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Premixed calcium silicate cement for endodontic applications

Injectability, setting time and radiopacity

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Calcium silicate-based materials (also called MTA) are increasingly being used in endodontic applications. However, the handling properties of MTA are not optimal when it comes to injectability and cohesion. Premixing the cements using glycerol avoids these issues. However, there is a lack of data on the effect of common cement variables on important properties of premixed cements for endodontic applications. In this study, the effects of liquid-to-powder ratio, amount of radiopacifier and amount of calcium sulfate (added to control the setting time) were screened using a statistical model. In the second part of the study, the liquid-to-powder ratio was optimized for cements containing three different amounts of radiopacifier. Finally, the effect of using glycerol rather than water was evaluated in terms of radiopacity. The setting time was found to increase with the amount of radiopacifier when the liquid-to-powder ratio was fixed. This was likely due to the higher density of the radiopacifier in comparison to the calcium silicate, which gave a higher liquid-to-powder ratio in terms of volume. Using glycerol rather than water to mix the cements led to a decrease in radiopacity of the cement. In conclusion, we were able to produce premixed calcium silicate cements with acceptable properties for use in endodontic applications.

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Introduction

Ceramic cements based on calcium silicate are commonly used in endodontics due to their good sealing ability, biocompatibility and bioactivity.[1,2] The cement available commercially is commonly referred to as mineral trioxide aggregate, or MTA, and its main constituent is Portland cement.[3] The cement is delivered as a powder that is to be mixed with a water-based liquid by the dentist. The mixture is then injected or packed into place using cement guns or carriers. The powder commonly consists of the Portland cement (calcium silicate) and a radiopacifier, commonly bismuth oxide, added for visibility on X-rays.[2,4] Calcium sulfate can also be added in order to accelerate the setting reaction. However, bismuth oxide has been found to have potentially toxic effects,[5,6] and alternative radiopacifiers, such as zirconium dioxide, have been evaluated with satisfactory results.[7,8]

During injection of the cement, filter pressing may occur, which reduces the calcium silicate content and strength of the final product. In addition, cement mixed with water has a low cohesion before setting, leading to potential washout of the cement. This could be avoided by using a premixed paste, where the liquid phase is exchanged for glycerol.[9] A premixed cement would simplify the dentist's work and also ensure a precise, repeatable liquid-to-powder ratio. Using glycerol instead of water may also permit the use of a lower liquid-to-powder ratio for the same level of injectability.[10] A consequence of using glycerol is that the setting time of the cement increases, as the glycerol needs to diffuse out and be replaced by physiological fluid for setting to occur. However, short setting times are of limited relevance for applications such as root fillings, where the cement is injected into a constrained space and washout is of limited concern.

Although there appears to be several potential advantages to using a premixed version of calcium silicate cement, to the authors' knowledge, there is no peer-reviewed published data on the properties of this type of cement.

In this study, the feasibility of producing premixed calcium silicate cement containing zirconium dioxide as a radiopacifier was evaluated. When designing a material, a statistical approach may be useful in order to evaluate the effect of several parameters simultaneously, using a limited number of specimens. In this study, this approach was opted for as a first step to screen the effects of liquid-to-powder ratio, amount of radiopacifier and amount of calcium sulfate on selected properties of a premixed calcium silicate cement. Output parameters, such as injectability, radiopacity and setting time, were evaluated. In a second step, the liquid-to-powder ratio was optimized for cements containing three different amounts of radiopacifier, and the setting time and radiopacity of these cements were evaluated. Finally, the effect of using glycerol rather than water was evaluated in terms of radiopacity.

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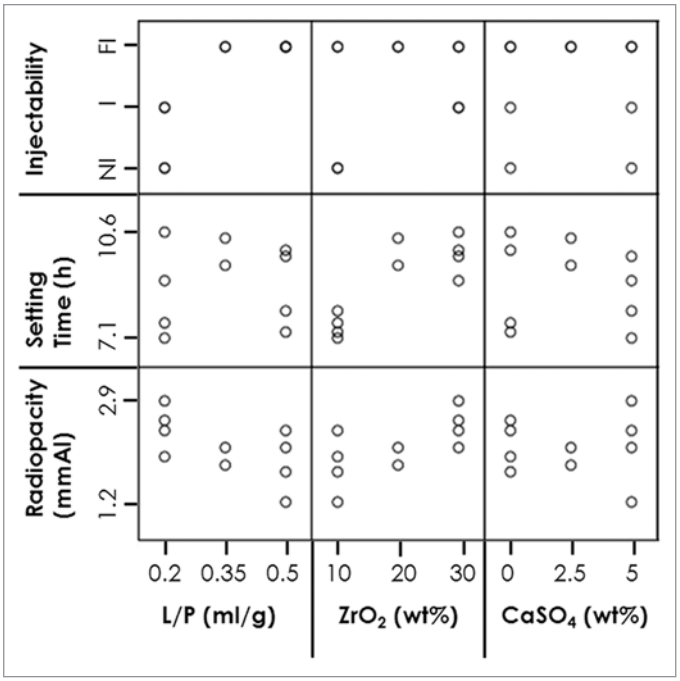

Figure 1. Injectability, setting time and radiopacity as a function of L/P ratio, amount of ZrO_2 and amount of $CaSO_4$ of the cements.

Results

Part I—statistical screening model. A matrix scatter plot of the results is shown in **Figure 1**. As expected, the liquid-to-powder ratio was found to have an effect on the injectability. Liquid-to-powder ratios of 0.35 and 0.5 ml/g were found to give fully injectable pastes in all cases, whereas with 0.2 ml/g, the paste was injectable (using the syringe) only with a large amount (30%) of radiopacifier. This was probably due to the high density of the radiopacifier compared with other components of the cement, giving rise to a higher liquid-to-powder ratio in terms of volume (ml/ml). A higher amount of radiopacifier also tended to give an increased setting time (8–10 h rather than 7–8 h), possibly for the same reason. The liquid-to-powder ratio also seemed to have an effect on the radiopacity, with an increase in the initial amount of liquid resulting in a lower radiopacity. This was likely due to the higher porosity of the samples containing a higher amount of liquid. The calcium sulfate appeared to have no appreciable effect on any of the variables. This may be due to a masking effect of the longer setting times obtained with the glycerol.

The results for the statistical screening models, obtained with MODDE (Umetrics), are shown in **Table 1**. The injectability of the cements was not included in the model, as it was not free to take on any value.

No significant interaction coefficients (β_{ij}) were found for any of the models, and the amount of $CaSO_4$ did not have a significant influence on any variable. The amount of radiopacifier was the only variable that had a significant effect on the setting time, giving an increase in setting time with an increase in the amount of radiopacifier, in accordance with the results observed in **Figure 1**. For the radiopacity, both the L/P ratio and the amount of radiopacifier had a significant effect, again in accordance with **Figure 1**. A predictive plot of these effects is shown in **Figure 2**.

Part II—optimization of the premixed cement. Based on the results above, it could be concluded that for the optimum cement, presenting a high injectability, low setting time and high radiopacity, there would be counterproductive effects between the liquid-to-powder ratio and the amount of radiopacifier. It was therefore decided to fix the amount of radiopacifier (20, 25 and 30%), minimize the L/P ratio for these cements and then evaluate the setting time and the radiopacity. The upper limit of 30% radiopacifier was based on the maximum amount found in the literature.[7,8] The results are shown in **Table 2**. No statistically significant difference was found between the groups for the setting times. The radiopacity was significantly higher for specimens containing 30% ZrO_2, as compared with 20% ZrO_2 ($p = 0.02$).

Part III. Specimens mixed with water were found to have a higher radiopacity than those mixed with glycerol, 2.69 ± 0.13 mmAl compared with 2.37 ± 0.10 mmAl, respectively. There was a statistically significant difference between the two groups ($p = 0.01$).

Discussion

This study showed the feasibility of producing injectable, self-setting, radiopaque calcium silicate cements using a premixed approach, where water is substituted for glycerol.

The use of glycerol permits a virtually unlimited working time and ease of injection. In fact, L/P ratios of as low as 0.24–0.28 ml/g were still injectable with a 20 G needle.

Setting times were long (7–10 h) but may be acceptable for applications such as root fillings, where early load-bearing is irrelevant, and the cements are injected into a confined space with a low risk for washout.[9] The setting times were found to increase with the amount of radiopacifier when the L/P ratio was fixed. This was likely due to the higher density of the radiopacifier (ZrO_2) in comparison to the calcium silicate, which gave a higher liquid-to-powder ratio in terms of volume. In fact, after optimizing the L/P ratio for different amounts of radiopacifier, similar setting times were observed (**Table 2**). A previous study also found an increase in setting times with the addition of radiopacifiers such as barium sulfate, gold and silver/tin alloy.[11]

The radiopacity was found to increase with the amount of radiopacifier, as expected, but also decreased with an increase in the L/P ratio. This was probably due to the higher amount of porosity obtained with a higher L/P ratio. The radiopacity of the cements in this study were all found to be lower than the 3 mmAl recommended in the standard for root canal sealing materials.[12] One reason could be that the glycerol gives rise to an elution of radiopacifier during setting. However, although specimens mixed with water rather than glycerol gave significantly higher radiopacity values (2.69 ± 0.13 mmAl compared with 2.37 ± 0.10 mmAl), the values did not reach those previously reported for 20 wt% ZrO_2, 3.87 ± 0.10 mmAl.[7] Another reason could be the purity of the aluminum scale: aluminum scales containing relatively large amounts of impurities, such as

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Table 1. Study responses and their corresponding regression coefficients: centered and scaled (above) and unscaled (below) coefficients

y	β_0	β_1-L/P [ml/g]	β_2-ZrO_2 [wt% of powder]	β_3-$CaSO_4$ [wt% of powder]	R^2	Q^2	Val.	Rep.
Setting time [h]	8.77 (0.55)	N.S.	0.98 (0.58)	N.S.	0.62	0.57	0.72	0.79
	6.57		0.11					
Radio-pacity [mmAl]	1.86 (0.07)	-0.15 (0.07)	0.26 (0.07)	N.S.	0.93	0.89	0.87	0.90
	1.67	-1.13	0.029					

Values in parenthesis represent the confidence interval at 95%. N.S., not significant; Val, validity; Rep, reproducibility.

copper, have been found to give significantly lower optical densities and a higher radiopacity.[13] An aluminum scale containing impurities may therefore give an underestimate of the radiopacity of the specimens that are being measured. However, the scale used in this study was produced from high-purity aluminum containing only small amounts of impurities (Grade EN AW-6082, Alumeco Sverige AB, Jönköping, Sweden). This was confirmed with energy-dispersive X-ray spectroscopy (EDAX, FEI Strata DB 235, FEI, Hillsboro, OR), which showed 99% aluminum content with 1% magnesium. Finally, the difference in values may be partly due to a difference in the set-up of the X-ray equipment, since previously found radiopacity values for Portland cement without radiopacifier (approximately 1.7 mmAl[7,11]) are similar to those found in this study for cements containing 20% ZrO_2 (1.8 ± 0.1 mmAl).

In conclusion, premixed calcium silicate cements were produced with acceptable properties for use as root fillers. Previously, premixed calcium phosphate cements have been investigated, but this permits an extension of the use of calcium silicate cements, which already have a good track record for endodontic applications.[7,14]

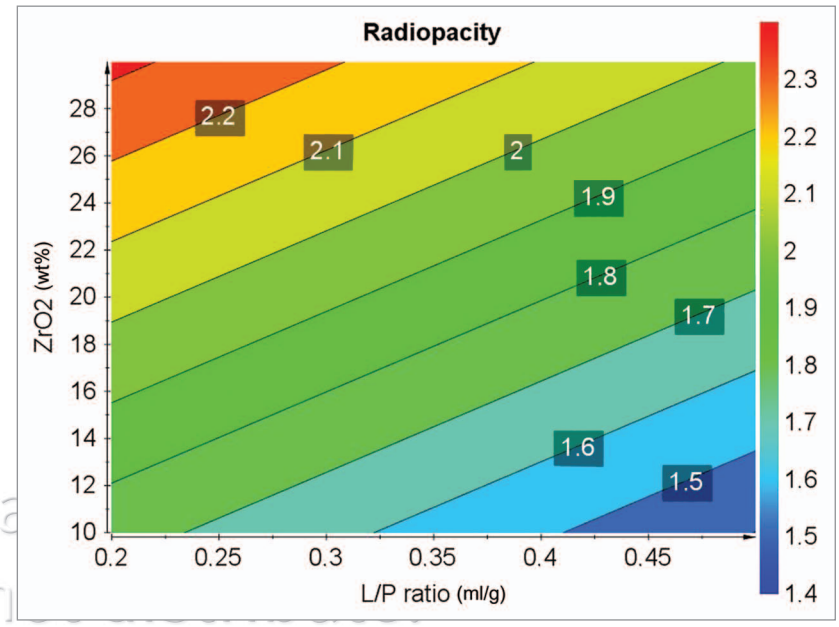

Figure 2. Predictive plot for the radiopacity of the cements (in mmAl) as a function of L/P ratio (ml/g) and amount of ZrO_2 (wt% of powder).

Materials and Methods

Materials. Portland cement (Ca_3SiO_5, Aalborg Portland A/S) was used as the base material in this study. Different amounts of zirconium dioxide (ZrO_2, Sigma Aldrich) and α-calcium sulfate hemihydrate (Bo Erlander AB) were manually mixed with the powder. The powder was then mixed with glycerol in order to obtain an injectable, premixed paste.

Study design. *Part I—statistical screening model.* A full factorial experimental design (**Table 3**) was used for the first part of this study, where the effects of a variation in liquid-to-powder ratio, amount of radiopacifier and amount of accelerator (calcium sulfate) were assessed in terms of the parameters described in the following methods sections. The liquid-to-powder ratios were chosen based on a preliminary study as well as the literature, where commonly used values are 0.3–0.5 ml/g.[7,11] The amounts of radiopacifier and calcium sulfate were also based on commonly used values in the literature, where 10–30% of radiopacifier and 3–6% calcium sulfate have been reported in references 7, 8 and 11. A statistical software package (MODDE, Umetrics) was used for the study design as well as statistical analysis and generation of predictive plots. The partial least squares (PLS) method was used to fit the results to interaction models, where initially all variables and their interactions were included:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + ... + \varepsilon \quad (1)$$

Insignificant variables (those whose confidence interval included zero) were then excluded and the models refitted. The models were evaluated in terms of goodness of fit (R2), prediction precision (Q2), model validity and reproducibility. The model validity assesses general model problems, such as outliers or the use of an incorrect model.

Part II–optimization of the premixed cement. Based on the results above, a second study was performed, where the liquid-to-powder ratio was optimized for formulations of interest, and the radiopacity and setting time of these formulations were evaluated as detailed below. These results were evaluated using analysis of variance (ANOVA) followed by Scheffe's test for multiple comparisons in PASW Statistics 18 (SPSS Inc.) (at a significance level of 0.05).

Part III—evaluation of the effect of glycerol on radiopacity. Finally, a study was performed to evaluate the effect of the

Table 2. Results of Part II

ZrO_2 [wt%]	L/P [ml/g]	Initial Setting Time [h]	Final Setting Time [h]	Radiopacity [mmAl]
20	0.28	7.2 (0.9)	8.4 (0.7)	1.8 (0.1)
25	0.26	6.8 (1.0)	8.1 (0.2)	2.1 (0.2)
30	0.24	6.8 (0.9)	8.6 (0.2)	2.3 (0.2)

Standard deviations are shown in parenthesis.

Table 3. The experimental design for the first part of the study

Formulation	Liquid/Powder (L/P) (ml/g)	Radiopacifier (wt% of powder)	Accelerator (wt% of powder)
1	0.2	10	0
2	0.5	10	0
3	0.2	30	0
4	0.5	30	0
5	0.2	10	5
6	0.5	10	5
7	0.2	30	5
8	0.5	30	5
9	0.35	20	2.5
10	0.35	20	2.5
11	0.35	20	2.5

mixing liquid. The highest radiopacifier amount from study II was used. The powders were then mixed with distilled water or glycerol at the optimized liquid-to-powder ratio found in study II. The specimens (5 per group) were then stored in phosphate buffered saline solution (PBS) at 37°C for 24 h. The radiopacity of the specimens was evaluated as described below. The results were analyzed using the Mann-Whitney U test in SPSS Statistics 19 (SPSS Inc.) at a significance level of 0.05.

Injectability. The injectability of the cement was assessed using a commercially available delivery system consisting of a Compules® Tips Gun (Denstply DeTrey GmbH, Konstanz, Germany) with 20 G needle tubes (AccuDose, Centrix Europe, Hofhelm, Germany). The paste was considered to be fully injectable (FI) if the gun and needle tubes could be used, and injectable (I) if injectable through a 1 ml syringe (tip diameter 1.9 mm).

Setting time. After mixing and injection/packing into molds, the cement paste was placed in PBS at 37°C in order to initiate the setting reaction. The setting time was assessed using the Gillmore needle method[12] on cylindrical specimens of 6 mm diameter and 3 mm height. Two to four batches of four specimens each were used per group. For the first part of the study, only the final setting time was recorded, whereas for the second part both initial and final setting time were evaluated.

Radiopacity. The radiopacity of the cement was assessed using 1 mm high specimens, at 50 kV and 3 mA in a Faxitron HP Cabinet X-ray System. Three to six specimens per group were used. An aluminum scale (1–5 mm, 1 mm steps) was used for calibration purposes. The gray scale values were assessed using the "curves" function in Adobe Photoshop CS4 (Adobe Systems Inc.) and converted into mmAl using the aluminum scale. A second-order polynomial equation was fitted to the curve using the least squares regression. This equation was then used to calculate the corresponding mmAl values of the calcium silicate specimens based on their greyscale values.

Conclusions

In this study, injectable, radiopaque, premixed cement for endodontic applications was produced. The effects of different variables were investigated, and it could be concluded that the amount of radiopacifier in a calcium silicate cement has a significant effect on the amount of liquid needed to reach a certain injectability, which, in turn, has an effect on setting time. Statistical design and analysis of experiments permit the interpretation of the effects of several variables simultaneously and may assist in understanding the complex interactions between factors affecting the performance of biomaterials and ceramic cements in particular.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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