The Development of Controlled Releasing Drug (CRD) Device For Root Canal Disinfection

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The Development of Controlled Releasing Drug (CRD) Device For Root Canal Disinfection

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This certifies that the master thesis of Youngbin Bok is approved.

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2003 년 12 월

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Abstract

The Development of Controlled Releasing Drug (CRD) device For Root Canal Disinfection

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(Directed by Professor Kee-Youn Kum, D.D.S., M.S.D., Ph.D.)

The aim of this *in vitro* study was to develop a slow releasing root canal disinfectant based on chlorhexidine digluconate (CHX) and polymers such as chitosan, polymethyl methacrylate (PMMA), polylactide-co-glycolide (PLGA).

Five different prototypes with different formulations were prepared. Group A; paper points, control, loaded with 20% CHX. Group B; as group A, but the points

was coated with chitosan. In Groups C, D and E, the paper points were treated in the same way as for group A and then coated three times with 5% PMMA(Group C, Aldrich®, USA), or coated three times with 3% PLGA (Group D, Sigma®, USA), or coated five times with 3% PLGA (Group E). The 10 different prototypes were randomly chosen in groups A, B, C, D, E and soaked with 3 ㎖ distilled water in cuvette. The concentrations of CHX in distilled water were determined using a UV spectrophotometer. The surfaces characteristics of each prototype were observed using a scanning electron microscope at magnifications of 100x and 5000x.

The results were as the follows;

1. Release rate of CHX was greatest in the Group A (Non-coated), followed by the group B (Chitosan coating), the group C (3X PMMA coating), the group D (3X PLGA coating), and the group E (5X PLGA coating) ($P<0.05$).
2. Pores were observed in coated surfaces of the group C, D and E by SEM.
3. When the pore size was smaller, the release rate was lower.

This data indicates that the release rate of CHX may be controlled by the polymer coating.

Key words: Controlled release drug device, Chlorhexidine digluconate, Chitosan, Polymethyl methacrylate, Polylactide-co-glycolide, Root canal disinfectant.

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I. Introduction

Endodontic disease is caused primarily by bacteria (Kakehashi S 1965, Sunqvist G 1976, Möller AJR 1981). Complete debridement and disinfection of the pulpal space are considered essential for predictable long-term success in endodontic treatment. Residual pulpal tissue, bacteria, and dentin debris may, however, persist in the irregularities of root canal systems, even after meticulous mechanical preparation (Abou-Rass M, Piccinino MV, 1982). Therefore, several irrigating solutions have been recommended for use in combination with

mechanical preparation. However, the efficacy of these procedures also depends upon the vulnerability of the species in the root canal system.

Most available root canal medicaments, such as camphorated parachlorphenol or iodine potassium iodide (IKI), are bactericidal. However, they are effective for only a few hours. After they have expired, microorganisms can repopulate the root canal (Byström A, Claesson R, Sundquvist G, 1985). Another commonly used medicament, calcium hydroxide, though it remains bioactive for weeks (Byström A, Claesson R, Sundquvist G, 1985), is not very effective against specific enteric bacteria such as *Enterococcus Facecalis* (Østavik D, Haapasalo M, 1990) that are frequently associated with failures of root canal treatment (Sundqvist G, Figdor D, Sjogren U, 1998). Also the ability of calcium hydroxide to affect microorganisms harbored in the dentinal tubules is questionable (Østavik D, Haapasalo M, 1987). In contrast, chlorhexidine digluconate(CHX) effectively eliminates oral microorganisms when it is applied to treat periodontal disease and its antimicrobial efficacy equals that of conventional root canal medicaments (Siqueira JF, M. de Uzeda, 1997). Unlike other medicaments, CHX binds to the dentin and thus induces substantive antimicrobial activity at the dentin surface (Parsons GJ et al, 1980). Such activity can be obtained by irrigating the root canal with CHX (White RR, Hays GL, Janer L.R, 1997). Nevertheless, to resist re-infection, the canal has to be exposed to CHX for longer times, preferably 1 week (Komorowski R et al, 2000). In addition, for patients who may miss a scheduled

revisiting time, an even longer period of drug exposure is required in order to protect the canal from reinfection. Hence, a major therapeutic goal is to develop a vehicle to deliver chlorhexidine to root canals for extended periods of times.

Chitosan, polylactide–co–glycolide (PLGA), and polymethyl methacrylate (PMMA) whose polymers used in this study, are well known for controlling drug release. Miyazaki et al (1988) observed the sustaining effect of chitosan on the release of indomethacin(water insoluble drug) from granules, a sustained plateau level of indometacin was obtained for drug/chitosan granules (1:2 mixture) versus a sharp peak for conventional commercial capsules in a rabbit model. The applicability of chitosan (degree of deacetylation: 92.7%) as a vehicle for the sustained release (SR) of water soluble drug (propranolol HCl) was examined. The retardation in drug release was observed to be proportional to the chitosan content and was attributed to the gel forming ability of chitosan in media of low pH (Sawayanagi Y et al, 1982)

PLGA is one of the best known biodegradable polymers, it is hydrolyzed without enzymes and metabolized by the body (Cam D, 1998). PLGA has been used as surgical sutures of bone-connecting devices and has been proven nontoxic (Visscher GE, 1985) Moreover, the degradation rate of PLGA can be regulated by changing its molecular weights, chemical composition, and crystallinity. Therefore, PLGA seems to be promising controlled drug release carrier.

PMMA has been used as a denture base, and recently it was used in a controlled drug release device. Several studies have shown that it can be used as a controlled drug release carrier for antibiotics, for the prevention and treatment of the osteomyelitis (Jerome CH, John JJ 2002, Bayston R, Milner RDG 1982, Eva Diez-Pena et al 2002).

Therefore, the aim of this *in vitro* study was to develop a slowly releasing root canal disinfectant using CHX and polymers such as chitosan, PLGA, and PMMA.

II. MATERIALS AND METHODS

1. Standard graph of CHX concentration and UV absorbance.

CHX solution (20% w/w, Sigma, USA) was diluted serially in 1:1 ratios, and the UV absorbance was measured each dilution using a UV spectrophotometer. A standard graph of CHX concentration versus UV absorbance was used to determine concentration.

2. Preparation of a prototype of CRD.

Paper points (Sure-Endo ™, #80, Korea) were used as the core material. We designed five different devices using the following formulations: group A; paper points were loaded with CHX. Group B; after loading with CHX points were coated with chitosan (Texan MedTech, Korea). Groups C, D and E, were as Group B except that the points were coated with three times with 5%PMMA (Group C, Aldrich®, USA), three times with 3% PLGA (Group D, Sigma®, USA), five times with 3% PLGA (Group E), repectively. Each group was randomly allocated with 10 samples which chose almost same weight.

3. In vitro Release test of CHX.

Each prototype was soaked in 3 ㎖ of distilled water. 10 ㎕ of this solution was then sampled at predetermined times (i.e., AT 3, 6, 10, 20, 30, 40 and 50 min and

at 1, 2, 3, 4, 5 and 6h, and at 7days). UV absorbance was measured using a UV spectrophotometer (Shimadzu, Japan)

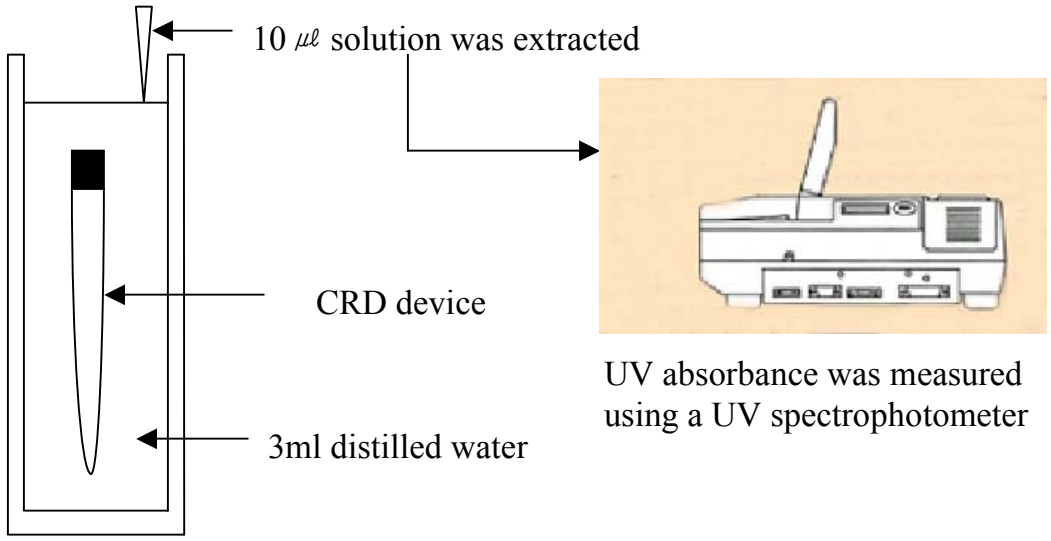


Figure 1. Schematic description of experimental methods

4. Findings of Surface

The surfaces characteristics of each prototype were observed under a scanning electron microscope (SEM, Hitachi, Japan) at magnifications of 100x and 5000x.

5. Statistical analysis.

One way ANOVA test was used to compare the release rates of CHX in each group.

III. Results

1. Standard graph of CHX concentration and UV absorbance.

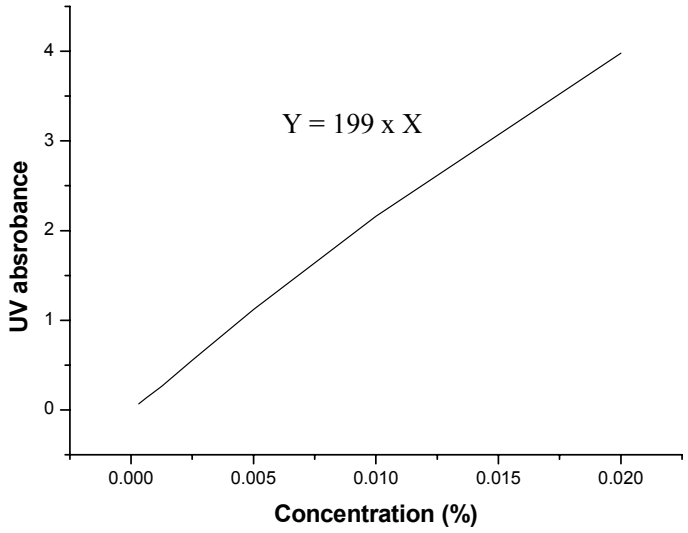


Figure 2. Standard graph of CHX concentration and UV absorbance (X: concentration of CHX, Y: UV absorbance).

	Paper points	CHX loading
Weight(g)	$0.017 \pm 7.37 \times 10^{-5}$	$0.033 \pm 8.43 \times 10^{-5}$

Table 1. The weight of prototype which was loaded of CHX on paper points.

From Table 1, we found that the weight of CHX loaded onto the paper points was 0.016g/point in all cases. If all loaded CHX has been released into 3 ㎖ distilled water, the concentration would have been about 0.55%. From Figure 1, we calculated that the UV absorbance of 0.55% CHX was about 1.1, which thus represented the maximum UV value.

2. Release rate of CHX from the CRD device

Statistically significant differences were found between the groups by One Way ANOVA ($p<0.05$). The release rate of the CHX was greatest in the group A (Non-coated), followed by group B (Chitosan coating), group D (three times 3% PLGA coating), group C (three times 5% PMMA coating), and group E (five times 3% PLGA coating).

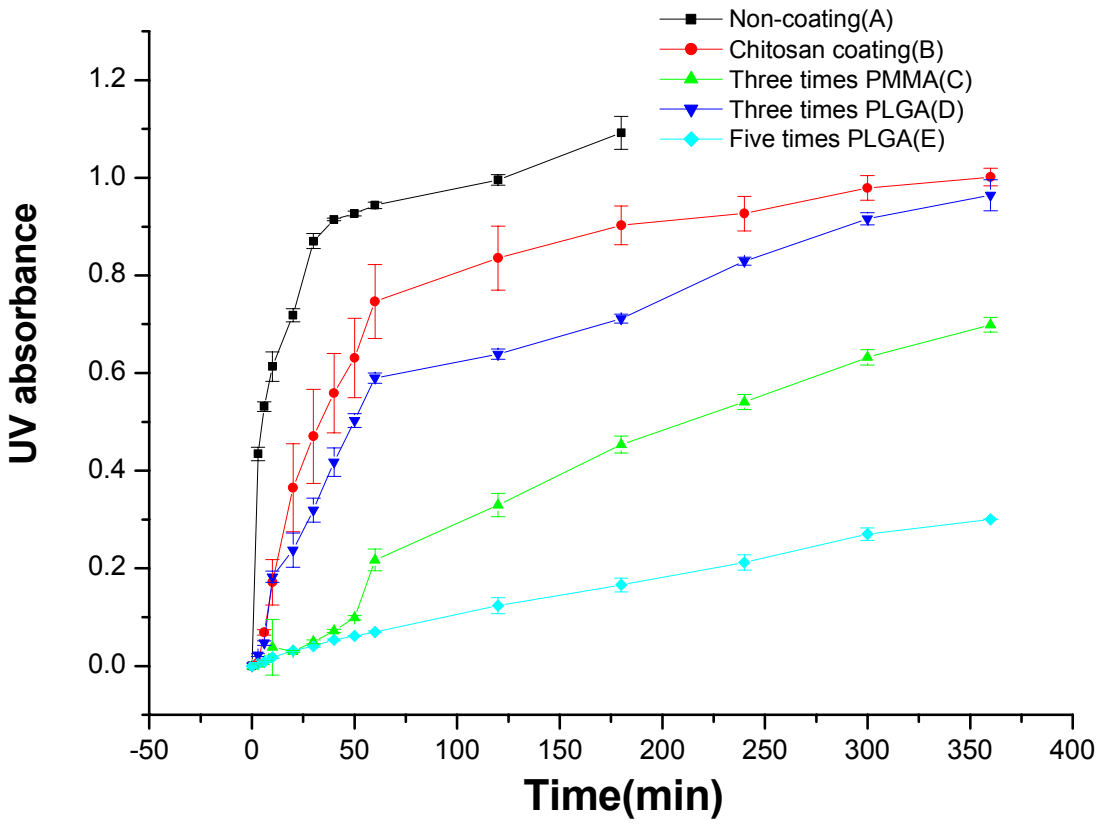


Figure 3. Short term release rate of CHX after immersion of CRD device in 3ml of distilled water.

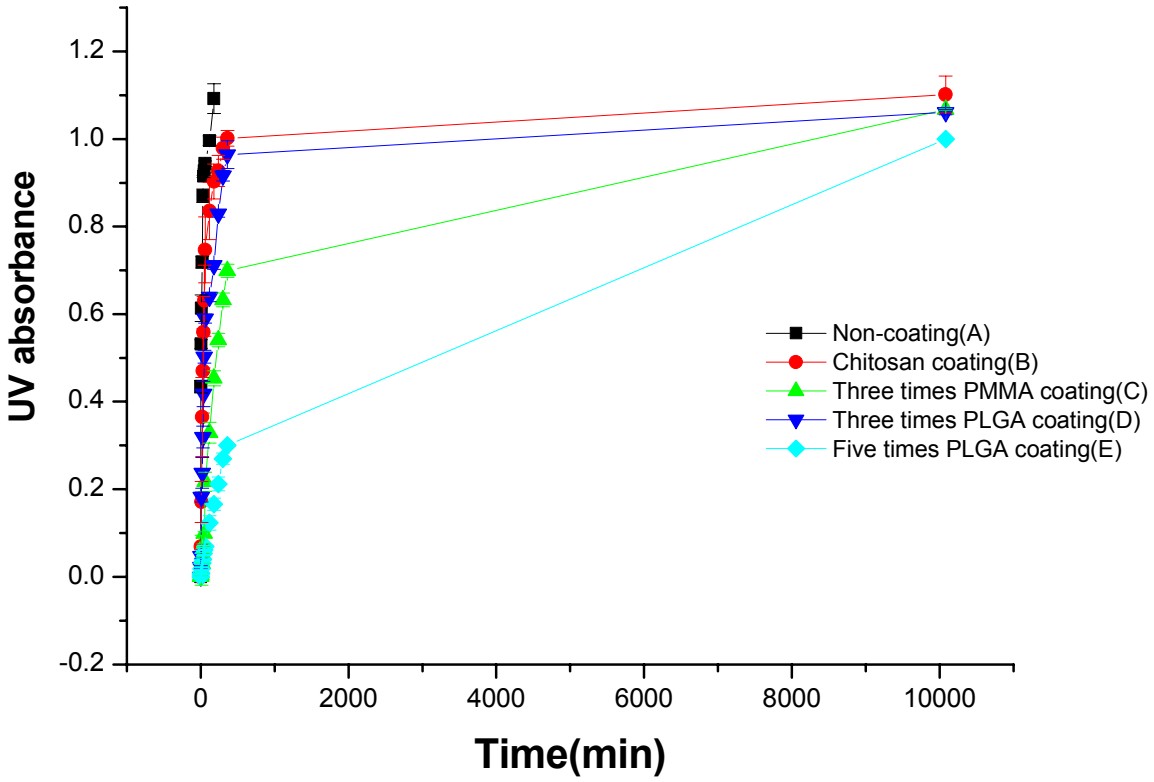
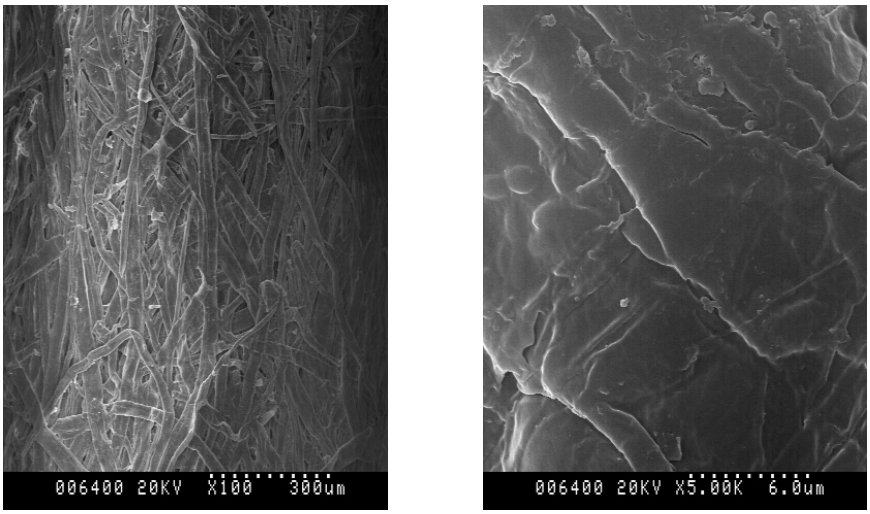


Figure 4. Long term release rate of CHX after immersing of the CRD device in 3ml of distilled water.

3. Surface characteristics of the CRD prototype by SEM

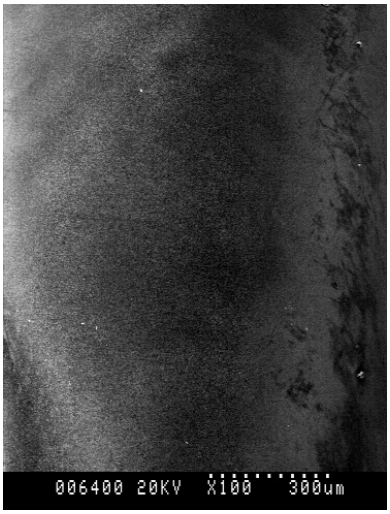
The surface characteristics of the CRD prototypes were determined by SEM. In group A (Non-coated), the fiber structure of paper point was unaffected.. In the polymer coating groups, a coated fiber structure and pores were observed. Pore

sizes were differed in the groups. In Figures 5 and 6, the pore size of group D is shown to be larger than that of group C. Figures 6 and 7 shown that different pore sizes change surface characteristics

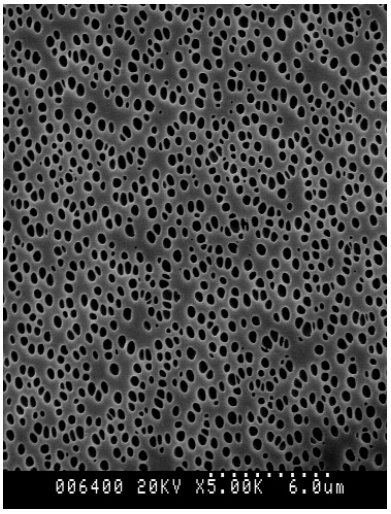


(a) (b)

Figure 5. SEM images of the non-coated paper point loaded CHX; (a) 100x (b) 5000x; the fiber structure of the paper point was observed without pores.

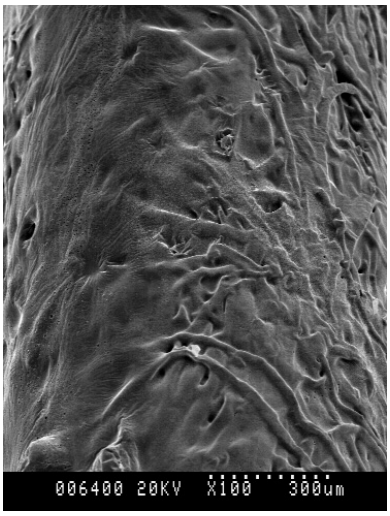


(a)

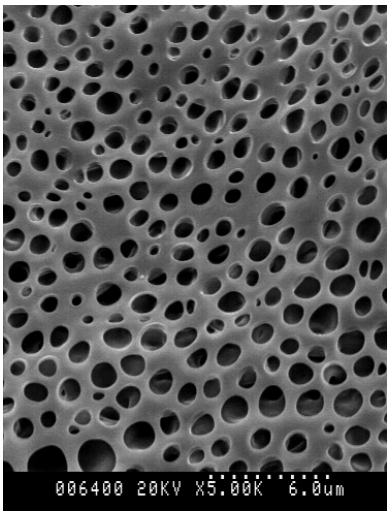


(b)

Figure 6. SEM images of a prototype CRD device coated with three times with 5% PMMA; (a) 100 x , (b) 5000 x.; pores were observed , all were about 0.15 μm.



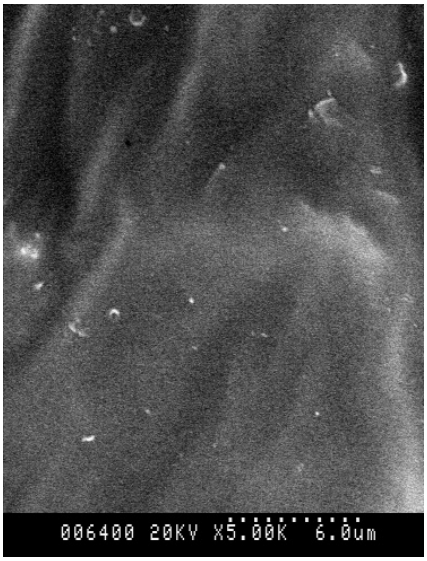
(a)



(b)

Figure 7. SEM images of a prototype CRD device coated with three times 3% PLGA coated; (a) 100x (b) 5000 x; pores of variable sizes were observed

(a)



(b)

Figure 8. SEM images of prototype CRD device coated five times with 3% PLGA (a) 100x (b) 5000 x; no pores were observed, because of their small size.

Ⅳ. Discussion

CHX has been suggested to prevent root canal reinfection (Jung S, Safavi K, Spångberg L, 1999). Unlike conventional medicaments, the positively charged molecules of CHX can adsorb onto dentin and prevent microbial colonization on the dentin surface for some time (Parson et al, 1980). When CHX is used as a root canal irrigant, its antimicrobial effect is short-lived (Jung S, Safavi K, Spångberg L, 1999). For long-term substantive antimicrobial activity to be achieved, the dentin must be exposed to CHX for a longer time than that afforded by irrigation (Heling et al, 1992a). A number of studies have developed the controlled release devices for CHX with substantive antimicrobial activity.

Huang J et al (2000), an in vitro study, developed a controlled release device. This cylindrical, needle-shaped device was prepared consisting of a matrix core and a polymer coating, and loaded with 30-45% CHX. The composition of the core, a blend of water-permeable polymers, and the thickness of the coating were tailored to allow various release rates. Four different formulations were prepared with different drug loadings and drug release mechanisms. The results obtained demonstrated that the releasing rate of the no coating formulation (F1) was very fast; in contrast the release rate of coatings containing formulations (F2, F3, F4) was far more controlled.

In our study, similar results were obtained. For group A (non-coated), the drug release was very fast, and within 2h all loaded CHX has been released. In

contrast, drug release from groups B, C, D and E were more controlled. Figure 3 shows that CHX was released over 7 days in groups B to E. This was similar to the results of the above studies groups D and E were of the same materials except for the thickness, and the release rate of the group E was slower than that of group D. This may have been caused by the surface characteristics. As seen in Figures 5, 6 and 7, pores were evident on polymer surface and the pore size differed in the groups. The pore size of group D was larger than the group C. No pores were observed in group E by SEM because of their small size. The release rate of the group E was lower than those of the other groups, thus we could conclude that the pores were smaller and the release rate was lower.

Sustained-release devices have been developed by several groups to treat periodontal disease. It has been demonstrated that a biodegradable device containing CHX was more effective than calcium hydroxide at disinfecting root canal dentin in bovine teeth (Heling I et al 1992a, Heling I et al 1992b). However, these devices were prepared for periodontal application and thus may have been unsuitable for root canal application. Unlike the periodontal pocket, the fluid present in root canals is minimal, and may be insufficient to facilitate drug release by degradation or diffusion. Secondly, in the case of a degradable polymer as carrier, the device may not have been completely degraded when the root canal should be filled. Remaining fragments may interfere with the permanent filling and sealing of the root canal, a result in leakage and bacteria ingress of bacteria.

Consequently, the infection of the filled root canal may occur (Petersson K et al, 1989). Third, owing to the size and shape of root canals, the materials and formulations useful for periodontal application may not have the mechanical strength needed to make the needle-shaped device for insertion into a root canal.

In our study, we tried to work around these problems. First, we used paper points as core materials as they were a more suitable shape for insertion into root canals. Secondly, we used the coating materials that are not degraded in root canals. Chitosan is not insoluble at an alkaline or neutral pH (Singla AK, Chawla M, 2001). PMMA which has been used for denture base is insoluble and non-degradable in the oral cavity. PLGA is biodegradable and has a the hydrolytic degradation mechanism and the degradation rate of PLGA can be controlled using the lactide, glycolide mole ratio(James MA, Matthew SS, 1997). Therefore, all the coating materials examined in the present study, are suitable for root canal treatment.

Based on the above results, we conclude that the different polymer coatings can be used to effectively on control the release of CHX. Further *in vivo* experiments are needed to evaluate the antimicrobial effects and the cytotoxicity of the CRD device.

Ⅴ. Conclusions

The aim of this *in vitro* study was to develop a slow releasing root canal disinfectant using CHX and polymers such as chitosan, PMMA, and PLGA. In this study, we used paper points, which are commonly met in clinics, as a core material. All the paper points were loaded with CHX, and coated with Chitosan, PMMA, and PLGA. All paper points either with coating or without it were placed in 3ml distilled water for a given period of time. Then we compared the releasing rate of CHX in all groups. The results were as follows.

1. The release rate of CHX was in the order of group A, group B, group D, group C, group E and it was statistically significance ($p< 0.05$)
2. The polymer coating was effective on controlled release of CHX.
3. Pore size was smaller, release rate was slower.

This data indicated that the release rate of CHX may be controlled by the surface coated with polymer

References

Abou-Rass M, Piccinino MV: The effectiveness of four clinical irrigation methods in the removal of root canal debris. *Oral surgery, Oral medicine and Oral pathology* 54: 323-8, 1998.

Baumgartner JC, Cuenin PR: Efficacy of several concentrations of sodium hypochlorite for root canal irrigation. *J of Endod* 18: 605-612, 1992.

Bayston R, Milner RDG: The sustained release of antimicrobial drugs from bone cement. *J Bone Joint Surg* 64B: 460-464, 1982.

Byström A, SundqvistG: Bacteriological evaluation of the efficacy of mechanical root-canal instrumentation in Endodontics therapy. *Scand J Dent Res* 89: 321-328, 1982.

Byström A, Claesson R, Sundquvist G: The antibacterial effect of camphorated paramonochlorophenol, camphorated phenol and calcium hydroxide in the treatment of infected root canals. *Endod Dental Traumatol* 1:170-175, 1985.

Cam D, Hyon SH, Ikada Y: Degradation of high molecular weight poly (L-lactide) in alkaline medium. *Biomaterials* 16:833-43, 1998.

Crank . J, The Mathematics of Diffusion. 2nd Edition ed. 1975, Oxford University Press, London.

Gomes BPFA, Ferraz CCR, Vianna ME: In vitro antimicrobial activity of several concentrations of sodium hypochlorite and chlorhexidine gluconate in the elimination of *Enterococcus faecalis. Int Endod* 34:424-428, 2001.

Gomes BPFA, Souza SFC, Ferraz CCR: Effectiveness of 2% chlorhexidine gel and calcium hydroxide against *Enterococcus faecalis* in bovine root dentin in vitro *Int Endod* 36:267-275, 2003.

Heling I, Sommer M, Steinberg D, Friedman M, Sela MN: Microbiological evaluation of the efficacy of chlorhexidine in a sustained-release device for dentine sterilization. *Int Endod* 25:15-19, 1992a.

Heling I, Steinberg D, Kenig S, Gavrilovich I, Sela MN, Friedman M: Efficacy of a sustained-release device containing chlorhexidine and $Ca(OH)_2$ in preventing secondary infection of dentinal tubules. *Int Endod* 25 :20-24, 1992b.

Heling I, Chandler NP: Antimicrobial effect of irrigant combinations within dentinal tubules. *Int Endod* 31: 8-14, 1998.

Huang J, Wong HL, Zhou Y, Wu XY, Grad H, Komorowski R: In vitro studies and modeling of a controlled-release device for root canal therapy. *J Cont Rel* 67:293-307, 2000.

Illum R: Chitosan and its use as a pharmaceutical excipient. *Pharm Res* 15: 1326-1331, 1998.

James MA, Matthew SS: Biodegradation and biocompatibility of PLA and PLGA microsphers. *Adv Drug Rev* 28:5-24, 1997.

Jung S, Safavi K, Spangberg L: the effectiveness of Chlorhexidine in the prevention of root canal reinfection [abstract]. *J Endod* 25:288, 1999.

Kakehashi S, Stanley HR, Fitzgerald RJ: The effects of surgical exposures of dental pulps in germ-free and conventional laboratory rats. *Oral Surg Oral Med Oral Pathol* 20:340-9, 1965

Kas HS : Chitosan: properties, preparation and application to microparticulate systems. *J Microencap* 14: 689-711, 1997.

Komorowski R, Friedman S, Grad H, Wu XY: Antimicrobial substantivity of chlorhexidine-treated bovine root dentin. *J Endod* 26: 652-655, 2000.

Miyazaki S, Yamaguchi H, Yokouchi C, Takada M, Hou WM: Sustained-release and intragastric-floating granules of indomethacin using chitosan in rabbits. *Chem Pharm Bull* 36: 4033-4038, 1988.

Möller AJR, Fabricius L, Dahlen G: Influence on periapical tissues of indigerousoral bacteria and necrotic pulp tissue in monkeys. *Scand J Dent Res* 89:475-84, 1965.

Molander A, Reit C, Dahlen G and Kvist T: Microbiological status of root-filled teeth with apical periodontits. *Int Endod* 31: 1-7, 1998.

Østavik D, Haapasalo M: Disinfection by endodontic irrigants and dressings by experimentally infected dentinal tubules. *Endod Dent Traumatol* 6:142-149,1990.

Østavik D, HaapasaloM: In-vitro infection and disinfection of dentinal tubules. *J Dent Res* 66:1375-1379, 1987.

Roseman TJ, Higuchi WI: Release of medroxyprogesterone acetate from a silicone polymer. *J Pharm Sc* 59: 353-357, 1970.

Parsons GJ, Patterson SS, Miller CH, Katz S, Kafrawy AH, Newton CW: Uptake and release of chlorhexidine by bovine pulp and dentin specimens and their subsequent acquisition of antibacterial properties. *Oral Surg* 49:455-459, 1980.

Peciuliene V, Balciuniene I, Eriksen HM, Haapasalo M: Isolation of Enterococcus faecalis in previously root-filled canals in a Lithuanian population. *J Endod* 26: 593-595, 2000.

Petersson K, Lewin B, Hakansson J, Olsson B, Wennberg A : Endodontic status and suggested treatment in a population requiring substantial dental care. *Endod Dent Traumatol* 5: 153-158, 1989.

Sawayanagi Y, Nambu N, Nagai T: Use of chitosan for sustained-release preparations of water-soluble drugs. *Chem Pharm Bull* 30: 4213-4215, 1982.

Senel S, Ikinci G, Kas S, Yousefi-Rad A, Sargon MF, Hincal AA: Chitosan films and hydrogels of cholrhexidine gluconate for oral mucosal delivery. *Int J Pharm* 193 : 197-203, 2000.

Singla AK, Chawla M: Chitosan: some pharmaceutical and biological aspects-an update. *J Pharm Pharm* 53:1047-1067, 2001.

Siqueira JF, M de Uzeda: Intracanal medicaments: evaluation of the antibacterial effects of chlorhexidine, metronidazole and calcium hydroxide associated with three vehicles. *J Endodon* 23:167- 69, 1997.

Sundqvist G, Figdor D, SjogrenU: Microbiologic analysis of teeth with failed endodontic treatment and the outcome of conservative re-treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 85: 86-93.1998.

Sundqvist G: Bacteriological studies of necrotic dental pulps. Umea University Odontological Dissertations No.7, 1976.

Visscher GE, Robinson RJ, Maulding HV, Fong JW, Person JE, Angentieri GJ: Biodegradation of and tissue reaction to 50:50 Poly (DL-lactide-co-glycolide) microcapsules. *J biomed Mater Res* 19:349, 1985.

White RR, Hays GL, Janer LR : Residual antimicrobial activity after canal irrigation with chlorhexidine. *J Endod* 23: 229-231, 1997.

Wu X.Y, Zhou Y: Studies of diffusional release of a dispersed solute from polymeric matrices by finite element method. *J Pharm Sci* 88: 1050- 1057, 1999.

국문요약

약물 제어 방출형 근관 소독재의 개발

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복영빈

치수 치근단 병변의 주요한 원인은 세균이지만, 근관 세정 및 성형 후에도 이러한 세균이 남아 있을 수 있으므로, 부가적인 근관 소독제의 역할이 필요하다. *Enterococcus faecalis* 는 근관 치료 실패의 주요 원인 균으로, 통상적인 근관 소독제인 calcium hydroxide 에도 저항성을 나타내므로 최근 이에 효과적인 chlorhexidine gluconate(CHX)에 대한 연구가 활발히 이루어지고 있다. 그러나, CHX 가 근관 세척제로 사용되어 짧은 시간 동안 dentin 표면에 접촉하게 되면, 그 효과가 줄어들게 되므로, 일정 기간 서서히 방출될 수 있는 제어 방출형 약물 전달 시스템이 필요하다. 이번 실험의 목적은 chitosan, polymethyl methacrylate (PMMA), polylactide-co-glycolide(PLGA) 등의 biopolymer 를 이용하여 CHX 를 제어 방출하는 근관 소독제를 개발하는 것이었다. 80 번 ISO size paper point (Sure-Endo ™, #80, Korea) 에 20% CHX 를 loading 한 후 다음과 같이 다섯 군으로 분류하였다. Group A; 아무 것도 coating 하지 않은 대조군, Group B;

Chitosan (Texan MedTech, Korea) coating 군, Group C; 5% PMMA (Aldrich®, USA) 3 회 coating 군, Group D; 3% PLGA (Sigma®, USA) 3 회 coating 군, Group E; 3% PLGA 5 회 Coating 군으로 각 군은 10 개의 sample 로 이루어져 있으며, CHX 함유되는 양을 동일하게 하기 위해, paper point 에 CHX 를 loading 한 무게를 측정하여 유사한 무게의 sample 을 선택하여 사용하였다. 모든 시편은 3ml 증류수가 담긴 cuvette 에 넣은 후 3, 6, 10, 20, 30, 40, 50 분 마다, 1, 2, 3, 4, 5, 6 시간 마다 각각 10 ㎕씩 채취하고, 1 주일 후 다시 10 ㎕을 채취하여 UV 흡광도를 측정하여 CHX 의 방출 속도를 비교하였다. 또한, 표면 관찰을 위하여 100 배와 5000 배의 SEM 사진을 촬영한 후 얻은 실험 결과는 다음과 같았다.

1. CHX 의 방출 속도는 Group A, Group B, Group D, Group C, Group E 순이었으며 각 군간에는 통계학적인 유의차가 있었다 ($p<0.05$).

2. Polymer coating 을 한 group B, C, D, E 에서는 CHX 방출이 7 일간 지속되었다.

2. SEM 사진에서 PMMA 나 PLGA 를 도포한 CRD 의 표면에서는 pore 가 관찰되었으며, pore size 가 커질수록 방출속도가 빨랐다.

결론적으로 polymer coating 두께에 따라 pore size 가 달라짐을 알 수 있었고 또한 약물의 방출 속도를 제어 할 수 있어 향 후 서방형 근관 소독제의 개발에 박차를 가할 수 있을 것으로 사료된다.

핵심되는 말 : 약물 제어 방출형 근관 소독제, Chlorhexidine gluconate, Chitosan, Polymethyl methacrylate, Polylactide-co-glycolide