I.K. Shim, C.P. Chung, S.J. Lee, Injectable polysaccharide microcapsules for prolonged release of minocycline for the treatment of periodontitis, Biotechnol. Lett. 27 (22) (2005) 1761–1766, https://doi.org/10.1007/s10529-005-3550-7.
[137] J.A. Prakash, T.S. Kumar, K.S. Venkataprasanna, R.R. Niranjan, M. Kaushik, D. B. Samal, G.D. Venkatasubbu, PVA/alginate/hydroxyapatite films for controlled release of amoxicillin for the treatment of periodontal defects, Appl. Surf. Sci. 495 (2019), 143543.
[138] M. Zussman, M. Zilberman, Injectable metronidazole-eluting gelatin-alginate hydrogels for local treatment of periodontitis, J. Biomater. Appl. 37 (1) (2022) 166–179, https://doi.org/10.1177/08853282221079458.
[139] A.J. Pulate, D.R. Shendge, S. Pandit, P. Sonyabapu, Shinde, V. Pathare, Design and development of clindamycin film for periodontal disease 32 (3) (2021) 3307–3317.
[140] A. Ariyana, D. Sinurat, I. Ervina, H. Bangun, Formulation and *in vitro* evaluation of alginate based metronidazole periodontal gel, Asian J. Pharm. Clin. Res. 7 (2013) 224–228.
[141] A.A. Obaidat, R.M. Altamimi, M.M. Hammad, Formulation and release of doxycycline HCL from an ion activated *in situ* gelling delivery system for the treatment of periodontal disease, J. Appl. Polym. Sci. 115 (2010) 811–816.

[142] F. Shafiei, M. Ghavami-Lahiji, T.S. Jafarzadeh Kashi, F. Najafi, Drug release kinetics and biological properties of a novel local drug carrier system, Dent Res J (Isfahan). 18 (2021) 94, https://doi.org/10.4103/1735-3327.330875.
[143] D.Z. Liu, W.P. Chen, C.P. Lee, S.L. Wu, Y.C. Wang, T.W. Chung, Effects of alginate coated on PLGA microspheres for delivery tetracycline hydrochloride to periodontal pockets, J. Microencapsul. 21 (6) (2004) 643–652, https://doi.org/10.1080/02652040400000512.
[144] K. Madhumathi, L. Rekha, T.S. Kumar, Tailoring antibiotic release for the treatment of periodontal infrabony defects using bioactive gelatin-alginate/apatite nanocomposite films, J. Drug Deliv. Sci. Technol. 43 (2018) 57–64.
[145] M. Yan, Y. Pan, S. Lu, X. Li, D. Wang, T. Shao, Z. Wu, Q. Zhou, Chitosan-CaP microflowers and metronidazole loaded calcium alginate sponges with enhanced antibacterial, hemostatic and osteogenic properties for the prevention of dry socket after tooth removal, Int. J. Biol. Macromol. 212 (2022) 134–145, https://doi.org/10.1016/j.ijbiomac.2022.05.094.
[146] A.R. Petrovici, M. Pinteala, N. Simionescu, Dextran formulations as effective delivery systems of therapeutic agents, Molecules. 28 (3) (2023) 1086, https://doi.org/10.3390/molecules28031086.
[147] Q. Hu, Y. Lu, Y. Luo, Recent advances in dextran-based drug delivery systems: from fabrication strategies to applications, Carbohydr. Polym. 264 (2021), 117999, https://doi.org/10.1016/j.carbpol.2021.117999.
[148] F.M. Chen, Y.M. Zhao, H. Wu, Z.H. Deng, Q.T. Wang, W. Zhou, Q. Liu, G.Y. Dong, K. Li, Z.F. Wu, Y. Jin, Enhancement of periodontal tissue regeneration by locally controlled delivery of insulin-like growth factor-I from dextran-co-gelatin microspheres, J. Control. Release 114 (2) (2006) 209–222, https://doi.org/10.1016/j.jconrel.2006.05.014.
[149] L. Wu, W. Chen, F. Li, B.R. Morrow, F. Garcia-Godoy, L. Hong, Sustained release of minocycline from minocycline-calcium-dextran sulfate complex microparticles for periodontitis treatment, J. Pharm. Sci. 107 (12) (2018) 3134–3142, https://doi.org/10.1016/j.xphs.2018.08.023.
[150] X. Zhao, Y. Yang, J. Yu, R. Ding, D. Pei, Y. Zhang, G. He, Y. Cheng, A. Li, Injectable hydrogels with high drug loading through B-N coordination and ROS-triggered drug release for efficient treatment of chronic periodontitis in diabetic rats, Biomaterials. 282 (2022), 121387, https://doi.org/10.1016/j.biomaterials.2022.121387.
[151] A. Li, I.N. Khan, I.U. Khan, A.M. Yousaf, Y. Shahzad, Gellan gum-based bilayer mucoadhesive films loaded with moxifloxacin hydrochloride and clove oil for possible treatment of periodontitis, Drug Des. Dev. Ther. 15 (2021) 3937–3952, https://doi.org/10.2147/DDDT.S328722.
[152] G.P. Swain, S. Patel, J. Gandhi, P. Shah, Development of moxifloxacin hydrochloride loaded *in-situ* gel for the treatment of periodontitis: *In-vitro* drug release study and antibacterial activity, J. Oral Biol. Craniofac. Res. 9 (3) (2019) 190–200, https://doi.org/10.1016/j.jobcr.2019.04.001.
[153] M.R. Dabhi, S.A. Nagori, M.C. Gohel, R.K. Parikh, N.R. Sheth, Formulation development of smart gel periodontal drug delivery system for local delivery of chemotherapeutic agents with application of experimental design, Drug Deliv. 17 (7) (2010) 520–531, https://doi.org/10.3109/10717544.2010.490247.
[154] K. Garala, P. Joshi, M. Shah, A. Ramkishan, J. Patel, Formulation and evaluation of periodontal in situ gel, Int. J. Pharm. Investig. 3 (1) (2013) 29–41, https://doi.org/10.4103/2230-973X.108961.
[155] T. Junmahasathien, P. Panraksa, P. Protiarn, D. Hormdee, R. Noisombut, N. Kantrong, P. Jantrawut, Preparation and evaluation of metronidazole-loaded pectin films for potentially targeting a microbial infection associated with periodontal disease, Polymers (Basel) 10 (9) (2018) 1021, https://doi.org/10.3390/polym10091021.
[156] M. Ranjbar-Mohammadi, M. Zamani, M.P. Prabhakaran, S.H. Bahrami, S. Ramakrishna, Electrospinning of PLGA/gum tragacanth nanofibers containing tetracycline hydrochloride for periodontal regeneration, Mater. Sci. Eng. C Mater. Biol. Appl. 58 (Jan 1 2016) 521–531, https://doi.org/10.1016/j.msec.2015.08.066.
[157] M. Paolantonio, S. D'Ercole, A. Pilloni, D. D'Archivio, L. Lisanti, F. Graziani, B. Femminella, G. Sammartino, L. Perillo, S. Tetè, G. Perfetti, G. Spoto, R. Piccolomini, G. Perinetti, Clinical, microbiologic, and biochemical effects of subgingival administration of a xanthan-based chlorhexidine gel in the treatment of periodontitis: a randomized multicenter trial, J. Periodontol. 80 (9) (2009) 1479–1492, https://doi.org/10.1902/jop.2009.090050.
[158] N.M. Munot, K.N. Gujar, Orodental delivery systems: an overview, Int J Pharm Pharm Sci 5 (3) (2013) 74–83.
[159] T.H. Stanley, M.A. Ashburn, Novel delivery systems: oral transmucosal and intranasal transmucosal, J. Pain Symp. Mgt. 7 (3) (1992) 163–171.
[160] J. Kim, S. Kim, D. Son, M. Shin, Phenol–hyaluronic acid conjugates: correlation of oxidative crosslinking pathway and adhesiveness, Polymers. 13 (18) (2021) 3130.
[161] M. Luo, X. Zhang, J. Wu, J. Zhao, Modifications of polysaccharide-based biomaterials under structure-property relationship for biomedical applications, Carbohydr. Polym. 266 (2021), 118097.
[162] B. Imre, L. García, D. Puglia, F. Vilaplana, Reactive compatibilization of plant polysaccharides and biobased polymers: Review on current strategies, expectations and reality, Carbohydr. Polym. 209 (2019) 20–37.