IEJ
Iranian Endodontic Journal

Pivotal Local Drug Delivery Systems in Endodontics; A Review of Literature

Fereshteh Shahri [a], **Ardavan Parhizkar** [b*]

[a] Dental Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [b] Iranian Center for Endodontic Research, Research Institute of Dental Sciences, Dental School, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article Type: **Review Article**

Received: 26 Nov 2019
Revised: 05 Mar 2020
Accepted: 19 Mar 2020
Doi: *10.22037/iej.v15i2.30374*

**Corresponding author*: Ardavan Parhizkar, ICER, Research Institute of Dental Sciences, Shahid Beheshti University of Medical Sciences, Daneshjoo Blvd., Daneshgah Square, Velenjak, Shahid Chamran Highway, Tehran, Iran. Postal code: 19839-63113

Tel: +98-21 22413897
E-mail: aparhizkar@sbmu.ac.ir

ABSTRACT

Endodontic pathosis is preliminary caused by bacteria and their by-products that interact with pulpal and periradicular host tissues. The purge of the root canal system (RCS) from bacteria is a necessity for successful endodontic treatment. Different approaches have been considered to reduce the number of microorganisms and confront microbiota in the radicular area; namely chemomechanical preparation and intracanal medication. However, various studies have shown that, due to the intricate anatomy of RCS, bacteria can persist in distant areas and significantly decrease the degree of success in endodontic ministrations. Thereby, elimination of bacteria remains a challenge, specifically from the infectious root canals. In recent years, local drug delivery systems (LDDS), loaded with drugs and/or antibacterial agents, have been deliberated for the removal of microorganisms or as a medicinal adjunct to mechanical instrumentation. Owing to the resistant species and complexities in the structure of root canals, it seems that LDDS may be able to closely affect microorganisms and improve the success rate of endodontic treatment. Furthermore, they are capable of limiting drugs to RCS, and can achieve a more effective therapeutic dose/concentration in the target site. Furthermore, and due to successful outcomes, administration of LDDS has also been given great attention for regenerative purposes. Micro/nanoparticles, liposomes, nanofibers, sealers and so forth represent typical delivery systems used for endodontic treatments. This study addresses pivotal LDDS used in endodontics and their applications.

Keywords: Bacteria; Endodontics; Local Drug Delivery; Microorganism; Root Canal System

Introduction

In recent years, local drug delivery systems (LDDS), as a novel mean of transferring medicinal drugs to different target sites, have been vastly studied. LDDS have shown to possess different properties, and been used in various applications; from central nervous system (CNS) diseases to oral infections [1]. In comparison with systemic drug administration methods, LDDS have demonstrated ability to limit the drug/agent to its desired organ/tissue (target drug delivery) and help provide an enhanced therapeutic concentration of the agent (controlled drug delivery). Furthermore, it seems that LDDS can reduce medicinal adverse effects via lowering the unwanted high systemic dose of the drug [2].

In medicine, LDDS have been used in the treatments of different conditions; including cancer [3], ocular diseases [4] and some CNS maladies such as Alzheimer's disease [5]. Following successful outcomes in medicine, LDDS were used in dentistry for the local treatment of periodontitis [6], oral candidiasis [7], oral cancer [8], and endodontic ministrations [9]. In 1979, Goodson *et al.* [10] reported local administration of antibacterial agents via fibers as a local delivery system for the treatment of periodontal pockets. Since then, the applications of LDDS have grown in other branches of dentistry, *i.e.* operative dentistry [11], oral and maxillofacial surgery [12] and endodontics [13].

Dental caries, as one of the most dominant chronic diseases, has shown to cause pain, and if not treated, end in tooth loss [14]. LDDS can maintain anti-caries agents on tooth surfaces through the

sustained release of the drug(s). Consequently, different types of delivery systems, specifically liposomes and particles, have been used to locally deliver antibiotics for the prevention and possible treatment of caries. Moreover, dental restorative materials, when reinforced with LDDS, have demonstrated potential for prevention of secondary caries and tooth-pulp stimulation [11].

Local drug delivery systems have had promising uses in oral and maxillofacial surgery. With the increased rehabilitation of edentulous regions using dental implants, the treatment of peri-implantitis has become of great concern [15]. Polymeric tetracycline HCl-containing fibers [16] and minocycline microspheres [17] have shown to reduce inflammation and improve the treatment of probing pockets. Osteomyelitis is also an increasing complication after oral and maxillofacial surgery. Traditional treatment procedures, including surgical debridement and systemic antibiotic therapy, have shown drawbacks. However, LDDSs such as vancomycin loaded N-trimethyl chitosan nanoparticles [18] and ciprofloxacin biodegradable implantable matrices [12] have caused higher efficacy in the treatment of osteomyelitis and abatement of its recurrence. Furthermore, the application of aspirin-chitosan nanoparticles [19] and collagen/nanohydroxyapatite/alginate hydrogel have shown to enhance new bone formation [20].

Periodontitis is a multi-factorial inflammatory condition that engages components responsible for supporting dental structure. Accumulation of bacterial biofilm/plaque in periodontal pockets is regarded as the main etiological factor for periodontitis [21]. Systemic antibacterials are traditionally used for periodontal treatments, however, hypersensitivity and gastrointestinal problems are the complications of systemic approach [6]. It has been shown that such adverse effects could be minimised if antibacterial agents were impregnated in a local carrier and directly transferred to the target site [22]. LDDS, such as fibers, films, strips, injectable gels and micro/nanoparticles have been used as vehicles for the treatment of different types of periodontitis [23].

Moreover, LDDS have been used for the treatment of oral cancer [8] and oral candidiasis [11]. It seems that nanoparticles, liposomes and hydrogels can transfer chemotherapeutic agents into cancerous cells, and lower their toxicity in normal tissues. Therefore, local administration of anticancer drugs can promote the therapeutic impact on cancerous cells and reduce unfavourable systemic adverse effects [8]. Clotrimazole nanofibers [7] and nystatin-loaded nanoemulsions [24] have demonstrated slow controlled release of antifungal agents without unwanted systemic concentration.

LDDS can also be used in different endodontic treatments; from traditional methods, *e.g.* apexification [25], to recently-introduced protocols such as vital pulp therapy (VPT) [26] and regenerative endodontics (RE) [27]. Seemingly, LDDS are sufficiently small to penetrate into dentinal tubules and reach the farthest areas inaccessible via conventional treatment strategies [28]. Therefore, if they are loaded with an antibacterial, LDDS could be able to transfer the drug(s) to the target site, control-release the agent in due time and manner, challenge the intracanal microorganisms [29], and act as a preventive measure for possible endodontic failure [30].

In modern endodontics, Different vehicles, *e.g.* nanofibers/hydrogel/microparticles/nanoparticles/liposomes, have been nominated for use as LDDS [31-34]. The aim of this study was to elaborate on various pivotal LDDS and their applications in endodontics and corresponding treatments.

Review

Endodontic treatment is a series of different methods, techniques and measures to remove microorganisms from the root canal system (RCS) [35]. Due to complexities of root canal anatomy and remote distant areas, such as isthmi, ramifications and difficulties of dentinal tubules, thorough bacterial debridement is a challenging task. In addition, bacterial persistence in these areas can considerably reduce the degree of success in endodontic treatment. Amongst intracanal microorganisms, *Enterococcus faecalis* (*E. faecalis*) seems more resistance to common treatments, and can result in endodontic failure [36]. To combat such pitfalls, chemical irrigates, inter-appointment medicine and systemic antibiotic therapy are used to achieve root canal disinfection.

Furthermore, owing to the diversity of intracanal microorganisms, facing radicular microbiota is of great challenge in root canal therapy. In necrotic and infected root canals, since there is a lack of blood supply, drug delivery to the damaged sites through systemic approaches can be demanding [37]. Therefore, LDDS have come into focus to possibly overcome the aforementioned limitations; since they appear to a) fringe drugs/antibiotics to RCS, b) be able to increase the success of the treatments [38], and c) control-release the transferred drugs. Novel LDDS can be discussed as particles, hydrogels, sealers, fibers, cements, core-shells, nanowires, filling materials and quantum dots.

Particles

Nowadays, micro/nanoparticles with their specific physical features, *i.e.* size, shape, surface charge and so forth, are considered a priceless drug delivery system [39]. In recent years, use of particles in dentistry, and specifically in endodontic treatments, has attained great interest; since they show efficient accessibility to intricacies and distant areas of RCS [13]. In a number of studies, application of particles as LDDS demonstrated

effective antibacterial and improved osteogenic activities. Thus, they were considered as favorable structures for endodontic ministrations, including regenerative procedures [9, 32]. Various local drug delivery particles for use in endodontic treatments can be further discussed as micro/nanoparticles; although a clear distinction between the two is not always possible:

1. Microparticles:

Microparticles, *aka*. micropellets, microgranules, microspheres, microcapsules, microsponges, and liposomal preparations, range from 1 µm to 100 µm and can demonstrate significant benefits; including a) core protection (encapsulated agent) from environmental impacts *e.g*. enzymatic degradation, b) cell preservation from drug toxicity, c) target drug delivery/efficacy, and d) drug release control in different time allocations [40]. Amongst microparticles, application of microspheres and liposomes for endodontic purposes are very much elaborated:

a. Microspheres

Microspheres, which present almost a spherical shape, are usually made of proteins/polymers/ceramics, show to possess a controlled drug releasing potential, and can play an important role in drug transfer and delivery approaches [41]. Sousa *et al.* [42] showed that "Polylactic co-glycolic acid" (PLGA)/Zein microspheres had significant delivering capabilities for amoxicillin (AMX) to the RCS. In this *in vitro* study, it was demonstrated that PLGA/Zein microspheres could separate AMX from the environment and maintain its antibacterial efficacy against *E. faecalis*. However, they showed that if the content of Zein changed, the release rate of the loaded antibiotic/agent from the microspheres could be modified. Another experimental study indicated that PLGA microspheres loaded with triple antibiotic paste (TAP), minocycline/metronidazole/ciprofloxacin, could display sufficient bactericidal activity for 11 days, while exhibiting satisfactory cell biocompatibility similar to the employment of microspheres alone [43]. Moreover, in another *in vitro* study, it was reported that PLGA microspheres containing simvastatin could showed a long-lasting sustained drug release. Devoid of initial rapid release, the PLGA microspheres may be considered as a favorable vector for tissue engineering process [44]. A novel experimental tested PLGA submicron particle impregnated with chlorhexidine (CHX), calcium and phosphorus exhibited several advantages; including i) improved bactericidal property, ii) increased ability of entrance into dentinal tubules, and iii) possible enhancement of microhardness of dentine. Thus, they could be regarded as efficacious disinfectants for use in root canal treatments [45]. In another *in vitro/in vivo* study by Fan *et al.* [46], it was indicated that loading quaternary ammonium silane, calcium and phosphorus into PLGA submicron particles could result in inhibiting the root canal infections caused by *E. faecalis* and improve mineralization abilities; thus, a favorable disinfectant for use in endodontic ministrations. In an *in vitro/vivo* study, Wang *et al.* [47] reported that injectable nanofibrous/PLGA microspheres with controlled release of bone morphogenetic protein-2 (BMP-2) may increase the differentiation of human stem cells of apical papilla (SCAP) and provoke dentine-like structures. However, the consequent dentine-like tissue was not exactly similar to the typical structure of tubular dentine and therefore, before their application in tissue engineering, further investigations on nanofibrous/PLGA microspheres seem necessary. In another *in vitro* study by Nurdin *et al.* [48], it was indicated that Terpenoid-loaded PLGA microparticles with an average size of 1-2 µm, showed that, at the pH of 6.5 and temperature of 37°C, there was slow controlled release of Terpenoid from PLGA microparticles, and that the drug had an effective antibacterial activity against *E.faecalis*. Terpenoid is a natural compound and has demonstrated anticancer/anti-inflammatory activities against a wide range of bacteria and viruses [49]. In addition, biodegradable polymeric microspheres have shown features which seem to facilitate the renovation of dentinal defects via their a) injectable property, and b) aptitude of medicine incorporation, which can cause less invasion and short handling time when compared to traditional trends [47].

Ceramic microspheres as a drug carrier system, appear to possess a substantial bioactive property; however, their deficiency in porosity may affect the process of controlled drug release [50]. Parallel to the application of calcium hydroxide (CH) as an intracanal medicament, CH microspheres have been experimentally studied for use in endodontic treatments. In an *in vitro* study, CH microspheres indicated prolonged controlled and sustained release of Ca^{2+} in RCS, a phenomenon which may theoretically decrease the number of appointments for traditional apexification procedure [25]. A recent *in vitro* and *ex vivo* study indicated that CH microparticles could be promising in vital pulp therapy (VPT). Priyadarshini *et al.* [51] showed that if CH microspheres were loaded with chlorhexidine (CHX), they could slowly release chlorhexidine on dentine surfaces during 15 days and thus, could be used as a pulp-capping material. CH has favorable effects in pulp capping procedures since it is alkaline, biocompatible and antibacterial, and can prompt reparative dentine construction. Moreover, chlorhexidine has shown to be a promising disinfectant for pulp capping process. It appears that the combination of CH and chlorhexidine could remove microorganisms better than CH alone.

b. Liposomes

Liposomes are small spherical constructs from cholesterol and non-cytotoxic natural phospholipids. Owing to their special features, from 0.025 µm to 2.5 µm large, biocompatible, and hydrophobic/hydrophilic, liposomes can be deemed a favorable

mean for drug delivery [52]. Liposomes are used in different ways, for instance the photodynamic therapy (PDT) of incorporated tetra (hydroxyphenyl)-chlorin (mTHPC) in liposomes has exhibited antibacterial activity against *E. faecalis* [53]. *E. faecalis* can show resistance against metronidazole, clindamycin and vancomycin, nevertheless, liposomes treated by PDT can be a promising approach to effectively remove *E. faecalis* [53], and thus, may be used in root canal systems [54]. In another study by Bultema *et al.* [55], liposomal bupivacaine and its impact on pain decrease in untreated teeth with symptomatic irreversible pulpitis were investigated. The study showed that liposomal bupivacaine did not have a significant effect on the reduction of pain or elimination of analgesics compared with bupivacaine infiltration. Another recent novel *in vitro* study by Sinjari *et al.* [34] demonstrated that curcumin liposomes (Cur-LIP) presented satisfactory results on improving the proliferation rate of cells and reducing the activity of cytokine factors in human dental pulp stem cells (hDPSCs) and therefore, can be potentially considered for regenerative endodontics. Curcumin have shown several properties including preventing inflammation and exhibiting antibacterial activity. Lately, natural compounds, due to their favorable properties, have been in the limelight in endodontic treatments [34].

2. Nanoparticles:

In recent years, nanoparticulate systems have attracted great attention as innovative drug delivery carriers [56]. Nanoparticle vehicles, namely nanospheres and nanocapsules, have shown to a) represent a well-stable structure in biological fluid environments, b) possess relatively easy production methods, c) demonstrate controlled release of agents/drugs, and d) be transferred more easily into human cells (easy cell uptake) in comparison to the larger carriers. Nanoparticle drug delivery vehicles are 1 nm to 100 nm large, and come in different forms/shapes; solid lipid, polymeric, carbon, silica and so forth [57]. Recently, nanoparticles have been considered for use in endodontics since they have exhibited promising features in transferring/delivering therapeutic agents to intracanal area and complexities where mechanical instrumentation is not possible [58]. In root canal ministrations, nanoparticles have already been considered for use as disinfectants/irrigants [28], root canal sealers [59], and have been impregnated into intracanal medicine [60]. Nowadays, the application of natural polymers, specifically chitosan and PLGA, has shown to be the main methodology for the preparation of nanoparticles; since the polymeric biomaterials have demonstrated biodegradability and biocompatibility [61].

Chitosan nanoparticles (CHSNPs) with their particular physiochemical features, *i.e.* small size, high "surface area/mass" ratio, and improved chemical reaction, have been regarded as suitable local carriers in transferring bioactive molecules for endodontic regenerative purposes [62]. A novel *in vitro* study by Kukreti *et al.* on lipopolysaccharide (LPS)-ministrated dentine tissue prototype (LPS-dentine) reported that dexamethasone-loaded CHSNPs could form a layer on dentine surfaces so that stem cells could attach to dentine, and preserve their proliferation and viability characteristics [63]. Moreover, it has been experimentally demonstrated that dexamethasone-loaded CHSNPs can improve the differentiation of SCAP [62]. Also, CHSNPs seem to be able to penetrate into infected dentinal tubules and better the disinfection of RCS [64]. Chitosan-conjugated rose Bengal nanoparticles (CHSRBNPs) appear to have effective antimicrobial activity against bacterial endotoxin. Shrestha *et al.* showed that PDT using CHSRBNPs and methylene blue could lower inflammation by neutralizing or inactivating endotoxin [65]. In addition, a nanocarrier, based on chitosan and gelatin, has been introduced for delivering calcium hydroxide for use in endodontic treatments. It was demonstrated that CH-loaded chitosan nanocarriers could promote controlled/prolong release of calcium ions in the radicular space [66]. However, dentine powder can act as a tissue inhibitor and may affect the antibacterial activity of CHSNPs [67]. In another study by Soares *et al.*, it was shown that chitosan scaffolds could also provide a suitable environment to support tertiary dentinogenesis, maintain cell viability and stimulate differentiation of dental pulp cells to odontoblast-like cells; which were able to deposit calcium-enriched matrices [68].

The effect of PLGA nanoparticles, loaded with methylene blue as photosensitizer, on the eradication of *E. faecalis* has been investigated in a recent *in vitro* study by Diogo *et al.* [69]. Photosensitizer entrapment in nanoparticle structures have shown several benefits in comparison to a free photosensitizer agent, including a) more concentration of the photosensitizer and production of a larger amount of reactive oxygen, b) relocation of the drug to the specific target site, and c) reduction of the probability of drug resistance. Thus, photoactive materials loaded into PLGA nanoparticles could be considered as an effective antibacterial for possible use in endodontic treatments [70]. In addition, moxifloxacin-loaded PLGA nanoparticles have demonstrated controlled release and sustained antibacterial activity against *E. faecalis* for 14 days, however, the antimicrobial action declined afterwards [71]. Recently, in a novel study by Toledano *et al.* [72], it was indicated that zinc-nanoparticles could enhance the remineralization process of dentine, and thus, cause lower microleakage. Therefore, zinc

nanoparticles can probably decrease the failure rate of endodontically treated teeth and could be recommended to be used before the obturation of root canals.

Nano-encapsulation of agents/drugs seems to provide prolonged release of medicine into dentinal tubules. CHX-encapsulated polymeric nanoparticles, dispersed in a hydrogel matrix, have exhibited improved bacterial intervention in RCS, and can be considered a favorable structure in enhancing antibacterial activity against *E. faecalis* in root canal disinfection [73]. In another *in vitro* study by Quiram *et al.* [74], it was shown that polymeric trilayered nanoparticles (TNPs) loaded with CHX digluconate could be an effective substitute to enhance root canal disinfection. It was indicated that TNPs, with the size of 140 nm to 295 nm, could cause CHX to penetrate into the smallest dentinal tubules and develop a possible mean for sustained and local delivery.

In recent years, bioactive glass (BG) has received significant attention in endodontics. Chemical components and various properties of BG have caused them to be biocompatible, antibacterial and having regenerative capabilities [75]. Bioactive glass nanoparticles (BGNPs) loaded with dexamethasone presented slow release of the drug over months and improvement in the proliferation rate of hDPSCs for 14 days [76]. Moreover, mesoporous BG have exhibited well-organized pores and thus, better bioactivity in comparison to conventional BG. Lee *et al.* in their *in vitro* study revealed that aminated (-NH2) mesoporous bioactive nanoparticles (MBNPs) could be favorable additives to pulpal regenerative materials. MBNP-NH2 showed to improve odontogenic differentiation ability of hDPSCs [77]. Mesoporous calcium silicate nanoparticles (MCSNPs) can also play an important role in developing biocompatible materials for dental pulp regeneration procedures. MCSNPs loaded with gentamicin have shown sustained release and better antibacterial activity when compared to gentamicin loaded calcium silicates [78].

Silver nanoparticles (AgNPs) have shown high bactericidal effect and thus, been used as a) an endodontic irrigant, b) an intracanal medicament against bacteria, and c) as an agent merged in different endodontic materials; *e.g.* sealers, cements and gutta-percha, with the aim of inhibiting recolonization of microorganisms [79]. Although it is claimed that bacteria are not able to develop resistance against AgNPs, there seem to be silver-resistant genes in some endodontics pathogens resulting in bacterial resistance to AgNPs in the long term [80]. Furthermore, AgNPs have shown the ability to remove smear layer and could be considered as a promising agent in the elimination of *E.faecalis* in root canal systems [81]. It also appears that if AgNPs is combined with 17% Ethylenediamine tetra acetic acid (EDTA), the antibacterial effect on planktonic cells and bacteria biofilm is enhanced due to the chelating capability of EDTA [82]. In an *in vivo* study by Ioannidis *et al.* [83], it was revealed that AgNPs, with graphene oxide (GO) particles and ultrasonic activation, could cause an enhanced antimicrobial activity and disruption of bacterial biofilm in the lateral root canals. Nonetheless, another study Rodrigues *et al.* [84] claimed that AgNPs may not be successful in the removal of *E. faecalis* in comparison with common endodontic irrigants used in infected root canal treatments.

Several studies have examined the effect of AgNPs loaded with CHX as a bactericidal combination in endodontic treatments. The antibacterial activity of AgNPs on gram negative/multidrug resistant microorganisms can be an efficacious supplement to CHX for endodontic disinfection since CHX-AgNPs could reduce CHX adverse effects via decreasing its concentration in the radicular area [85]. CHX-AgNP combination has demonstrated improved antibacterial activity against *E.faecalis*, *Klebsiella pneumoniae*, and *Candida albicans* in comparison to the bactericidal effect of these antimicrobials when consumed alone [86]. AgNPs and CHX have recently been incorporated into lyotropic liquid crystalline (LLC) and have shown significant sustained antibacterial activity against *E. faecalis* longer than one month. LLC with 3D constructions have been devised and developed as an innovative drug delivery system owing to its biodegradability and controlled drug release capability [85]. Nevertheless, further investigation on the application of LCC as a drug delivery system is required.

Hydrogels

Hydrogels, which exhibit a cross-linked hydrophilic polymer network, indicate suitable physical properties relatively similar to the dental pulp tissue [87]. Moreover, hydrogels, due to their effective incorporation and release of agents, can play an important role in improving revascularization of the RCS and encouraging regeneration of pulp-dentine complex [88]. Hyaluronic acid (HYA) based hydrogels can be employed as biocompatible scaffolds for supporting the regeneration process of hDPSCs [89]. Furthermore, in an *in vitro* study by Chrepa *et al.* [90], it was shown that HYA-based injectable hydrogels could have a promising capability in improving cell viability, mineralisation and differentiation of SCAP into odontoblast-like cells. However, fast degradation rate via chemical/enzymatic hydrolysis and weak mechanical features can be considered as drawbacks of HYA-based hydrogels [89]. A novel injectable experimental HYA-based hydrogel, reinforced with cellulose nanocrystals (CNCs) impregnated with platelet lysate (PL), showed to be capable of vascularizing damaged tissues in regenerative therapies. In addition, HYA/CNCs/PL hydrogels could significantly improve the viability of hDPSCs [87]. It was also

reported that, in an *in vitro* study, PL incorporated into HYA-based hydrogels could potentially provoke the expression of markers related to osteogenesis and mineralized matrix deposition via hDPSCs [91]. Owing to the capability of hydrogels as a drug delivery system for direct pulp capping and regenerative approaches [26], novel hydrogels have been devised and developed. A novel experimental injectable silver-doped bioactive glass/chitosan hydrogel (Ag-BG/CS) has been introduced as a promising combination in pulp capping, especially for the treatment of early diffuse pulpitis. It has been shown that Ag-BG/CS can impel stronger development of reparative dentine, improve the protection of pulp vitality in comparison to MTA, and stimulate pulp tissue self-curing process [92]. An *in vitro* investigation introduced a novel chitosan/β-glycerophosphate (CS/β-GP) hydrogel, loaded with vascular endothelial growth factor (VEGF), as a valuable system for pulp capping treatments. VEGF/CS/β-GP hydrogel seemed to be able to provide sustained release of VEGF, leading to the improvement of odontogenic differentiation properties of hDPSCs [33].

Besides, methylcellulose hydrogel incorporated with (1 mg/mL) double antibiotic paste (DAP) can present a significant bactericidal activity against single and dual microbial biofilms of *Prevotella Intermedia* and *E. faecalis* without negatively affecting the characteristics of hDPSCs. Nevertheless, a higher concentration of DAP in the hydrogel can cause adverse effects on the proliferation rate and mineralization process of hDPSCs [93]. Recently, an injectable gelatin methacryloyl (GelMA) hydrogel enriched with CHX and modified by halloysite nanotube seems to have shown bacterial growth inhibition with minimal cytotoxicity. Therefore, GelMA based hydrogel could be regarded as a capable potential for sustained drug release in RCS for endodontic treatments [94].

Sealers

Failure in endodontic treatments, due to the remaining microorganisms, *e.g. E.faecalis*, in the complexities of root canal system and the lack of access *via* routine chemomechanical approaches, is frequent [95]. Therefore, employment of intracanal medication carriers could potentially reduce the number of lasting microorganisms and thus, prepare a better matrix for a more successful outcome [96]. In a study by Akbarianrad *et al.* [59], it was shown that sealers, with micro/nanoparticles loaded with antimicrobials, could reduce microorganisms; since the antibacterial component could be carried and penetrated into dentinal tubules. Moreover, loaded particles into sealers seem to enhance the sustained release of antimicrobial [97]. In an *in vitro* study by Dornelles *et al.* [98], amoxicillin-loaded microspheres were impregnated into an experimental endodontic sealer, showing efficacious antimicrobial activity after 96 h. Chitosan nanoparticles can also be a favorable antibacterial carrier to be added to root canal sealers, since they show severe antibacterial activity; specifically on gram-positive bacteria. In an *in vitro* study by Loyola-Rodríguez *et al.* [99], it was demonstrated that chitosan nanoparticles could specify satisfactory antibacterial properties when added to sealers. Furthermore, MTA Fillapex sealer loaded with Allium sativum and chitosan indicated an enhanced antibacterial effect on *E.faecalis*. In addition, Gutta-flow 2 sealer, in combination with 20% chitosan, showed improvement in bactericidal efficacy [100]. It seems that drug/antibacterial material encapsulation into sealers could be considered as an alternative method in the treatment of primary and secondary endodontic infections [98].

Due to the importance of sealers as carriers for antibacterial agents/medications, novel therapeutic sealers have been also experimentally devised. In an *in vitro* study by Baras *et al.* [30], incorporation of dual dimethylaminohexadecyl methacrylate (DMAHDM) and silver nanoparticles (AgNPs) into an experimental therapeutic sealer exhibited a) an enhanced capability in decreasing polysaccharide production of *E. faecalis*, and b) preventing endodontic re-infection without altering the physical and sealing properties of the tested resin-based sealer. In another similar investigation by Monteiro *et al.* [101] regarding resin-based sealers, an experimental dual-cure resin sealer was loaded with halloysite nanotubes (HNTs) covered with alkyltrimethylammonium bromide (ATAB) and indicated significant antibacterial effect on the biofilm and planktonic *E. faecalis* without a cytotoxic impact on human cell viability. Furthermore, quaternary ammonium compounds (QACs) have been loaded in different resin-based dental materials due to their capability of producing potent and prolonged antibacterial activity [102]. In another investigation by Baras *et al.* [103], an experimental endodontic sealer with triple bioactive components, DMAHDM, AgNPs, and amorphous calcium phosphate nanoparticles (NACPs), indicated promotion of dentine minerals regeneration and reduction of bacterial biofilm. Furthermore, Baras *et al.* [104] devised a similar bioactive sealer, consisting of DMAHDM and NACP, which showed promising capability in preventing the growth of *E. faecalis* without affecting the solubility of sealers. Seemingly, the addition of contact-killing materials, *e.g.* DMAHDM and ATAB, to root canal sealers could *i)* prolong the durability of endodontic treatments, and *ii*) decrease the probability of endodontic re-treatments [102].

Besides, loading bioactive glass (BG), hydroxyapatite (HA), and fluorine substituted hydroxyapatite (FHA) nanoparticles into epoxy-based sealers have shown significant antimicrobial activity against *E. faecalis* and *Streptococcus (S). mitis*. Therefore, they

have been regarded as potential promising biomaterials with antibacterial activity in endodontic treatments [105]. In addition, in an *in vitro* study conducted by Camargo *et al.* [106], it was shown that an experimental resin-epoxy based sealer loaded with N-Acetylcysteine (NAC) could indicate an enhanced antimicrobial effect on *E. faecalis* in comparison to unmodified epoxy sealers. The resin-epoxy based sealer containing NAC and the bioactive beta-tricalcium phosphate (β-TCP) nanoparticles could also be considered as a potential in attaining tight seal and provoking periapical healing process. A novel experimental zinc oxide eugenol sealer containing polyhexamethylene biguanide (PHMB) showed an enhanced prolonged inhibition of *E.faecalis*. Nonetheless, expect for the concentration of 0.05% to 0.2%, PHMB altered the physical properties of zinc oxide-eugenol (ZOE) sealer [107]. In an *in vitro* study, Mohammad *et al.* [108] evaluated the bactericidal effect of zinc oxide (ZnONPs)/silver nanoparticles incorporated into zinc oxide (ZnO)-based sealers. The sealer loaded with silver nanoparticles indicated the greatest antibacterial effect on *E. faecalis* whilst the sealer enriched with ZnO nanoparticles exhibited the least bactericidal effect against the microorganism. Another *in vitro* study demonstrated that ZnO-based sealers loaded with fluorinated graphene can possess more antibacterial effect on *E. faecalis* in comparison to the sealer loaded with ZnO nanoparticles, whilst ZnO-based sealers indicated less antibacterial activity when employed alone [109].

AH-Plus, loaded with CHX or cetrimide (CTR), alone or in combination with both, has shown to possess an effective role in the prevention of biofilm development and improved bactericidal activity against *E. faecalis* [110]. Weckwerth *et al.* [111], in an *in vitro* study, reported that loading ketoconazole and fluconazole in several sealers including AH-Plus, Sealer 26, Endofill, Fillapex and Sealapex, can improve their antifungal activity and enhance the antibacterial action without altering physical properties of sealers; expect for Fillapex setting time, and Endofill/AH-Plus flowability. Therefore, their application for root canal obturation of teeth with possible fungal infections, may be a good approach particularly in endodontic failure treatments.

Recently, nanostructured silver vanadate decorated with silver nanoparticles ($AgVO_3$) have been experimentally employed as a new antibacterial nanomaterial additive for endodontic sealers [97, 112]. In an *in vitro* study by Teixeira *et al.* [112], it was shown that $AgVO_3$ could present amplified bactericidal activity. In addition, silver component exhibited antimicrobial effect similar to (or even higher than) the broad-spectrum antibiotics, causing a decrease in the attachment of microorganisms and formation of biofilm. Nevertheless, the use of nanomaterials in commercial sealers could have cytotoxic effect [113]. As a result, further investigations are required.

Fibers

The unique form and morphology of fibers make them a perfect choice to be used as LDDS [114]. Fibers exhibit a cylindrical shape, demonstrate a high surface for volume ratio, and are usually made from gelatin/alginate/polymer/ceramic materials. They seem to be capable of releasing drugs/agents over a large surface area [115, 116]. As a result, they have been considered for use in endodontics.

Antibiotic containing polydioxanone (PDS)-based scaffolds, *i.e.* metronidazole (MET)/ciprofloxacin (CIP)-polymer based nanofibrous scaffold, have shown effective antimicrobial delivery for regenerative endodontics [117]. Another experimental PDS-based nanofiber scaffold, loaded with triple antibiotic paste, has demonstrated significant antibacterial effect on Porphyromonas (*P.) gingivalis* in infected dentinal models [118]. Antibiotic containing scaffolds seem to provide controlled antibacterial release with considerably lower therapeutic dose than that of the double and triple antibiotic pastes, and thus, they can result in a possible increase in the growth and differentiation of hDPSCs [119]. Besides, a tubular three-dimensional (3D) scaffold with antibiotic-eluting nanofibers have recently been developed for intracanal disinfection for use in regenerative endodontics [120]. It appears that the eluting nanofibers can stay close to dentine surfaces, prepare a matrix for an increase in the activity of antibacterial agents in the farthest points of dentinal tubule, cause apex closure and produce an osteodentine-like narrow layer [120]. In another study by Soares *et al.* [31], it was demonstrated that loading low concentration of simvastatin on polylactic acid (PLA)-based nanofibrous scaffold can provoke dentine regeneration process *via* enhancing the regenerative capabilities of stem cells and decreasing the expression of inflammatory markers.

Clindamycin-modified triple antibiotic-PDS polymer-based (CLIN-m) nanofibers have shown significant antibacterial properties against most microorganisms, and is considered as a suitable substitute for minocycline containing pastes [121]. Clindamycin appears to be an effective antimicrobial against root canal microbiota [122]. In an *in vitro* study by Karczewski *et al.* [123] CLIN-m nanofibers have shown more preventive properties against bacterial development when compared to CLIN nanofibers. Furthermore, CLIN-m and CLIN nanofibers have indicated protection for the viability of hDPSCs up to 50% and 70%, respectively. In addition, loading CLIN into the ethylene vinyl acetate fibers can decrease the development of common endodontic pathogens; including *Prevotella intermedia*, *Fusobacterium nucleatum* and *Streptococcus intermedius* [124]. In another experimental study, it was reported that, ornidazole incorporated into nanofibers could represent effective antimicrobial activity against anaerobic microbiota as well as

showing minimal toxicity on pulpal cells. Therefore, it can be used as a promising material for direct pulp capping [125]. CHX is deemed an efficacious agent against a broad spectrum of endodontic bacteria including gram-positive and gram-negative microorganisms [126]. An experimental study demonstrated that incorporating CHX into Polyvinyl alcohol (PVA) nanofibers could present an enhanced antimicrobial action, similar to CHX gel, against *E. faecalis* and *C. albicans* [127]. Another in vitro study indicated that polymer-coated, *i.e.* chitosan/PLGA/PMMA, fiberous structures can make controlled CHX release into RCS [128]. It seems that PLGA-based scaffolds loaded with antibiotics can also be used for regenerative endodontic process [129].

Curcumin, as it was previously mentioned, has shown anticancer, antioxidant, anti-inflammatory and antibacterial properties, [130] and could be considered as a root canal disinfectant or irrigant [131]. In an *in vitro* study by Sotomil *et al.* [131], it was shown that irrigation with curcumin, at the minimum concentration of 2.5 mg/mL, showed more antibacterial effect than that of triple antibiotic paste (TAP). However, if fibers were impregnated with curcumin, less antibacterial activity would be seen in comparison with TAP. However, photoactivation process seem to boost the antibacterial activity of curcumin loaded fibers. Nonetheless, further investigations on the use of curcumin as an antibacterial agent, is necessary.

Other Novel Local Drug Delivery Systems in Endodontics

Cements

Endodontic cements can function as a promising drug carrier. A novel experimental calcium phosphate cement (CPC), containing metformin and chitosan, has shown to cause significant improvement in the regeneration process of dentine. It was demonstrated that CPC-chitosan-metformin composite could increase the differentiation of dental pulp cells without negatively affecting their viability and proliferation rate [132]. In another *in vitro* study by Guerreiro-Tanomaru *et al.* [133], it was reported that loading 10% - 20% HA nanoparticles into Portland cement associated with zirconium oxide (ZrO_2) could a) enhance the antibacterial activity of the cement against *E. faecalis*, b) improve its radiopacity, and c) decrease the final setting time. However, it could result in unwanted harmful effects on the compressive strength and fluidity of the cement [133]. Another *in vitro* study on the incorporation of AgNPs into Portland cement with ZrO_2 and mineral trioxide aggregate (MTA) showed that the mentioned combination could present an improved antimicrobial activity against planktonic cells and *E. faecalis* as well as enhancing the mechanical properties of the cement [134]. An experimental tested ProRoot MTA and calcium enriched mixture (CEM) cements loaded with AgNPs also seemed to possess a promoted antibacterial action [135].

Core-shell nanostructures

Due to the capabilities of core-shell nanostructures as a drug delivery system [136], novel core-shell nanosystems have attracted attention. Core particles coated with shell materials seem to improve the stability and control-release the core substances. They can be synthesized from polymers, metals and ceramic structures [136-138]. the core-shell nanosystem consisting of chitosan nanoparticles loaded with dexamethasone, and coated with alginate solution enriched with tumor growth factor (TGF)-β could promote cell attachment/migration and odontogenic differentiation properties of SCAP. Moreover, the loaded core-shell nanosystem appears to be able to enhance the ingrowth of connective tissue into the apical portion of root canal area [139]. Another investigation indicated desirable antibacterial effect of a novel core-shell silver nanoparticle (AgNPs@SiO_2) on endodontic prolonged disinfection process. AgNPs@SiO_2-based irrigants represent valuable bactericidal activity at least for 7 days, whilst individual AgNPs could not signify antimicrobial activity after 2 days [140]. An innovative experimental paste, containing core-shell structured CaO/ZnO nanospheres-eugenol, has indicated favorable root canal sealing, improved bactericidal features and good cytocompatibility properties, and may have potential for use in endodontic treatments [141].

Nanowires and filling materials

Copper nanostructures may be able to play an effective role in the treatment of endodontic infections owing to their antimicrobial activity. An experimental study indicated that copper nanowires could seriously affect aerobic microorganisms and bacteria, causing potential bactericidal action against *E. faecalis* strains [142]. Root canal filling/obturation materials can also be used as drug delivery carriers [143]. In an *in vitro* study by Lee *et al.* [144], it was demonstrated that incorporating amoxicillin into the nanodiamond embedded gutta-percha could reduce the remaining bacteria and lead to the prevention of secondary endodontic infection [144]. Moreover, depositing zinc oxide thin film on argon plasma treated gutta-percha cones *in vitro* seemed to have presented improved antibacterial effect on *E. faecalis* and Staphylococcos (*S.*) *aureus* without showing cytotoxic impact [145]. In addition, gutta percha, containing CH and CHX, was experimentally used for root canal disinfection and showed an antimicrobial activity against *Escherichia coli*, *S. aureus* and *Pseudomonas aeruginosa* [146].

Furthermore, gutta-perch points have been loaded with antibiotics and used in the radicular area to combat microorganisms. Metronidazole has been experimentally used and loaded on filling materials and has been regarded quite effective [147,148].

Quantom dots

Quantum dots (QD) are deliberated as potential drug nano carriers. QD have shown to improve the effectiveness and decrease the side effects of the transferred drug in medicine, specifically cancer research [149]. A novel experimental investigation indicated that Graphene oxide QD seemed to have no effect on the proliferation rate, viability and metabolism of hDPSCs; and could be regarded biocompatible [150]. Thus, QD can be theoretically considered as a drug delivery system for use in endodontic treatments.

Conclusions

Local drug delivery systems have shown to overcome many drawbacks of systemic medicinal ministrations and can be regarded as favourable means of drug transfer in the treatment of ailments and maladies. LDDS seem to be capable of transferring agents/drugs to the target site; minimising cytotoxicity of the medicine in the intended tissue/organ. In dentistry, these small-sized vehicles have been used for the treatment of different oral diseases; from dental carious lesions and mouth infections to oral cancers and malignancies.

Root canal pathosis is one of the most prevalent problems amongst dental-originated diseases. The success of an endodontic treatment relies mainly on the reduction of root canal microorganisms. Thorough removal and possible eradication of root canal microbiota and their various by-products from the RCS is necessary for endodontic success. However, there are complexities in the radicular area which cannot be reached through common chemomechanical approaches. LDDS, with their small size, various morphologies and specific features, can enter tiny dentinal tubules and access distant areas.

Whilst achieving a therapeutic dose of systemic medications in the root canal space is a challenge, LDDS can be used as a promising potential due to their ability to control/sustain release of antibacterial drug. A number of *in vitro* studies have indicated that loading medicaments in local delivery vehicles could function as enhanced intracanal medication/irrigant for the elimination of bacterial biofilms. Furthermore, LDDS can be applied as a successful therapeutic vehicle in pulp regeneration and revascularization processes, causing improvement in the viability and differentiation characteristics of hDPSCs. Additionally, LDDS could play an effective role in vital pulp therapy through stimulating the formation of dentinal structures.

In conclusion, LDDS seem to increase the success rate of endodontic treatments, prevent re-infections of root canal systems, reduce treatment sessions, and lead to patients' convenience. Nevertheless, more investigations and additional clinical trials are required to evaluate the effects of LDDS on the outcomes of endodontic treatments.

Conflict of Interest: 'None declared'.

References

1. Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, et al. Drug delivery systems: An updated review. Int J Pharm Invest. 2012;2(1):2-11.
2. Nguyen S, Hiorth M. Advanced drug delivery systems for local treatment of the oral cavity. Ther Deliv. 2015;6(5):595-608.
3. Norouzi M, Nazari B, Miller DW. Injectable hydrogel-based drug delivery systems for local cancer therapy. Drug Discov Today. 2016;21(11):1835-49.
4. Sapino S, Chirio D, Peira E, Abellan Rubio E, Brunella V, Jadhav SA, et al. Ocular drug delivery: A special focus on the thermosensitive approach. J Nanomaterials (Basel). 2019;9(6):884.
5. Salatin S, Barar J, Barzegar-Jalali M, Adibkia K, Jelvehgari M. Thermosensitive in situ nanocomposite as an intranasal delivery system of rivastigmine hydrogen tartrate: development, characterization, ex vivo permeation and cellular studies. Colloids Surf B Biointerfaces. 2017;1(159):629-38.
6. Rajpoot AS, Parihar AS, Thakur S, Choudhary K, Rajput P, Chaudhary A. Local drug delivery in periodontics. Int j res health allied sci. 2017;3(4):63-7.
7. Tonglairoum P, Ngawhirunpat T, Rojanarata T, Panomsuk S, Kaomongkolgit R, Opanasopit P. Fabrication of mucoadhesive chitosan coated polyvinylpyrrolidone/cyclodextrin/clotrimazole sandwich patches for oral candidiasis. Carbohydr Polym. 2015;132:173-9.
8. Calixto G, Bernegossi J, Fonseca-Santos B, Chorilli M. Nanotechnology-based drug delivery systems for treatment of oral cancer: a review. Int J Nanomedicine. 2014;9:3719-35.
9. Chung SH, YS P. Local drug delivery in endodontics: A literature review. J Drug Deliv Sci Tec. 2017;39:334-40.
10. Goodson JM, Haffajee A, Socransky SS. Periodontal therapy by local delivery of tetracycline. J Clin Periodontal. 1979;6(2):83-92.
11. Liang J, Peng X, Zhou X, Zou J, Cheng L. Emerging applications of drug delivery systems in oral infectious diseases prevention and treatment. Molecules. 2020;25(3):516.
12. Hanafy AF, Ali HSM, El Achy SN, Habib EE. Dual effect biodegradable ciprofloxacin loaded implantable matrices for

osteomyelitis: controlled release and osteointegration. Drug Dev Ind Pharm. 2018;44(6):1023-33.
13. Puri K, Puri N. Local drug delivery agents as adjuncts to endodontic and periodontal therapy. J Med life. 2013;6(4):414-9.
14. El Gezawi M, Wölfle UC, Haridy R, Fliefel R, Kaisarly D. Remineralization, regeneration, and repair of natural tooth structure: influences on the future of restorative dentistry practice. ACS Biomater Sci Eng. 2019;5(10):4899-919.
15. Niovaes Junior AB, Ramos UD, Rabelo MS, Figueredo GB. New strategies and developments for peri-implant disease. Braz Oral Res. 2019;33(suppl 1):e071.
16. Mombelli A, Feloutzis A, Bragger U, Lang NP. Treatment of peri-implantitis by local delivery of tetracycline Clinical, microbiological and radiological results. Clin Oral Implants Res. 2001;12(4):287-94.
17. Renvert S, Lessem J, Dahle´n G, Renvert H, Lindahl Ch. Mechanical and repeated antimicrobial therapy using a local drug delivery systemin the treatment of peri-implantitis: a randomized clinical trial. J Periodontal. 2008;79(5):836-44.
18. Zhang Y, Liang RJ, Xu JJ, Shen LF, Gao JQ, Wang XP, et al. Efficient induction of antimicrobial activity with vancomycin nanoparticle-loaded poly(trimethylene carbonate) localized drug delivery system. Int J Nanomedicine 2017;12:1201-14.
19. Zhang J, Ma S, Liu Z, Geng H, Lu X, Zhang X, et al. Guided bone regeneration with asymmetric collagen-chitosan membranes containing aspirin-loaded chitosan nanoparticles. Int J Nanomedicine. 2017;12:8855-66.
20. Cao J, Wang L, Lei De, Liu YP, Du Zh, Cui FZ. Local injection of nerve growth factor via a hydrogel enhances bone formation during mandibular distraction osteogenesis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113(1):48-53.
21. Gupta R, Debnath N, Rawat P, Hota S, Chandra Das A, Kumar A. Local drug delivery - A new concept in dentistry. J Clin Den Res Edu 2014;3(7):67-72.
22. Vandekerckhove BN, Quirynen M, Van Steenberghe D. The use of Tetracycline-containing controlled release fibers in the treatment of refractory periodontitis. J Periodontal. 1997;68(4):353-61.
23. Pragati S, Ashok S, Kuldeep S. Recent advances in periodontal drug delivery systems. J Drug Deliv Sci Technol. 2011;1(1):1-14.
24. Fernandez Campos F, Calpena Campmany AC, Rodriguez Delgado G, Lopez Serrano O, Clares Naveros B. Development and characterization of a novel nystatin-loaded nanoemulsion for the buccal treatment of candidosis: Ultrastructural effects and release studies. J Pharm Sci. 2012;101(10):3739–52.
25. Strom TA, Arora A, Osborn B, Karim N, Komabayashi T, Liu X. Endodontic release system for apexification with calcium hydroxide microspheres. J Dent Res. 2012;91(11):1055-9.
26. Komabayashi T, Wadajkar A, Santimano S, Ahn C, Zhu Q, Opperman LA, et al. Preliminary study of light-cured hydrogel for endodontic drug delivery vehicle. J Investig Clin Dent. 2016;7(1):87-92.
27. Silva CR, Babo PS, Gulino M, Costa L, Oliveira JM, Silva-Correia J, et al. Injectable and tunable hyaluronic acid hydrogels releasing chemotactic and angiogenic growth factors for endodontic regeneration. Acta biomater. 2018;1(77):155-71.
28. Haseeb R, Lau M, Sheah M, Montagner F, Quiram G, Palmer K, et al. Synthesis and characterization of new chlorhexidine-containing nanoparticles for root canal disinfection. J Mater Sci. 2016;9(6):452.
29. Gilad JZ, Teles R, Goodson M, White RR, Stashenko P. Development of a clindamycin-impregnated fibre as an intracanal medication in endodontic therapy. J Endod. 1999;25(11):722-7.
30. Baras BH, Melo MAS, Sun J, Oates TW, Weir MD, Xie X, et al. Novel endodontic sealer with dual strategies ofdimethylaminohexadecyl methacrylate andnanoparticles of silver to inhibit root canal biofilm. Dent Mater. 2019;35(8):1117-29.
31. Soares DG, Zhang Z, Mohamed F, Eyster TW, de Souza Costa CA, Ma PX. Simvastatin and nanofibrous poly(l-lactic acid) scaffolds to promote the odontogenic potential of dental pulp cells in an inflammatory environment. Acta Biomater. 2018;68:190-203.
32. Cuppini M, Zatta KC, Mestieri LB, Grecca FS, Leitune VCB, Guterres SS, et al. Antimicrobial and anti-inflammatory drug-delivery systems at endodontic reparative material: Synthesis and characterization. Dent Mater. 2019;35(3):457-67.
33. Wu S, Zhou Y, Yu Y, Zhou X, Du W, Wan M, et al. Evaluation of chitosan hydrogel for sustained delivery of VEGF for odontogenic differentiation of dental pulp stem cells. Stem Cells Int. 2019;2019(6):1-14.
34. Sinjari B, Pizzicannella J, D'Aurora M, Zappacosta R, Gatta V, Fontana A, et al. Curcumin/liposome nanotechnology as delivery platform for anti-inflammatory activities via NFkB/ERK/pERK pathway in human dental pulp treated with 2-hydroxyethyl methacrylate (HEMA). Front Physiol. 2019;10.
35. Cohen S. Pathways of the Pulp2006.
36. Pagonis TC, Chen J, Fontana C, Devalapllay H, Ruggiero K, Song x, et al. Nanoparticle-based endodontic antimicrobial photodynamic therapy. J Endod. 2010;36(2):322-8.
37. Siqueira JF Jr. Strategies to treat infected root canals. J Calif Dent Assoc. 2001;29(12):825-37.
38. Mohammadi Z, Abbott PV. On the local applications of antibiotics and antibiotic-based agents in endodontics and dental traumatology. Int Endod J. 2009;42(7):555-67.
39. Anselmo AC, Mitragotri S. Impact of particle elasticity on particle-based drug delivery systems. Adv Drug Deliv Rev. 2017;108:51-67.
40. Lengyel M, Kállai-Szabó N, Antal V, Laki AJ, Antal I. Microparticles, microspheres, and microcapsules for advanced drug delivery. Sci Pharm. 2019;87(3):20.
41. Das MK, Ahmed AB, Saha D. Microsphere a drug delivery system-A review. Int J Curr Pharm Res. 2019;11(4):34-41.
42. Sousa FF, Luzardo-Alvarez A, Pérez-Estévéz A, Seoane-Prado

R, Blanco-Méndez J. Development of a novel AMX-loaded PLGA/zein microsphere for root canal disinfection. Biomed Mater. 2010;5(5):055008.
43. Torshabi M, Nojehdehian H, Tabatabaei FS. In vitro behavior of poly-lactic-co-glycolic acid microspheres containing minocycline, metronidazole, and ciprofloxacin. J Investig Clin Dent. 2017;8(2):1-8.
44. Masaeli R, S Jafarzadeh Kashi T, Dinarvand R, Tahriri M, Rakhshan V, Esfandyari-Manesh M. Preparation, characterization and evaluation of drug release properties of simvastatin-loaded PLGA microspheres. Iran J Pharm Res. 2016;15(Suppl):205-11.
45. Fan W, Li Y, Liu D, Sun Q, Duan M, Fan B. PLGA submicron particles containing chlorhexidine, calcium and phosphorus inhibit Enterococcus faecalis infection and improve the microhardness of dentin. J Mater Sci Mater Med. 2019;30(2):17.
46. Fan W, Li Y, Sun Q, Tay FR, Fan B. Quaternary ammonium silane, calcium and phosphorus-loaded PLGA submicron particles against Enterococcus faecalis infection of teeth: An in vitro and in vivo study. Mater Sci Eng C Mater Biol Appl. 2020;111:110856.
47. Wang W, Dang M, Zhang Z, Hua J, Eyster TW, Ni L, et al. Dentin regeneration by stem cells of apical papilla on injectable nanofibrous microspheres and stimulated by controlled BMP-2 release. Acta Biomater 2016;36:63-72.
48. Nurdin D, Chaldun E, Hardiansyah A, Fikkriyah A, Dharsono A, Dikdik K, et al. Preparation and characterization of terpenoid-encapsulated PLGA microparticles and its antibacterial activity against Enterococcus faecalis. Key Eng Mater. 2019;829:263-9.
49. Guimarães AG, Serafini MR, Quintans-Júnior LJ. Terpenes and derivatives as a new perspective for pain treatment: a patent review. Expert Opin Ther Pat. 2014;24(3):243-65.
50. Wu C, Zreiqat H. Porous bioactive diopside (CaMgSi2O6) ceramic microspheres for drug delivery. Acta biomater. 2010;6(3):820-9.
51. Priyadarshini BM, Selvan ST, Narayanan K, Fawzy AS. Characterization of Chlorhexidine-Loaded Calcium-Hydroxide Microparticles as a Potential Dental Pulp-Capping Material. Bioengineering (Basel). 2017;4(3):59.
52. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y, et al. Liposome: classification, preparation, and applications. Nanoscale Res Lett. 2013;8(1):102.
53. Kranz S, Guellmar A, Völpel A, Gitter B, Albrecht V, Sigusch BW. Photodynamic suppression of Enterococcus faecalis using the photosensitizer mTHPC. Lasers Surg Med. 2011;43(3):241-8.
54. Ossmann A, Kranz S, Andre G, Völpel A, Albrecht V, Fahr A, et al. Photodynamic killing of Enterococcus faecalis in dentinal tubules using mTHPC incorporated in liposomes and invasomes. Clin Oral Investig. 2015;19(2):373-84.
55. Bultema K, Fowler S, Drum M, Reader A, Nusstein J, Beck M. Pain reduction in untreated symptomatic irreversible pulpitis using liposomal bupivacaine (exparel): a prospective, randomized, double-blind trial. J Endod. 2016;42(12):1707-12.
56. Jain S, Cherukupalli SK, Mahmood A, Gorantla S, Rapalli VK, Dubey SK, et al. Emerging nanoparticulate systems: Preparation techniques and stimuli responsive release characteristics. J Appl Pharm Sci. 2019;9(08):130-43.
57. Elizabeth P-S, Néstor M-M, David Q-G. Chapter 23 - Nanoparticles as dental drug-delivery systems. In: Subramani K, Ahmed W, editors. Nanobiomaterials in Clinical Dentistry (Second Edition): Elsevier; 2019. p. 567-93.
58. Plotino G, Cortese T, Grande NM, Leonardi DP, Giorgio GD, Testarelli L, et al. New Technologies—to improve root canal disinfection. Braz Dent J. 2016;27(1):3-8.
59. Akbarianrad N, Mohammadian F, Alhuyi-Nazari M, Rahbani-Nobar B. Applications of nanotechnology in endodontic: A Review. Nanomed J. 2018;5(3):121-6.
60. Song E, Ge S. Application of antimicrobial nanoparticles in dentistry. Molecules. 2019;24(6):1033.
61. Lee J, Yun S. Hydroxyapatite-containing gelatin/chitosan microspheresfor controlled release of lysozyme and enhanced cytocompatibility. J Mater Chem. 2014;2:1255-63.
62. Shrestha S, Torneck CD, Kishen A. Dentin conditioning with bioactive molecule releasing nanoparticle system enhances adherence, viability, and differentiation of stem cells from apical papilla. J Endod. 2016;42(5):717-23.
63. Kukreti H, Li FC, Singh K, Sodhi R, Kishen A. Efficacy of bioactive nanoparticles on tissue-endotoxin induced suppression of stem cell viability, migration and differentiation. Int Endod J. 2020.
64. Shrestha A, Fong SW, Khoo BC, Kishen A. Delivery of antibacterial nanoparticles into dentinal tubules using high-intensity focused ultrasound. J Endod. 2009;35(7):1028-33.
65. Shrestha A, Cordova M, Kishen A. Photoactivated polycationic bioactive chitosan nanoparticles inactivate bacterial endotoxins. J Endod. 2015;41(5):686-91.
66. Farhadian N, Godiny M, Moradi S, Hemati-Azandaryani A, Shahlaei M. Chitosan/gelatin as a new nano-carrier system for calcium hydroxide delivery in endodontic applications: Development, characterization and process optimization. Mater Sci Eng C. 2018;92:540546.
67. Anwar M, Darrag M, Al-Madboly L, Ghoneima W. Effect of two tissue inhibitors on the antimicrobial activity of chitosan nanoparticles and chlorhexidine. Tanta Dent J. 2019;16:163.
68. Soares D, Bordini E, Cassiano F, Bronze-Uhle E, Pacheco L, Zabeo G, et al. Characterization of novel calcium hydroxide-mediated highly porous chitosan-calcium scaffolds for potential application in dentin tissue engineering. J Biomed Mater Res B. 2020.
69. Diogo P, F Faustino MA, P M S Neves MG, Palma PJ, P Baptista I, Gonçalves T, et al. An insight into advanced approaches for photosensitizer optimization in endodontics-A critical review. J Funct Biomater. 2019;10(4):44.
70. Pagonis TC, Chen J, Fontana CR, Devalapally H, Ruggiero K,

Song X, et al. Nanoparticle-based endodontic antimicrobial photodynamic therapy. J Endod. 2010;36(2):322-8.
71. Makkar H, Patri G. Fabrication and appraisal of Poly (Lactic-Co-Glycolic Acid) – Moxifloxacin nanoparticles using vitamin E-TPGS: a potential intracanal drug delivery agent. J Clin Diagn Res. 2017;11(6):ZC05-ZC8.
72. Toledano M, Osorio E, S.Aguilera F, Muñoz-Soto E, Toledano-Osorio M, T.López-López M, et al. Polymeric nanoparticles for endodontic therapy. J Mech Behav Biomed. 2020;103:103606.
73. Haseeb R, Lau M, Sheah M, Montagner F, Quiram G, Palmer K, et al. Synthesis and characterization of new chlorhexidine-containing nanoparticles for root canal disinfection. Materials (Basel). 2016;9(6):452.
74. Quiram G, Montagner F, Palmer KL, Stefan MC, Washington KE, Rodrigues DC. Novel chlorhexidine-loaded polymeric nanoparticles for root canal treatment. J Funct Biomater. 2018;9(2):29.
75. Profeta AC, Prucher GM. Bioactive-glass in endodontic therapy and associated microsurgery. Open Dent J. 2017;11:164-70.
76. Lim HC, Nam OH, Kim MJ, El-Fiqi A, Yun HM, Lee YM, et al. Delivery of dexamethasone from bioactive nanofiber matrices stimulates odontogenesis of human dental pulp cells through integrin/BMP/mTOR signaling pathways. Int J Nanomedicine. 2016;11:2557-67.
77. Lee JH, Kang MS, Mahapatra C, Kim HW. Effect of aminated mesoporous bioactive glass nanoparticles on the differentiation of dental pulp stem cells. PLoS ONE. 2016;11(3):0150727.
78. Huang CY, Huang TH, Kao CT, Wu YH, Chen WC, Shie MY. Mesoporous calcium silicate nanoparticles with drug delivery and odontogenesis properties. J Endod. 2017;43(1):69-76.
79. Salas-Orozco M, Nino-Martínez N, Martínez-Castañon GA, Méndez FT, Compeán-Jasso ME, Ruiz F. Mechanisms of resistance to silver nanoparticles in endodontic bacteria: a literature review. J Nanomater. 2019;2019.
80. Salas-Orozco MF, Martínez NN, Martínez-Castañón GA, Méndez FT, Patiño-Marín N, Ruiz F. Detection of genes related to resistance to silver nanoparticles in bacteria from secondary endodontic infections. J Nanomater. 2019;2019.
81. González-Luna PI, Martínez-Castañón GA, Zavala-Alonso NV, Patiño-Marin N, Niño-Martínez N, Morán-Martínez J, et al. Bactericide effect of silver nanoparticles as a final irrigation agent in endodontics on Enterococcus faecalis: an ex vivo study. J Nanomater. 2016;2016(1):1-7.
82. Martinez-Andrade JM, Avalos-Borja M, Vilchis-Nestor AR, Sanchez-Vargas LO, Castro-Longoria E. Dual function of EDTA with silver nanoparticles for root canal treatment-A novel modification. PLoS ONE. 2018;13(1):0190866.
83. Ioannidis K, Niazi S, Mylonas P, Mannocci F, Deb S. The synthesis of nano silver-graphene oxide system and its efficacy against endodontic biofilms using a novel tooth model. Dent Mater. 2019;35(11):1614-29.
84. Rodrigues CT, de Andrade FB, de Vasconcelos LRSM, Midena RZ, Pereira TC, Kuga MC, et al. Antibacterial properties of silver nanoparticles as a root canal irrigant against Enterococcus faecalis biofilm and infected dentinal tubules. Int Endod J. 2018;51(8):901-11.
85. Zheng T, Huang X, Chen J, Feng D, Mei L, Huang Y, et al. A liquid crystalline precursor incorporating chlorhexidine acetate and sliver nanoparticles for root canal disinfection. Biomater Sci. 2018;6(3).
86. Charannya S, Duraivel D, Padminee K, Poorni S, Nishanthine C, Srinivasan MR. Comparative evaluation of antimicrobial efficacy of silver nanoparticles and 2% chlorhexidine gluconate when used alone and in combination assessed using agar diffusion method: an in vitro study. Contemp Clin Dent. 2018;9(Suppl 2):S204-S9.
87. Silva CR, Babo PS, Gulino M, Costa L, Oliveira JM, Silva-Correia J, et al. Injectable and tunable hyaluronic acid hydrogels releasing chemotactic and angiogenic growth factors for endodontic regeneration. Acta Biomater. 2018;77:155-71.
88. Amrollahi P, Shah B, Seifi A, Tayebi L. Recent advancements in regenerative dentistry: A review. Mater Sci Eng C. 2016;69:1383-90.
89. Ahmadian E, Eftekhari A, Dizaj SM, Sharifi S, Mokhtarpour M, Nasibova AN, et al. The effect of hyaluronic acid hydrogels on dental pulp stem cells behavior. int J Biol Macromol. 2019;140:245-54.
90. Chrepa V, Austah O, Diogenes A. Evaluation of a commercially available hyaluronic acid hydrogel (restylane) as injectable scaffold for dental pulp regeneration: An in vitro evaluation. J Endod. 2017;43(2):257-62.
91. Almeida LDF, Babo PS, Silva CR, Rodrigues MT, Hebling J, Reis RL, et al. Hyaluronic acid hydrogels incorporating platelet lysate enhance human pulp cell proliferation and differentiation. J Mater Sci Mater Med. 2018;29(6):88.
92. Zhu N, Chatzistavrou X, Papagerakis P, Ge L, Qin M, Wang Y. A silver-doped bioactive glass/chitosan hydrogel with potential application in dental pulp repair. ACS Biomater Sci Eng. 2019;5(9):4624-33.
93. Mclntyre PW, Wu JL, Kolte R, Zhang R, Geregory RL, Bruzzaniti A, et al. The antimicrobial properties, cytotoxicity, and differentiation potential of double antibiotic intracanal medicaments loaded into hydrogel system. Clin Oral Investig. 2019;23(3):1051-9.
94. Ribeiro JS, Bordini EAF, Ferreira JA, Mei L, Dubey N, Fenno JC, et al. Injectable MMP-responsive nanotube-modified gelatin hydrogel for dental infection ablation. ACS Appl Mater Interfaces. 2020.
95. Campos P, De J, Fuente-Hernández J, Tenorio F, Acosta-Torres L. Biocompatible antimicrobial irrigants and nanoparticles-sealers for endodontics. Entreciencias. 2013;1:9-28.
96. Shih YH, Lin DJ, Chang KW, Hsia SM, Ko SY, Lee SY, et al. Evaluation physical characteristics and comparison antimicrobial and anti-inflammation potentials of dental root canal sealers containing hinokitiol in vitro. PLoS ONE. 2014;9:e94941.

97. Teixeira ABV, Silva CCH, Alves OL, dos Reis AC. Endodontic Sealers Modified with Silver Vanadate: Antibacterial, Compositional, and Setting Time Evaluation. BioMed Research Internationa. 2019;2019:1-9.
98. Dornelles NBJ, Collares FM, Genari B, de Souza Balbinot G, Samuel SMW, Arthur RA, et al. Influence of the addition of microsphere load amoxicillin in the physical, chemical and biological properties of an experimental endodontic sealer. J Dent. 2018;68:28-33.
99. Loyola-Rodriguez JP, Torres-Méndez F, Espinosa-Cristóbal LF, García-Cortes JO, Loyola-Leyva A, Gonzalez FJ, et al. Antimicrobial activity of endodontic sealers and medications containing chitosan and silver nanoparticles against Enterococcus faecalis. J Appl Biomater Func. 2019;17(3):228080001985177.
100. Beshr K, Abdelrahim R. Antibacterial efficacy of Allium sativum (garlic) and chitosan incorporated into two root canal sealers against Enterococcus faecalis: comparative study. Tanta Dent J. 2019;16.
101. Monteiro JC, Garcia IM, Leitune VCB, Visioli F, de Souza Balbinot G, Samuel SMW, et al. Halloysite nanotubes loaded with alkyl trimethyl ammonium bromide as antibacterial agent for root canal sealers. Dent Mater. 2019;35(5):789-96.
102. Baras BH, Melo MAS, Thumbigere-Math V, Tay FR, Fouad AF, Oates TW, et al. Novel Bioactive and Therapeutic Root Canal Sealers with Antibacterial and Remineralization Properties. Materials (Basel). 2020;13(5):1096.
103. Baras BH, Sun J, Melo MAS, Tay FR, Oates TW, Zhang K, et al. Novel root canal sealer withdimethylaminohexadecyl methacrylate,nano-silver and nano-calcium phosphate to kill bacteria inside root dentin and increase dentin hardness. Dent Mater. 2019;35:1479-89.
104. Baras BH, Wang S, Meloa MAS, Tay F, Fouade AF, Arola DD, et al. Novel bioactive root canal sealer with antibiofilm and remineralization properties. J Dent. 2019;83:67-76.
105. Jerri Al-Bakhsh BA, Shafiei F, Pourhajibagher M, Shekofteh K, Hashemian A, Behroozibakhsh M. The antibacterial activity of an epoxy resin-based dental sealer containing bioactive glass, hydroxyapatite, and fluorohydroxyapatite nanoparticles against Enterococcus Faecalis and Streptococcus mitis. Nanomed J. 2020;7(1):13-20.
106. Camargo CHR, Gomes LCL, França MCM, Bittencourt TS, Valera MC, Camargo SEA, et al. Incorporating N-acetylcysteine and tricalcium phosphate into epoxy resin-based sealer improved its biocompatibility and adhesiveness to radicular dentine. Dent Mater. 2019;35(12):1750-6.
107. Dong W, Chen R, Lin YT, Huang ZX, Bao GJ, He XY. A novel zinc oxide eugenol modified by polyhexamethylene biguanide: Physical and antimicrobial properties. Dent Mater J 2020;39(2).
108. Mohammed HF, Ibrahim MM, El-Fattah HA, El-Fattah A, Shalaby TI. Antibacterial effect of two types of nano particles incorporated in zinc oxide based sealers on Enterococcus faecalis (in vitro study). Alex Dent J. 2016;41:169-75.
109. Sridevi A, Sindhu J, Naveen DN, Nirupama DN, Nainan MT. Antibacterial effect of fluorinated graphene and zinc oxide nanoparticles incorporated in zinc oxide-based sealers on Enterococcus faecalis (in vitro study). Saudi J Dent Res. 2019;6(2):81-7.
110. Bailón-Sánchez ME, Baca P, Ruiz-Linares M, Ferrer-Luque CM. Antibacterial and anti-biofilm activity of AH Plus with chlorhexidine and cetrimide. J Endod. 2014;40(7):977-81.
111. Weckwerth PH, De Souza Lima FL, Greatti VR, Duarte MAH, Vivan RR. Effects of the association of antifungal drugs on the antimicrobial action of endodontic sealers. Braz Oral Res. 2015;29(1):1-7.
112. Teixeira ABV, Vidal CL, Albiasetti T, de Castro DT, dos Reis AC. Influence of adding nanoparticles of silver vanadate on antibacterial effect and physicochemical properties of endodontic sealers. Iranian Endod J. 2019;14(1):7-13.
113. Teixeira ABV, de Castro DT, Schiavon MA, dos Reis AC. Cytotoxicity and release ions of endodontic sealers incorporated with a silver and vanadium base nanomaterial. Odontology. 2020.
114. Akhgari A, Shakib Z, Sanati S. A review on electrospun nanofibers for oral drug delivery. Nanomed J. 2017;4(4):197-207.
115. Sharifi F, Sooriyarachchi Ac, Altural H, Montazami R, Rylander MN, Hashemi N. Fiber-based approaches as medicine delivery systems. ACS Biomater Sci Eng. 2016;2(9):1411-31.
116. Manickam L, Rana D, Ramalingam M. Ceramic nanofiber composites. 2017. p. 33-54.
117. Palasuk J, Kamocki K, Hippenmeyer L, Platt JA, Spolnik KJ, Gregory RL, et al. Bimix antimicrobial scaffolds for regenerative endodontics. J Endod. 2014;40(11):1879-84.
118. Albuquerque MT, Evans JD, Gregory RL, Valera MC, Bottino MC. Antibacterial TAP-mimic electrospun polymer scaffold – effects on P. gingivalis-infected dentin biofilm. Clin Oral Investig. 2016;20(2):387-93.
119. Kamocki K, Nor JE, Bottino MC. Dental pulp stem cell responses to novel antibiotic-containing scaffolds for regenerative endodontics. Int Endod J. 2015;48(12):1147-56.
120. Bottino MC, Albuquerque MTP, Azabi A, Münchow EA, Spolnik KJ, Nör JE, et al. A novel patient-specific three-dimensional drug delivery construct for regenerative endodontics. J Biomed Mater Res B Appl Biomater. 2019;107(5):1576-86.
121. Montero-Miralles P, Martın-Gonzalez J, Alonso-Ezpeleta O, Jimenez-Sanchez MC, Velasco-Ortega E, Segura-Egea JJ. Effectiveness and clinical implications of the use of topical antibiotics in regenerative endodontic procedures: a review. Int Endod J. 2018;51(9):981-8.
122. Zargar N, Rayat Hosein Abadi M, Sabeti M, Yadegari Z, Akbarzadeh Baghban A, O D. Antimicrobial efficacy of clindamycin and triple antibiotic paste as root canal medicaments on tubular infection: An in vitro study. Aust Endod J. 2018;45(1):86-91.
123. Karczewski A, Feitosa SA, Hamer EI, Pankajakshan D, Gregory RL, Spolnik KJ, et al. Clindamycin-modified triple antibiotic nanofibers: A stain-free antimicrobial intracanal drug delivery system. J Endod. 2018;44(1):155-62.

124.Gilad JZ, Teles R, Goodson M, White RR, Stastienko P. Development of a clindamycin impregnated fiber as on intercanal medication in endodontic therapy. J Endod. 1999;25(11):722-7.
125.Tort H, Aybala-Oktay E, Tort S, Rasit-Bayar G, Toksoy-Topcu F, Kilic E, et al. Evaluation of ornidazole-loaded nanofibers as an alternative material for direct pulp capping. J Drug Deliv Sci Tec. 2017;41:317-24.
126.Rahimi S, Janani M, Lotfi M, Shahi S, Aghbali A, Vahid Pakdeld M, et al. A review of antibacterial agents in endodontic treatment. Iran Endod J. 2014;9(3):161-8.
127.Vaishali A, Madhu Varma K, Arun Bhupathi P, Sreenivasa Bharath T, Ramesh MV, Venkata Karteek Varma P. In vitro evaluation of antimicrobial efficacy of 2% chlorhexidine loaded electrospun nanofibers. J Pierre Fauchard Acad (India Section). 2017;31(2):105-8.
128.Lee DY, Spangberg LS, Bok YB, Lee CY, Kum KY. The sustaining effect of three polymers on the release of chlorhexidine from a controlled release drug device for root canal disinfection. Oral surg oral med oral pathol oral radiol endodo. 2005;100(1):105-11.
129.Leong DJ, Setzer FC, Trope M, Karabucak B. Biocompatibility of two experimental scaffolds for regenerative endodontics. Restor Dent Endod. 2016;41(2):98-105.
130.Tomeh MA, Hadianamrei R, Zhao X. A review of curcumin and its derivatives as anticancer agents. Int J Mol Sci. 2019;20(5):1033.
131.Sotomil JM, Münchow EA, Pankajakshan D, Spolnik KJ, Ferreira JA, Gregory RL, et al. Curcumin—a natural medicament for root canal disinfection: effects of irrigation, drug release, and photoactivation. J Endod. 2019;45(11):1371-7.
132.Qin W, Chen JY, Guo J, Ma T, Weir MD, Guo D, et al. Novel calcium phosphate cement with metformin-loaded chitosan for odontogenic differentiation of human dental pulp cells. Stem Cells Int. 2018;2018:1-10.
133.JM G-T, Vázquez-García F, Bosso-Martelo R, Bernardi M, Faria G, Tanomaru-Filho M. Effect of addition of nano-hydroxyapatite on physico-chemical and antibiofilm properties of calcium silicate cements. J Appl Oral Sci. 2016;24(3):204-10.
134.Vázquez García F, Tanomaru-Filho M, Chávez-Andrade GM, Bosso Martelo R, Basso-Bernardi MI, Guerreiro-Tanomaru JM. Effect of silver nanoparticles on physicochemical and antibacterial properties of calcium silicate cements. Braz Dent J. 2016;27(5):508-14.
135.Jonaidi-Jafari N, Izadi M, Javidi P. The effects of silver nanoparticles on antimicrobial activity of ProRoot mineral trioxide aggregate (MTA) and calcium enriched mixture (CEM). J Clin Exp Dent. 2016;8(1):22-6.
136.Kumar VB, Kumar KS, Paik P. Recent advancement in functional core-shell nanoparticles of polymers: synthesis, physical properties, and applications in medical biotechnology. J Nanopart. 2013;1.
137.Ghosh-Chaudhuri R, Paria S. Core/shell nanoparticles: classes, properties, synthesis mechanisms, characterization, and applications. Chem Rev. 2012;112(4):2373-433.
138.Srdić VV, Mojić B, Nikolić M, Ognjanović S. Recent progress on synthesis of ceramics core/shell nanostructures. Process Appl Ceram. 2013;7(2):45-62.
139.Shrestha S, Kishen A. Temporal-controlled bioactive molecules releasing core-shell nano-system for tissue engineering strategies in endodontics. Nanomedicine 2019;18:11-20.
140.Ertem E, Gutt B, Zuber F, Allegri S, Le Ouay B, Mefti S, et al. Core-shell silver nanoparticles in endodontic disinfection solutions enable long-term antimicrobial effect on oral biofilms. ACS App Mater Interfaces 2017;9(40):34762-72.
141.Wang L, Liu Y, Peng X, Sun Y, Liu X, Liu H, et al. Preparation and characterization of CaO/ZnO core-shell structured nanoparticles. Chem Res Chin Univ. 2020.
142.Sánchez-Sanhueza G, Rebolledo S, López J, Encalada M, Bello-Toledo H, Rojas D, et al. Synthesis of copper canowires and their antimicrobial activity on strains isolated persistent endodontic infections. J Nanosci Nanotechnol. 2018;18(7):4507-14.
143.Chung SH, Park Y-S. Local drug delivery in endodontics: A literature review. Journal of Drug Delivery Science and Technology. 2017 2017/06/01/;39:334-40.
144.Lee DK, Kim SV, Limansubroto AN, Yen A, Soundia A, Wang CY, et al. Nanodiamond-gutta percha composite biomaterials for root canal therapy. ACS Nano. 2015;9(11):11490-501.
145.Alves MJ, Grenho L, Lopes C, Borges J, Vaz F, Vaz IP, et al. Antibacterial effect and biocompatibility of a novel nanostructured ZnO-coated gutta-percha cone for improved endodontic treatment. Mater Sci Eng C. 2018;92:840-8.
146.Jhamb A, Chaurasia VR, Masamatti VKS, Agarwal JH, Tiwari S, Nair D. In vitro evaluation of antimicrobial activity of different Gutta-percha points and calcium hydroxide pastes. J Int Soc Prev Community Dent. 2014;4(2):92-5.
147.Parhizkar A, Nojehdehian H, Asgary S. Triple antibiotic paste: momentous roles and applications in endodontics: a review. Restor Dent Endod. 2018;43(3):e28.
148.Wang D, Wang Z, Gao J. The development and in vitro release rate determination of controlled-release delivery gutta-percha point containing metronidazole compound. Hua Xi Kou Qiang Yi Xue Za Zhi. 2003;21:361-3.
149.Zhao MX, Zhu BJ. The research and applications of quantum dots as nano-carriers for targeted drug delivery and cancer therapy. Nanoscale Res Lett. 2016;11(1):207.
150.Li X, Guo H, Ren S, Fan R, Yu Y, Zhang H, et al. Fluorescent labelling in living dental pulp stem cells by graphene oxide quantum dots. Artif Cells Nanomed Biotechnol. 2019;47(1):115-22.

Please cite this paper as: Shahri F, Parhizkar **A**. Pivotal Local Drug Delivery Systems in Endodontics; a Review of Literaturet. Iran Endod J. 2020;15(1): 65-78. *Doi: 10.22037/iej.v15i2.30374.*