

Apexit[®] Plus



Scientific Documentation

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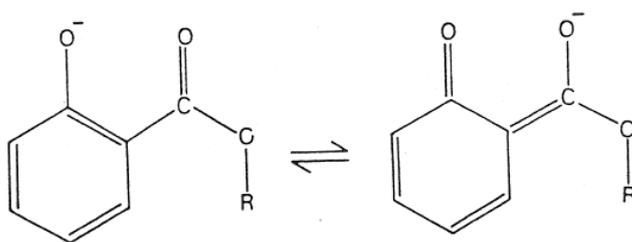
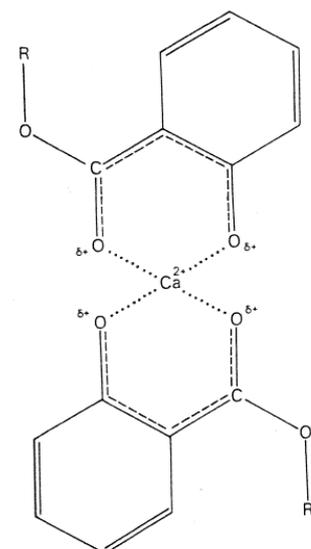
1. Introduction

During endodontic treatment, the root canal filling materials are responsible for ensuring a permanent, biocompatible, bacteria and fluid tight seal of the chemo-mechanically cleaned and shaped root canal system. In general, a root canal filling is composed of two materials: a solid filler (core material) and a sealer. The most commonly used core material is gutta percha, which can be placed into the root canal in a cold or a warm state. Originally, also metal cones were used, but they did not prove to be clinically successful. Irrespective of the compaction technique used, gutta percha alone is not able to completely seal the root canal system. The main purpose of the root canal sealer is to fill out the incongruencies between the root canal wall and the gutta percha cones [1].

Setting mechanism

Apexit Plus is a two-component material, which sets by complex formation. For this complex formation the three components calcium hydroxide, salicylate and water are needed and the following reaction is postulated: Traces of water cause small quantities of $\text{Ca}(\text{OH})_2$ to dissolve releasing hydroxide ions that subsequently react with acidic phenol groups of the salicylate. The resulting phenolate ion is stabilized by conjugation with the carbonyl group of the esters (Fig A). Free calcium ions react with the negatively charged oxygen atoms of phenolate and the carbonyl groups to form a chelate complex (Fig B). In a disalicylate, $\text{Ca}(\text{OH})_2$ does not react at an intramolecular but at an intermolecular level, hence the two salicylate groups provided by two different dimeric molecules will be linked by one calcium ion. As a result, an ionic polymer link is formed. Higher temperatures and relative humidity (residual moisture in the root canal) during setting accelerate the reaction.

Apexit Plus differs from Apexit in that it is supplied in a more convenient delivery form and has a more hydrophylic formulation. Consequently, the material is more reliable if used in thicker layers.

A**B**

2. Technical data

2.1 Composition

Base	Weight percent
Calcium hydroxide / Calcium oxide	36.9
Hydrated collophonium	54.0
Fillers and other auxiliary materials (highly dispersed silicon dioxide, phosphoric acid alkyl ester)	9.1

Activator	Weight percent
Disalicylate	47.6
Bismuth hydroxide / Bismuth carbonate	36.4
Fillers and other auxiliary materials (highly dispersed silicon dioxide, phosphoric acid alkyl ester)	16.0

2.2 Physical values

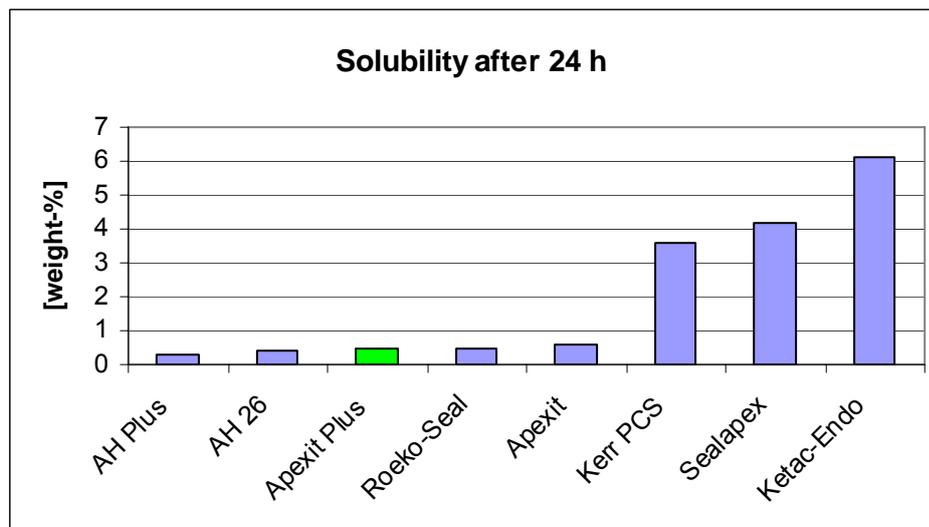
Flow (ISO 6876)	24 mm
Working time (ISO 6876)	3 h
Setting time (37°C, ≥ 95% RH; ISO 6876)	2:15 h
Film thickness (ISO 6876)	11 µm
Dimensional change after setting (ISO 6876)	+ 0.4 %
Water solubility (ISO 6876)	0.4 - 0.6 %
Radiopacity (ISO 6876)	385 % Al
Ball indentation hardness	17 MPa

3. Examination of the material properties

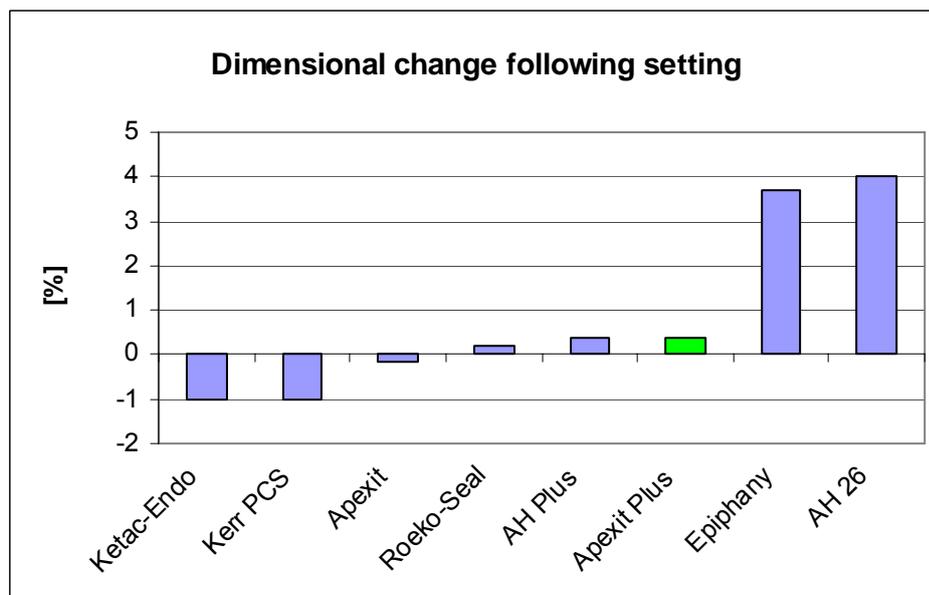
3.1 Solubility, dimensional stability and film thickness

To ensure a permanent seal of the root canal and prevent the penetration of bacteria into the apical periodontium, the root canal sealer must be insoluble or at least only hardly soluble. Furthermore, the material must remain dimensionally stable following setting.

The low solubility of endodontic sealers is a requirement of the ISO 6876 standard. To comply with this standard, the solubility of the sealer after 24-hour immersion in water must not exceed 3 % (w/w).

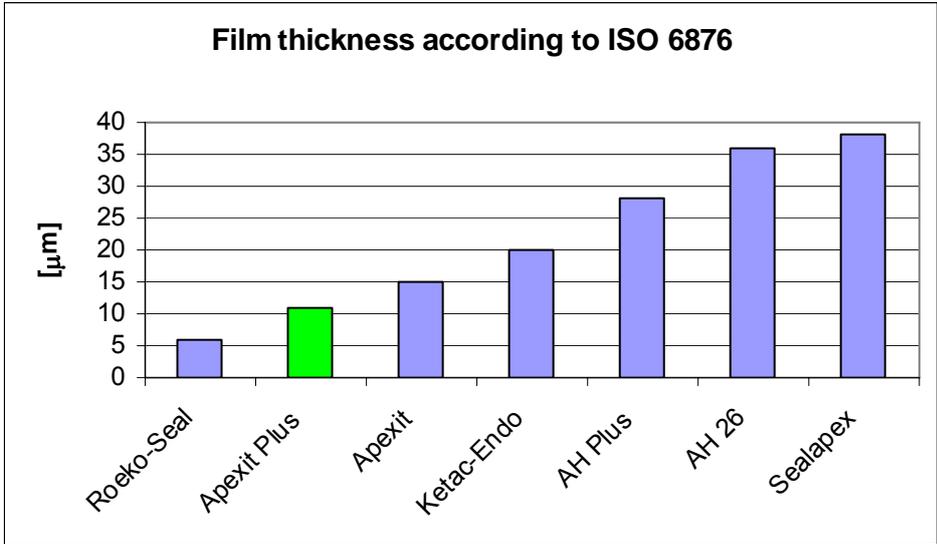


Solubility of different commercial root canal sealers according to ISO 6876. References: Apexit, Apexit Plus [2]; AH Plus [3]; Kerr PCS [4]; AH26, Roeko-Seal, Ketac-Endo, Sealapex [5].



Dimensional changes following setting and storage in water for 30 days. Source: Apexit Plus [6], Epiphany [2], others [7].

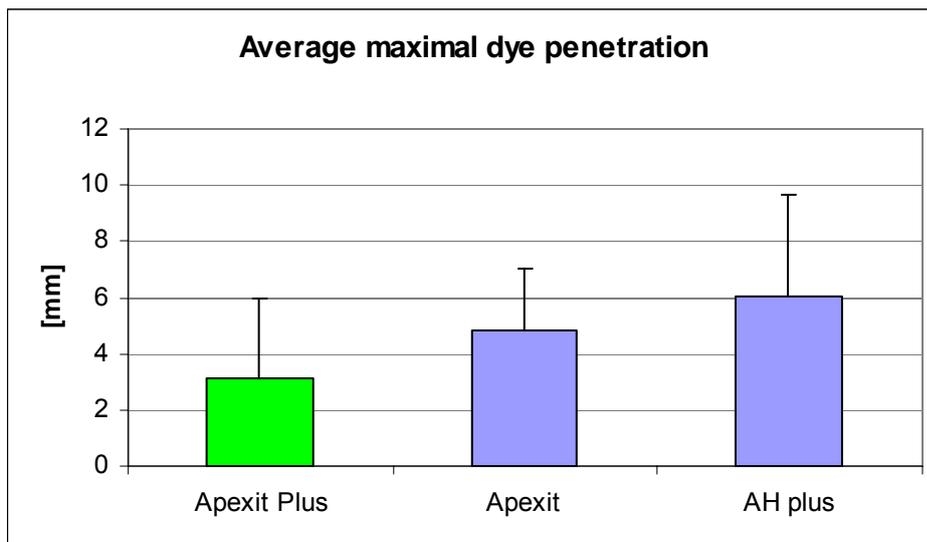
The film thickness describes the ability of the material to adapt to the geometry of the canal wall. The lower the film thickness, the better is the adaptation of the material. ISO 6876 requires a maximum film thickness of 50 µm.



3.2 Tightness of the seal – dye penetration

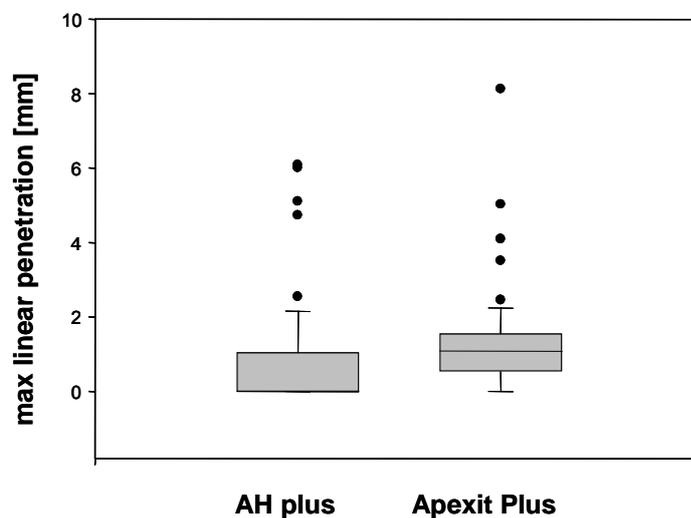
3.2.1 Coronal seal

The coronal sealing capability of Apexit Plus used in conjunction with cold gutta percha (vertical condensation) was compared with that of Apexit and AH plus [2]. Six monoradicular teeth were sealed and subsequently immersed in fuchsine solution under vacuum for 24 h (active penetration). The penetration depth of the dye was evaluated by examining various tooth sections. Compared with AH plus (6.04 ± 3.66 mm) and Apexit (4.85 ± 2.21 mm), the Apexit Plus group showed less dye penetration (3.15 ± 2.8 mm). However, this difference was not statistically significant ($p > 0.05$).



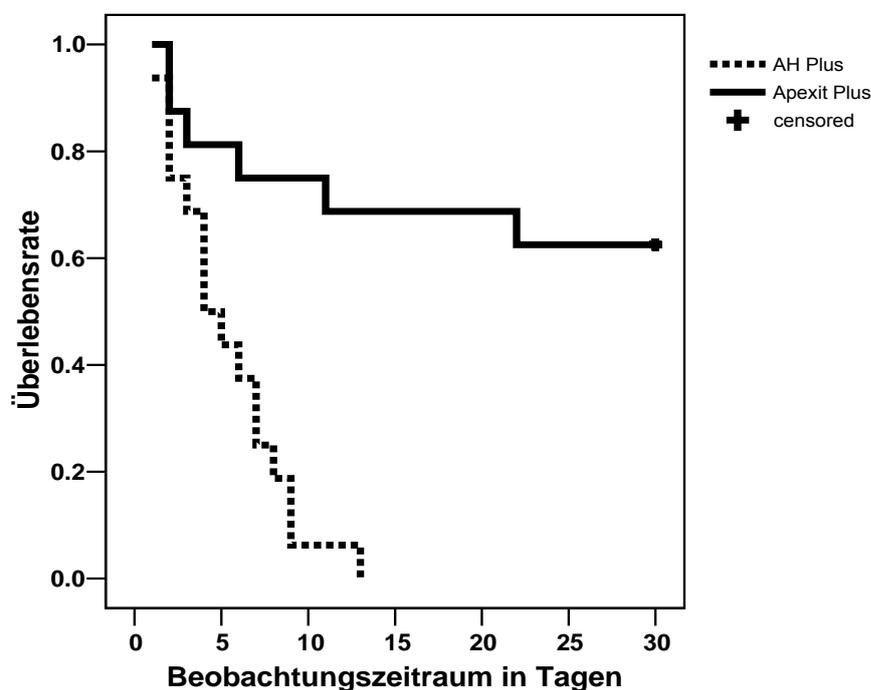
3.2.2 Apical seal

The apical sealing capability of Apexit Plus used in conjunction with warm gutta percha (Obtura Spartan, Fenton USA) was studied by Pascon et al. in comparison to that of AH plus [8]. In this study, 50 single rooted teeth were sealed and subsequently soaked in India ink at 37 °C for 30 days. Subsequently, the teeth were completely decalcified with hydrochloric acid (clearing method) and the maximum penetration depth of the dye was determined visually. Apexit Plus showed an average maximum linear dye penetration of 1.29 ± 1.4 mm, while AH plus exhibited 0.84 ± 1.52 mm ($p < 0.05$).



3.3 Tightness of the seal – bacteria penetration

The coronal seal of Apexit Plus in conjunction with cold gutta percha (lateral condensation) was compared to AH plus by Dahl et al (NIOM) in a bacteria penetration study [9]. In this investigation, 15 single rooted teeth were sealed and subsequently examined in a two-chamber system. The upper chamber contained a medium which was inoculated with *Streptococcus mutans*, while the lower chamber contained a sterile medium. The time it took for the bacteria to penetrate into the lower chamber (onset of cloudiness) was measured. The results showed that Apexit Plus has better sealing properties, which are statistically significant.



Überlebensrate = Survival rate

Beobachtungszeitraum in Tagen = Observation period in days

Coronal seal: The penetration of bacteria into the lower chamber was monitored for a period of 30 days [9]. The onset of cloudiness in the lower chamber was regarded as evidence and the probability of survival calculated by means of the Kaplan-Meier method.

4. Clinical studies

4.1 Indications

4.1.1 Application with cold gutta percha

Lateral condensation

The sealing of root canals treated with Apexit Plus using the lateral condensation technique was compared to that of teeth treated with AH plus in an *in vitro* investigation involving bacteria leakage tests [9]. In this study, Apexit Plus showed significantly more effective sealing than AH plus. Apexit Plus is currently the subject of a clinical investigation using the lateral condensation technique. To date, the root canal sealer has shown reliable clinical behavior [2].

Vertical condensation

The sealing capacity of Apexit Plus used in conjunction with vertically condensed gutta percha was compared with that of Apexit and AH plus by means of dye penetration methods in an *in vitro* pilot study [2]. The sealing properties of Apexit Plus were shown to be equally effective as those of the other products tested in the study.

Single cone technique

The *in vitro* results of the study involving the single cone technique and Apexit revealed a heterogeneous picture. Abt [11] and Al-Khatir [12] compared the single cone technique with lateral condensation *in vitro*. The single cone technique was shown to produce significantly poorer sealing results. Nevertheless, Apexit produced the same or even better results than other root sealers used in the single cone technique [11, 13-14]. Apexit was not suitable for layers of > 1 mm. Layers of this thickness, however, are only used in the single cone technique. As the setting properties of Apexit Plus have been improved, this material can now be reliably used in the single cone technique.

Studies on Apexit

The clinical effectiveness of the existing Apexit used in conjunction with cold gutta percha has been examined in various clinical studies. A success rate of 92 % [15] and 94% [16], has been observed (lateral condensation, 20 – 24-month recall). The tightness of the seal produced with laterally condensed gutta percha and Apexit was also studied in various *in vitro* investigations using dye [11, 17-26], bacteria [27-31] and tubule penetration [32], as well as fluid movement tests [33-34]. In seven comparisons Apexit showed poorer sealing, in 31 comparisons equal sealing and in six comparisons better sealing than the other products tested.

4.1.2 Application with warm gutta percha

The clinical effectiveness of Apexit Plus used in conjunction with warm gutta percha is currently the subject of two clinical studies (Thermafil and System B). To date, the sealer has demonstrated clinically reliable behaviour [35-36].

The apical sealing properties of Apexit Plus in comparison to those of AH plus with warm gutta percha have been investigated in an *in vitro* study [8]. Apexit Plus showed good sealing behaviour in this study.

Studies on Apexit

The clinical effectiveness of Apexit used in conjunction with warm gutta percha has been examined in a number of clinical studies. In a two-armed clinical study, 84 teeth were sealed with the lateral condensation technique and 78 filled with warm gutta percha. The clinical success rate after two years was 93.7 % (lateral condensation) and 90.0 % (Thermafil) [37]. Comparable results were reported by Briseno and Kremers in their study (success rate of 90.6 % after 20 months for 85 fillings) [38]. These positive clinical results are consistent with the data obtained from *in vitro* investigations in which Apexit was examined using warm gutta percha. These tests did not reveal any shortcomings in the material's sealing properties either [37, 39-40]. Only in a study by Saunders and Saunders [17] did Apexit show poorer sealing behaviour in comparison to the results achieved in the lateral condensation technique. However, the same study showed that Apexit produces better sealing results with warm gutta percha than Sealapex.

4.2 Clinical studies

4.2.1 Dr. A. Peschke, Ivoclar Vivadent R&D, Liechtenstein

Study set-up: The aim of this study was to clinically assess Apexit Plus used in conjunction with the cold lateral condensation technique. In addition to the clinical parameters, the Periapical Index (PAI) according to Ørstavik was used as a standard of evaluation.

Results: So far, 12-month recall data are available for 34 of the 43 teeth treated with Apexit Plus, and 3-year recall results for 10 of the teeth treated. The radiographic examination showed a mean distance between the root canal filling and the radiologic apex of 1.2 mm (\pm 1.1). All the root canal fillings were laterally well adapted and free of voids. In 15 of the 43 cases, a certain amount of Apexit Plus excess (also called “puff”) was observed either at the apex or in the lateral canals during the initial radiographic examination. However at the six-month recall, it was found that this excess material had been resorbed in most cases without negatively affecting the quality of the root canal filling. Post-operative problems were reported in only three of the cases. They disappeared spontaneously within the first 2 days following obturation. As far as clinical parameters are concerned, all the root canal fillings can be considered a success within the current observation period. The radiographic examination at all the recall dates, i.e. after 6, 12 and 36 months, showed a significant reduction in the PAI rating compared with the previous or preoperative findings as well as with the findings at the time of obturation.



(1) pre-operative view; (2) measurement; (3) at baseline; (4) at 6-month recall; (5) at 12-month recall, (6) at 36-month recall

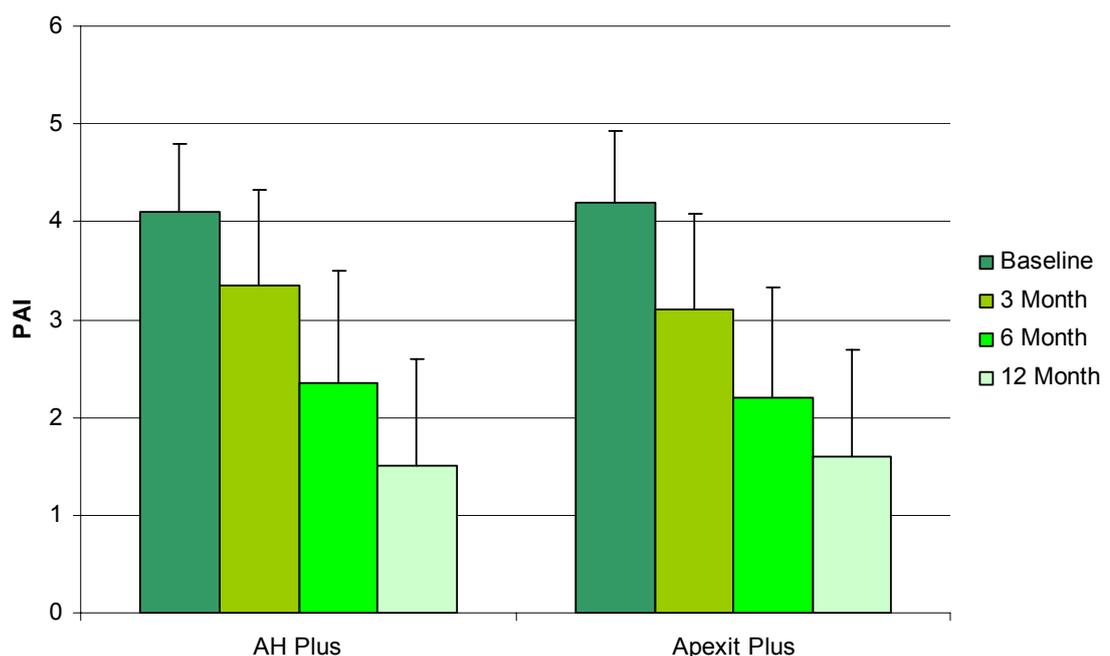
Maximum PAI (% of cases)	Pre-operative (N=45)	Obt. (N=43)	6 months. (N=38)	12 months (N=34)	36 months (N=10)
PAI 1	0.0	4.7	23.7	41.2	60.0
PAI 2	9.3	9.3	15.8	23.5	30.0
PAI 3	18.6	46.5	44.7	32.4	10.0
PAI 4	48.8	20.9	10.5	2.9	0.0
PAI 5	23.3	18.6	5.3	0.0	0.0
Mean PAI	3.9 ± 0.9	3.4 ± 1.0	2.5 ± 1.1	1.9 ± 0.9	1.5 ± 0.7

Overview of the changes of mean PAI values observed in the study conducted by Dr. Peschke: The differences recorded were of high statistical significance at all the observation dates ($p < 0.01$ Wilcoxon test).

4.2.2 Prof. Dr. E. Pascon, University of Toronto, Canada

Study set-up: The aim of this study was to clinically evaluate Apexit Plus used in conjunction with warm gutta percha (Thermafil) in comparison with AH Plus. The Periapical Index (PAI) according to Ørstavik was used as a standard of assessment in addition to the clinical parameters.

Results: Twenty teeth each were treated with Apexit Plus and AH Plus. All the patients remained in the study for a period of 12 months. At the 12-month recall, a significant reduction of the PAI value and thus an improvement of the clinical situation was observed in both groups. No difference was found between the two root canal sealers in regard to treatment success. A success rate (PAI = 1 or 2) of 90 % was recorded for both materials.

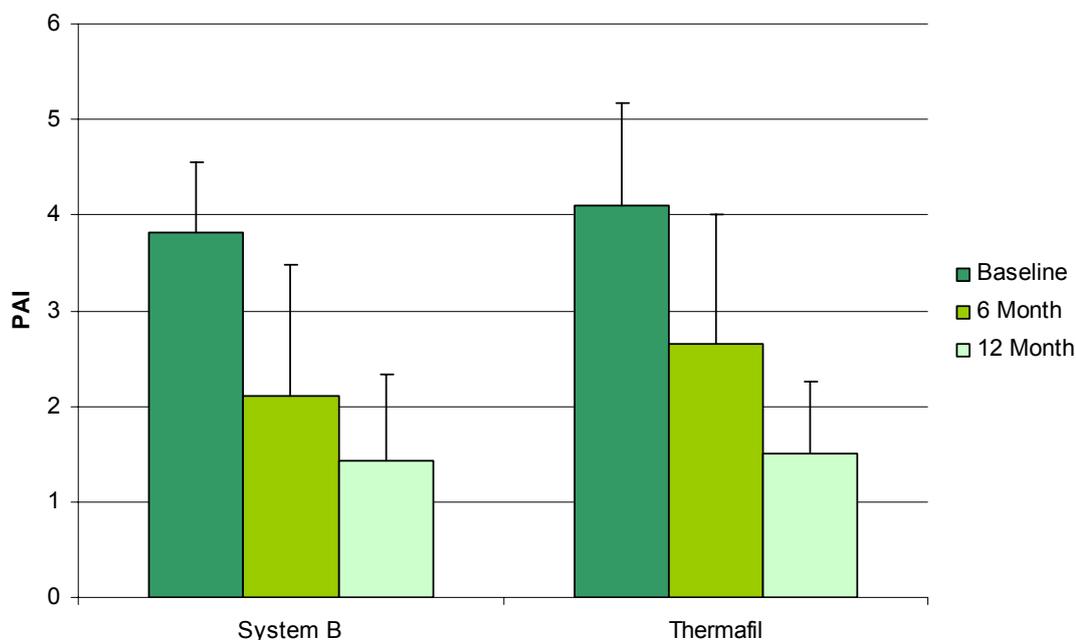


4.2.3 Prof. Dr. R. Di Lenarda, University of Trieste, Italy

Study set-up: The aim of this study was to clinically evaluate Apexit Plus used in conjunction with two different thermal techniques: Thermafil compared with System B. The Periapical Index (PAI) according to Ørstavik was used as a standard of assessment in addition to the clinical parameters.

Results: Twenty patients were treated with Thermafil and 21 patients with System B. There were 5 drop-outs of the study in the System B group. In the radiographic examination after six months, both treatment methods were shown to produce a reduction in the PAI rating compared to the baseline finding. Radiographic examination after 12 months revealed complete healing of the lesions in more than half of the patients. No statistically significant difference was found between the two groups in regard to the healing success (Kruskal-Wallis test). For all cases, the clinical parameters were uneventful.

	Thermafil	System B
Total number of cases	20	21
Mean PAI at baseline	4.1±1.1	3.8±0.7
Mean PAI after 6 months	2.7±1.3	2.1±1.4
Mean PAI after 12 months	1.5±1.1	1.4±0.9
Completely healed after 12 months	10/20	12/16



5. Biocompatibility

5.1 Exposition

The root canal sealer Apexit Plus is composed of a self-curing two-component system based on calcium hydroxide and salicylate and is indicated for permanent root canals fillings. Once it has been placed in the root canal, it will be covered, preventing any direct contact with the oral environment. The apical opening of the root canal offers the only contact to living tissue.

Apexit Plus is an improved version of Apexit, which has been successfully used in clinical situations since 1990. The main difference in the two formulations is the heightened hydrophilic property of the new product. The two formulations are very similar from a toxicological point of view. Furthermore, no new substances have been used in Apexit Plus. The toxicological profile of the two products is therefore comparable.

Name	Apexit Plus (wt%)	Apexit (wt%)
Calcium hydroxide / oxide	18.5	18.8
Disalicylate	23.8	18.2
Hydrated colophonium	27	18.5
Bismuth oxide / carbonate	18.2	18.2
Fillers and auxiliary materials	12.5	16.5
Zinc oxide, zinc stearate, paraffin oil, pigments	0	9.8

5.2 Toxicity

5.2.1 Toxicity of the starting materials

- All the inorganic salts used have an LD₅₀ of > 5,000 mg/kg (ORL-RAT). [41]
- Hydrated colophonium has an LD₅₀ of > 5,000 mg/kg (ORL-RAT) [41] and is accepted as a food-contact material without restriction of the migration limit in Europe and in the US.
- Disalicylate has an LD₅₀ (ORL-RAT) of > 5,000 mg/kg [42]

5.2.2 Toxicity of the finished product

The data available for the starting materials do not provide any evidence of elevated toxicity of the product. This assumption has been confirmed by the following investigations:

The toxicity of Apexit Plus has been examined in a cytotoxicity test (XTT). For this purpose, samples made of Apexit Plus were extracted with two solutions and the extracts were tested. The results of the tests did not reveal any cytotoxicity [43].

Apexit has been tested with regard to its cytotoxic potential in numerous independent studies. No evidence of a toxic effect was found in any of these investigations. Root canal sealers based on calcium hydroxide exhibit a very high biocompatibility. The cytotoxic potential of Apexit was examined with eluates and in direct cell contact assays. Depending on the test set-up used, Apexit did not exhibit any toxic potential [44], or compared with other test materials, only minimal toxic potential [45-48]. In order to rule out a cytotoxic effect of Apexit during the setting period, Schwarze et al. examined eluates, which were collected within 24 hours after mixing. The results of these eluates were also negative [49]. In a long

term study, the same authors examined whether there was a possibility of chronic toxicity. For this purpose, extracted human teeth were obturated with root canal sealers and immersed in water for a period of 52 weeks. The eluate was examined with regard to its cytotoxic potential on a weekly or bi-weekly basis. All the results related to Apexit were negative [50]. Furthermore, the oral LD₅₀ in the rat was determined and no acute toxicity was found (LD₅₀ > 5000 mg/kg bw). [51].

5.3 Genotoxicity

The data available for the starting materials do not provide any evidence of a genotoxic effect [41].

The genotoxicity of Apexit Plus was examined in an AMES test (plate incorporation test and extraction). No evidence of genotoxicity was found in this test [52].

The genotoxicity of Apexit was examined in prokaryotic and eukaryotic test systems *in vivo* and *in vitro*. The mutagenic potential of extracts in prokaryotic test systems was established in an AMES test [53] as well as with the *Umu* system [54]. The inhibition of DNA synthesis in human HeLa cells served as the eukaryotic test system [54]. In none of the three *in vitro* tests was any evidence of genotoxic potential found. Heil et al studied the capability of eluates of Apexit to induce breaks in the DNA chain *in vivo* (Muschel model). They were unable to find any indication of *in vivo* genotoxicity [54].

Considering that Apexit and Apexit Plus have a very similar chemical composition and taking into account the molecular biological mechanisms causing the mutagenicity of substrates, the data for Apexit can be fully applied to Apexit Plus.

5.4 Sensitization

Apexit Plus contains hydrated collophonium, which is a derivative of a natural product. A sensitizing reaction in rare cases cannot be excluded. The remaining components are not known to have a sensitizing effect. Ivoclar Vivadent is not familiar with any cases in which an allergy has been caused by Apexit.

The effect of Apexit on immune-competent cells has been examined *in vitro* and *in vivo* (rats) and no evidence of an immune modulating or sensitizing effects was found [55].

5.5 Irritation

The pH of the non-set mixed paste is in the basic range (~ pH 8.5). Accidental contamination of the skin or eyes may lead to temporary local irritation.

5.6 Local tissue compatibility

Apexit has been tested in various histocompatibility studies. In an unspecific implant test in the rat (bone implant test [56]), Apexit showed short-term irritation, which was restricted to the tissue that was in contact with the test material. When Apexit was implanted into the subcutaneous connective tissue of rats, severe necrosis was observed [57]. However, this was comparable to what was found in a parallel study involving another root canal sealer. Furthermore, it disappeared with time. In contrast to the study involving rats, a test in which Apexit was implanted in subcutaneous or peritoneal tissue of mice showed only very minimal tissue inflammation, which was no longer observed after five days [58].

Investigations on the specific histocompatibility were conducted in the dog and in macaque monkeys. In the study involving dogs, overfilling of the canals caused mild to severe inflammation (infiltration with giant cells) of periapical tissue [59]. In contrast, the studies on monkeys [60] showed that overfilling of the canals caused mild inflammation without the

involvement of polynuclear macrophages. If the root canals were properly sealed, no negative reactions of the periapical tissue were observed.

Evaluation of the scientific literature (PubMed) and market surveillance by Ivoclar Vivadent did not reveal any evidence that Apexit is not biocompatible. Because of the very similar (composition) or same (solubility) chemical properties, as well as the same indication of Apexit Plus and Apexit, the data of Apexit can be used in the evaluation of local tissue compatibility.

5.7 Conclusion

Based on the available data and the current standard of knowledge, it can be assumed that Apexit Plus can be used as a root canal sealer without an elevated toxicological risk to the patient.

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Issued: December 2007
Replaces Version of: August 2005
