

Evaluation of calcium ion release and change in pH on combining calcium hydroxide with different vehicles

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Abstract

Introduction: Intracanal medicaments have traditionally been used in endodontics to disinfect root canals between appointments. Calcium hydroxide is widely used as an intracanal medicament for disinfection and to promote periapical healing. It is stable for long periods, harmless to the body, and bactericidal in a limited area. The efficacy of calcium hydroxide as a disinfectant is dependent on the availability of the hydroxyl ions in the solution that depends on the vehicle in which the calcium hydroxide is carried. In general, three types of vehicles are used: Aqueous, viscous or oily. Some *in vitro* studies have shown that the type of vehicle has a direct relationship with the concentration and the velocity of ionic liberation as well as with the antibacterial action when the paste is carried into a contaminated area. **Aim of the Study:** To evaluate the calcium ion release and measure the change in pH of the environment that occurred when calcium hydroxide was combined with different vehicles (distilled water, propylene glycol, calcium hydroxide containing gutta-percha points and chitosan) over different time periods. **Materials and Methods:** Forty single rooted mandibular first premolar teeth were decoronated for this study. Working length was established and the root canals were enlarged and irrigation accomplished with 2 ml of NaOCl solution after every file. The teeth were then randomly divided into four groups. The canals were then packed with different preparations of calcium hydroxide using the following vehicles-distilled water, propylene glycol, gutta-percha points and chitosan. Calcium ion release in different groups was analyzed using an ultraviolet spectrophotometer at 220 nm. The change in pH of was determined using a pH meter. Results were statistically evaluated using one-way ANOVA test. **Result:** For calcium ion release, Group 2 showed cumulative drug release of 81.97% at the end of 15 days, whereas Group 1, 3 and 4 showed a release of 99.53, 17.98, 74.93% respectively with a significant difference among all groups. Group 1 reached the highest Ca^{2+} level (39.79%) at the end of 1 day but showed almost complete release of calcium hydroxide at the end of 15 days. Group 3 showed least calcium ion release (17.98%) at 15 days. Group 4 showed a sustained release of Ca^{+2} ions from 74% at 15 days to 95% at the end of 30 days. After the 1st h; Group 1 showed the highest pH level (11.8). However, pH reduced to 7.8 at the end of 30 days in this group. Group 2 showed the highest pH value (10.35), followed by Group 4 (10.32) after 30 days. **Conclusion:** Chitosan can be used as a promising vehicle for calcium hydroxide to maintain an alkaline pH and to allow sustained release of calcium ions in the root canal system.

Keywords: Calcium hydroxide, chitosan, intracanal medicament

Introduction

Reduction of endodontic microbiota during root canal therapy has been achieved by a series of antimicrobial strategies such as preparation, irrigation, intracanal dressing, etc.^[1]

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An intracanal medicament is a drug, traditionally used in endodontics to disinfect root canals between appointments.^[2] Intracanal medicaments are stable for varying periods, harmless to the body, and bactericidal in a limited area. Calcium hydroxide is the preferred material for an intracanal dressing because of its favorable antimicrobial action.^[3]

The mechanism of action of calcium hydroxide is attributed directly to its ability of dissociating into calcium and hydroxyl ions resulting in increased pH locally.^[4] *In vitro* studies have shown that the type of vehicle has a direct relationship with the concentration and the velocity of ionic liberation and the antibacterial action.^[5]

An aqueous vehicle promotes solubility, causing it to be rapidly resorbed by macrophages; canal must be redressed several times until the desired effect is achieved.^[6]

Viscous vehicles such as glycerine, polyethylene glycol are used. According to Silva, the high molecular weight of these vehicles minimizes the dispersion and maintains

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the paste for longer intervals, thus reducing the number of appointments.^[7]

Propylene glycol is widely employed as a useful vehicle for pharmaceutical preparations.^[8] Its hygroscopic nature permits the absorption of water, which ensures a good sustained release. Simon *et al.* recommend propylene glycol as the best vehicle for calcium hydroxide.^[9]

Calcium hydroxide has poor handling properties; its uniform distribution throughout the canal is difficult. Presence of residual calcium hydroxide can impede the properties of endodontic sealers. Recently, Roeko introduced calcium hydroxide releasing gutta-percha points that contain calcium hydroxide instead of zinc oxide at a concentration of 50–54% (wt.%). They combine the efficiency of calcium hydroxide in a matrix of bio-inert gutta-percha, which can be easily inserted and removed from the pulp space when their function is accomplished.

Chitosan is a cationic polymer derived from the exoskeleton of crustaceans (such as crabs).^[10]

Chitosan contains copolymers of glucosamine and N-acetyl glucosamine. Chitosan has been widely studied in the biomedical field and has been found to have antimicrobial and antifungal properties. The use of chitosan as an excipient in pharmaceutical formula is a recent development. The ability of chitosan to retain high amounts of water is a property, which could be of particular value in relation to slow-release formulations.^[11]

The aim of this study was to investigate the release of calcium ions and measure the pH change in the surrounding environment when calcium hydroxide was combined with different vehicles at different time intervals.

Materials and Methods

Specimen preparation

Extracted teeth were mechanically cleaned using an ultrasonic scaler. The teeth were verified radiographically as having patent and almost straight canals with similar size apical foramen. The crowns of all the teeth were removed at the cement enamel junction using a diamond disc. The length of each tooth was standardized to 15 mm. The root canals were enlarged initially to size 20 using K files. A size 10 K file was then placed in the canal until visible at the apical foramen. Working length was established 1 mm short of this length.

Canal preparation

Root canals were enlarged up to size 40 apically using K files. Irrigation was accomplished by 2 ml of 2.5% NaOCl solution. 2 ml of 17% ethylenediaminetetraacetic acid (EDTA) was used for final irrigation and then 5 ml of distilled water to remove any precipitate of EDTA [Table 1].

Table 1: Groups 1-4

Groups	
Group 1	Distilled water
Group 2	Propylene glycol
Group 3	Calcium hydroxide containing gutta-percha points
Group 4	Chitosan

Each tooth was stored in 5 ml of saline. The teeth were then randomly divided into four groups ($n = 10$).

Preparation of calcium hydroxide pastes

Group 1: Ca (OH)₂ powder was mixed with distilled water in powder to liquid ratio of 6:4.

Group 2: Propylene glycol was mixed with water using cyclomixer, the calcium hydroxide (1% w/v) suspended in water was then added to the gel base. It was mixed with magnetic stirrer at 800 rpm to obtain a homogenous distribution.

Group 3: Gutta-percha points (Hygenic) impregnated with calcium hydroxide.

Group 4: Chitosan, from crab shells, was soaked in 2% v/v acetic acid to obtain a gel base. To this formed base, calcium hydroxide (1% w/v) was added and mixed with magnetic stirrer.

For Group 1, 2 and 4 accurately measured quantities of different formulations were placed into the root canal using lentulo spirals until the canals were packed. For Group 3, calcium hydroxide point corresponding to size 40 was placed passively.

The orifice of the root canal of the teeth was sealed with glass ionomer cement. The teeth were then suspended in the glass vials containing 10 ml of distilled water with the help of moulding wax and hence that only the apical third of the roots were immersed into distilled water.

Measurement of calcium ion concentration

Solutions of 3.0 ml were then withdrawn periodically at 24 h, 7, 15, and 30 days, each time replacing with fresh distilled water. The solutions were then analyzed using an ultraviolet spectrophotometer (1601 PC, Shimadzu, Japan) at 220 nm.

pH measurement

The change in pH of the distilled water was determined using a pH meter at different time intervals of 24 h, 7, 15, and 30 days.

Result

Calcium ion release

Concentration of the drug was calculated from the standard calibration curve prepared in water. The *in vitro* drug release plot of time versus the cumulative percentage of drug release was constructed from the data obtained.

Statistical analysis

One-way ANOVA using SPSS 16.0(SPSS Inc) [Table 2].

Multiple comparisons with Tukey honest significant difference showed statistically significant difference among all groups at all time periods except between Group 3 and 4 at 24 h [Graph 1].

Among all the groups tested, chitosan showed a cumulative drug release of 91.51%. This indicates a better controlled release over a period of 30 days.

pH measurement

pH measurement was done using pH meter. The values at 1, 7, 15 and 30 days are as follows [Graph 2]. Statistical analysis was done [Table 3].

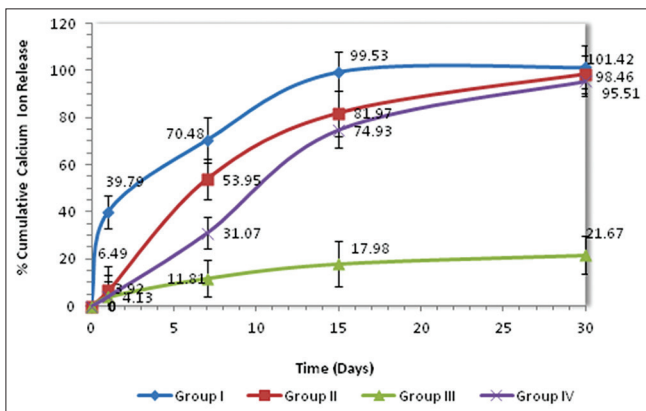
The pH values of all groups gradually increased over time. After 30 days, all four experimental groups showed an

increase in pH of the surrounding medium compared with the baseline values.

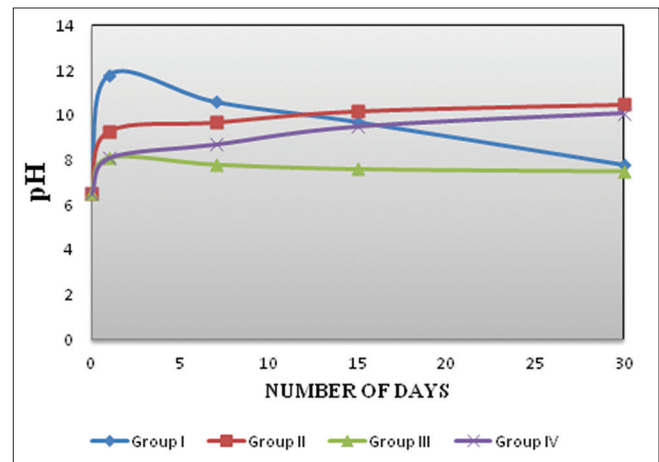
Discussion

Ca (OH)₂ is widely used for its biological and anti microbial activity. The effectiveness of Ca (OH)₂ based paste depends on the diffusion of hydroxyl ions in concentrations to reach adequate pH levels.^[12] It possesses a highly alkaline nature which has been shown to control the resorptive process. To be effective, Ca (OH)₂ must be placed in adequate quantity and condensed into the root canal space, in combination with the vehicle.

Various techniques are used for homogenous placement of intracanal medicaments, such as the use of mesing gun, lentulo, counter-clockwise rotation of a K file. The lentulospiral is said to be most effective in carrying the paste to working length.^[13]



Graph 1: Mean calcium ion release percentage from different groups at 1, 7, 15 and 30 days



Graph 2: Mean pH in different groups at 1, 7, 15 and 30 days

Table 2: Mean and SD for calcium ion release

	Group 1		Group 2		Group 3		Group 4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1-day	39.79	0.63149	6.4900	0.33813	3.9200	0.24404	4.1300	0.26268
7 days	70.48	0.65625	53.9500	0.62761	11.8100	0.33483	31.0700	0.18288
15 days	99.53	0.30569	81.9700	0.82603	17.9800	0.38816	74.9300	0.17670
30 days	1.0142E2	0.56332	98.4600	0.32387	21.6700	0.41379	91.5100	0.35418

SD: Standard deviation

Table 3: Means and SD of pH of the vehicles used in this study at different time periods

	Group 1		Group 2		Group 3		Group 4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1-day	11.4800	0.42895	9.3500	0.36893	8.3300	0.25841	8.2600	0.33066
7 days	10.4200	0.48717	9.8100	0.33813	7.9100	0.21833	8.6700	0.27909
15 days	9.4200	0.41580	10.2200	0.10328	7.5100	0.17920	9.5400	0.18974
30 days	7.6200	0.30478	10.3500	0.18409	7.4100	0.15951	10.320	0.16193

P=0.087. SD: Standard deviation

Several methods have been used to determine the calcium ion release such as atomic absorption spectrometry, ultraviolet spectrophotometer, and flame photometry.^[14] In this study, an ultraviolet spectrophotometer was used since it is simple, versatile, cost-effective and provides rapid and accurate analysis.

Nerwich *et al.*, measured pH changes in root dentin over 4 weeks and considered this as a reasonable time interval to expect effective therapeutic benefits from Ca (OH)₂ based materials.^[15]

When calcium hydroxide is mixed with distilled water, Ca⁺² and OH⁻ are rapidly released. There is a high degree of solubility when the paste remains in direct contact with the tissue fluids. This property of rapid release is desirable in clinical situations requiring short term inter appointment disinfection. In the present study, Group 1 (distilled water) showed a rapid increase in pH from 6.5 to 11.8 at 24 h, followed by a gradual decrease over 15 days to 7.8 in 30 days. It showed an initial high calcium ion release of 39.79% at 24 h, followed by 70.48% at 7 days, and almost complete release (99.53%) by 15 days.

Aqueous vehicles have rapid dissociation, achieving high values of pH in the initial periods, as observed in our results, agreeing with the findings of Esberard and Spångberg, who state that the best vehicle for Ca (OH)₂ is an aqueous solution.^[16,17] Noriyasu *et al.*, concluded that Ca (OH)₂ when used with distilled water showed a change in pH that was statistically greater as compared to the use of Ca (OH)₂ powder alone. The highest calcium concentration was observed after 3 days, peak pH change was found after 14 days, after which pH declined over time.^[18] However, since the alkaline pH and ion release were not maintained for a period over 15 days, aqueous vehicles require frequent change of intracanal dressings.

Viscous vehicles are also water-soluble substances, but they release Ca⁺² and OH⁻ ions more slowly for extended periods, because of their high molecular weights, which minimize the dispersion.^[19] As a result, the number of appointments is reduced. Prolonged release is beneficial in clinical situations such as inhibiting inflammatory root resorption, healing of large periapical lesions.

The first report using a Ca (OH)₂ paste containing propylene glycol as vehicle was by Saijjo.^[20] Its hygroscopic nature allows the absorption of water, this ensures a good sustained release of Ca (OH)₂ for long periods. Another advantage is its consistency, which improves the handling qualities of the paste.^[9] Simon *et al.*, recommend propylene glycol as the best vehicle in Ca (OH)₂ preparation. It induces the most favourable release of hydroxyl and calcium ions in comparison to other vehicles.^[9]

In the present study, propylene glycol was used as a vehicle in Group 2 to compare its proven efficacy with

newer vehicles that are, chitosan and gutta-percha points containing calcium hydroxide. Group 2 showed a gradual increase in pH from 9.3 at 24 h to 10.2 at 15 days, this was maintained up to 30 days. The pH values were significantly higher as compared to Groups 1 and 3 ($P = 0.000$). Calcium ion release increased gradually from 6.49% at 24 h, to 53.95% at 7 days. At 15 days, ion release was 81.97%, showing almost complete release by 30 days (98.46%) indicating a sustained release of calcium ions. During inter-group comparison; the ion release was statistically significant at all time intervals ($P = 0.000$).

A viscous vehicle containing paste may remain within the root canal for the interval of 2–4 months and the alkaline properties of calcium hydroxide in such a paste will only be exhausted after a long period.^[6] Theoretically, pH may be maintained in the area during this period and a slow ionic release will occur. Estrela *et al.*, in their study on the use of polyethylene glycol as vehicle observed an alkaline pH in the samples for over 45 days.^[21]

Despite its several advantages, Ca (OH)₂ has poor handling properties, its distribution throughout the entire canal poses a problem, and removal of calcium hydroxide from the root canal can be time-consuming. The European Society of Endodontology Guidelines demand complete removal of the suspension from the canal. The residual calcium hydroxide left in the canal has been shown to interact with zinc oxide based sealers forming calcium eugenolate and also affects its distribution into the lateral canals.^[22] In order to overcome this drawback, Ca (OH)₂ releasing gutta-percha points were introduced. These points are said to have increased the mobility of hydroxyl ions through dentin. Some studies reported short-term efficacy of these points.^[23,24]

In the present study, Ca (OH)₂ containing gutta-percha points (Group 3) showed an increase in pH at 24 h to 8.1, followed by a decline to almost neutral (7.8) at 7 days. A cumulative calcium ion release of 3.92% was observed at 24 h, there was no statistically significant difference when compared to Group 4 at the same time interval. At all other time intervals, differences were found to be statistically significant. At 7 days, 11.81% ion release and at 30 days 21.67% was observed, which was significantly lower when compared to other groups. In our study, the pH increase attained by gutta-percha point was significantly low when compared to other groups. It increased from a baseline of 6.5 to a maximum of 8.1 pH units at 24 h, followed by a gradual decline over the time period of the study.

Previous study reported maximum pH values of 10.9.^[25] The calcium hydroxide containing gutta-percha points showed a significantly lower alkalizing potential than Ca (OH)₂ mixed with distilled water. Calt *et al.* showed that calcium hydroxide gutta-percha points did not induce any changes in pH and

calcium ion levels.^[26] Schäfer *et al.*, studied the alkalinizing action on root dentin over 7 days with either gutta-percha points containing Ca (OH)₂ or an equivalent quantity of aqueous calcium hydroxide suspension and concluded that the gutta-percha points were unable to alkalinize the root dentin over a period of 7 days.^[23] These results are comparable to those of our study in which Ca (OH)₂ points showed significantly low calcium ion release compared with other groups. These points may be used in clinical situations requiring short term disinfection where the canals are narrow and placement of Ca (OH)₂ pastes by conventional methods is cumbersome.

Chitosan, a natural and biodegradable polymer, has been evaluated *in vitro* as a drug carrier in hydrocolloids and gels. An important property of chitosan for study as an excipient is its ability to become hydrated and form gels in acidic aqueous environments and is thus used to prepare slow release drug delivery systems.^[27] At early stages, a stagnant gel layer controls the diffusion, but as time passes, the network of the gel starts to disintegrate and thus diffusion is facilitated. The use of controlled release systems has certain advantages compared with conventional dosage forms, as they can minimize side-effects, and prolong the efficacy of the drug. Drug release rate is regulated, which aids in reducing the frequency of administration, thus assuring better patient compliance. It has been suggested persistence of formulations at sites of drug action or absorption could be prolonged through use of chitosan. It has also been suggested that chitosan increases drug bioavailability and might be valuable for delivery of drugs to specific regions such as stomach, buccal mucosa.^[28]

In the present study, Group 4 showed a low calcium ion release over the first 7 days as compared to the other groups. At 24 h, there was no statistically significant between Groups 3 and 4. However, the ion release increased from 31.07% to 74.93% over 15 days and was maintained over a period of 30 days. In comparison, Group 1 (99.53%) had an almost complete release by 15 days. These differences were statistically significant ($P = 0.000$). Furthermore, an alkaline pH of 10.32 was maintained at 30 days, which was significantly higher when compared to Group 1 and 3 ($P = 0.000$), but comparable to Group 2.

Kristl *et al.*, conducted a study to determine the efficacy of chitosan gels as drug carriers and observed that the drug release was slow and sustained.^[29] Senel *et al.*, employed chitosan as an oral mucosal delivery agent for chlorhexidine against *Candida albicans*. Along with prolonged release of chlorhexidine, the highest antifungal activity was also obtained with 2% chitosan gel containing 0.1% CHX.^[30] Silva *et al.*, investigated the efficacy of smear layer removal using chitosan compared with different chelating agents: 15% EDTA, 10% citric acid, 1% acetic acid. They concluded that 15% EDTA and 0.2% chitosan were associated with the greatest effect on root dentine demineralization.^[31]

In the present study, Ca (OH)₂ points proved to be ineffective in maintaining an alkaline pH and releasing calcium ions for more than 7 days. Distilled water as a vehicle provides an alkaline pH but only for a short duration of time. Propylene glycol and chitosan were able to maintain a high pH and chitosan showed a better sustained release of calcium ions. Chitosan can hence be used as a promising vehicle for Ca (OH)₂ in cases requiring long term dressing.

There is a lack of data and deficiency of studies regarding the use of chitosan as drug carrier in endodontic literature. Furthermore, most have determined the properties of the chitosan-based formulations solely by means of *in vitro* methods. Information on the *in vivo* behaviour of the formulations, especially in human beings, has been lacking. Studies determining the effect of chitosan on the dental tissues, allergic potential, systemic actions must be conducted. Results of *in vivo* studies would reveal the value of chitosan as a pharmaceutical excipient, and allow products containing chitosan to be marketed. A product that allows easy administration of chitosan based formulations must be developed for use in the day-to-day dental practice.

Studies are required using intracanal medicaments other than calcium hydroxide to determine the versatile nature of chitosan as a drug carrier.

Conclusion

From the results of this *in vitro* study, it can be concluded that:

- All vehicles used except gutta-percha points containing calcium hydroxide maintain an alkaline pH for over 7 days
- Propylene glycol and chitosan as vehicles maintain an alkaline pH for a period of 1 month, in comparison with distilled water and calcium hydroxide points
- Chitosan, when used as a vehicle, showed better controlled and sustained release of calcium ions from calcium hydroxide for 1 month as compared to distilled water and calcium hydroxide points, but comparable to propylene glycol
- Chitosan can be used as a promising vehicle for calcium hydroxide for the sustained release of calcium ions in the root canal system.

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