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REVIEW ARTICLE

Do *in vitro* solubility studies on endodontic sealers demonstrate a high level of evidence? A systematic review

Ankur Razdan[a,b], Ana Raquel Benetti[b] and Lars Bjørndal[a]

[a]Section of Cariology and Endodontics, Department of Odontology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [b]Section of Dental Materials, Department of Odontology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Objective: To systematically review the quality of evidence of available *in vitro* solubility studies on endodontic sealers according to prespecified evidence criteria.

Material and methods: This systematic review was based on the PRISMA guidelines and the AMSTAR measurement tool. A systematic duplicate search of the literature on endodontic sealer solubility studies was conducted in PubMed and Embase databases (until 18 October 2017). Mapping terms to subject headings and free text terms were used and combined with hand searching before exclusion of duplicates. Studies specifically dealing with endodontic sealer solubility were selected. The evidence level was graded (low, medium or high) independently by two investigators following systematic data extraction in pilot forms, which was based on prespecified evidence criteria and the modified CONSORT checklist for *in vitro* studies on dental materials.

Results*:* The search retrieved 1053 articles, from which 88 were assessed in full. From the 63 articles retained in the final analysis, 11 were classified as having moderate and 52 as low quality of evidence (0 high). The studies graded as low had low sample size ($n < 10$) and/or insufficient details to allow replicability. Most of the studies did not conform to the modified CONSORT checklist and did not include parameters considered relevant in the prespecified criteria.

Conclusions: Existing *in vitro* studies on the solubility of endodontic sealers do not demonstrate a high quality of evidence. Most of these studies do not present systematic reporting nor employ relevant parameters prespecified in our evidence criteria.

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Introduction

Sealer dissolution may have implications in the prognosis of endodontic treatment. If sealer dissolution takes place within the canal, the apical seal may be compromised and regrowth of residual dormant bacteria may occur.

In case of sealer extrusion, extruded sealers may initiate a severe, albeit transient, inflammatory reaction even in the absence of periapical infection [1]. Additionally, studies suggest delayed or impaired periapical healing in teeth with extruded endodontic fillings [2–6], or more specifically, extruded sealers [7–9], in the presence of apical periodontitis. The stable surface offered by the extruded obturation material most likely favours continued growth of bacteria from infected dentinal tubules, thus explaining much of the associated impaired prognosis described in the literature [3,9–12].

It has been previously suggested that a reduction in the contact of extruded sealer with the periradicular tissues may minimize the damage caused [1]. Additionally, sealer solubility results in the release of ions and this may lead to antimicrobial or remineralization potential [13,14]. However, the role of persistent root canal infection as the cause of recurrent disease and late endodontic treatment failure should not be underestimated [15].

Sealer dissolution is thus a relevant property worthy of due consideration. However, the quality of evidence of *in vitro* solubility studies on endodontic sealers is unknown. Studies estimating the dissolution of endodontic sealers often employ standard *in vitro* solubility tests [16–19] (Table S1, Supplementary information) that face challenges, especially with respect to testing newer hydraulic, calcium silicate-based endodontic sealers. Several issues are not properly addressed in these tests, such as evaporation of the free mixing liquid during the drying step of the standard tests [20], reduced solubility in the presence of body fluids [21], and/or water uptake by the sealers [22]. Moreover, clinical conditions are very different from those employed *in vitro* and the ability of a laboratory test to be directly related to the clinical behaviour of the materials has long been questioned [23]. Therefore, the ability of various *in vitro* studies to estimate the dissolution of current endodontic sealers over a period of time is an important question, the answer to which is uncertain.

CONTACT Lars Bjørndal labj@sund.ku.dk Department of Odontology, Faculty of Health and Medical Sciences, University of Copenhagen, Nørre Allé 20, 2200 Copenhagen, Denmark

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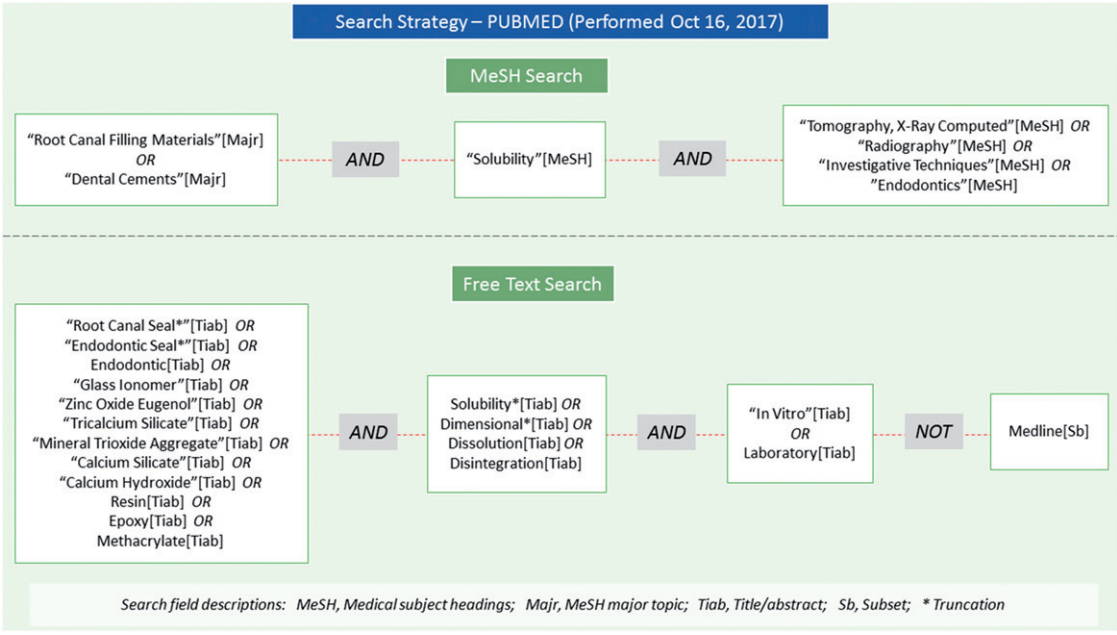

Figure 1. Search strategy used in the PubMed database.

Within this context, the aims of this study were to:

- (i) Systematically assess the quality of evidence of *in vitro* solubility studies on endodontic sealers; and
- (ii) Examine the methodological parameters employed in these studies relative to the clinical situation according to prespecified evidence criteria.

Material and methods

To ensure methodological quality of the present review, the PRISMA guidelines were followed [24] and the AMSTAR measurement tool was consulted [25]. In order to assess the quality of the reviewed studies, the modified CONSORT checklist of items for reporting *in vitro* studies on dental materials [26] and the Cochrane Risk of Bias Tool [27] were consulted.

Eligibility criteria

Studies were selected according to the following eligibility criteria: original *in vitro* studies investigating solubility, dissolution, disintegration or water uptake of endodontic sealers (see definitions of terminology in Table S2, Supplementary information). Only full-text original articles published or available online (no language restrictions) until 18 October 2017 were selected; no abstracts, reports or personal communications, unpublished results or grey literature were included. Review articles were used only to identify relevant studies that did not appear in the original search made on the databases.

Exclusion of articles dealing with solubility of root-end filling materials and those including solvents of filling materials as immersion media was done, as they did not comply with the overall aim of the study.

Information sources

A systematic search of the literature on endodontic sealer solubility was conducted until 18 October 2017 using the PubMed (National Library of Medicine, Bethesda, MD, United States) and Embase (Elsevier Life Sciences IP Limited, Amsterdam, The Netherlands) databases.

Search

Employing a predefined search strategy, the electronic searches were conducted independently by two investigators (AR and ARB) using the search builder utility in each database (Figures 1 and 2). In each database, the search was performed by (i) mapping terms to subject headings (MeSH in PubMed; Emtree in Embase) and (ii) employing free text terms. The records obtained from each database were alphabetically ordered to enable removal of duplicates within the two databases and searches. The extra articles identified and screened by the second investigator (ARB) were included in the final list of articles considered for the systematic review. Hand searching (supplementary searching following a snowballing technique) was undertaken, wherein references of the included studies and those of the key authors of the included studies were incorporated (Figure 3). Similar articles suggested by PubMed were also screened and included in the list of hand-searched articles.

Study selection

All retrieved records were initially screened for their titles and abstracts. Relevant articles were then selected for full-text assessment, from which eligible studies were retained for qualitative synthesis (Figure 3). The studies were selected

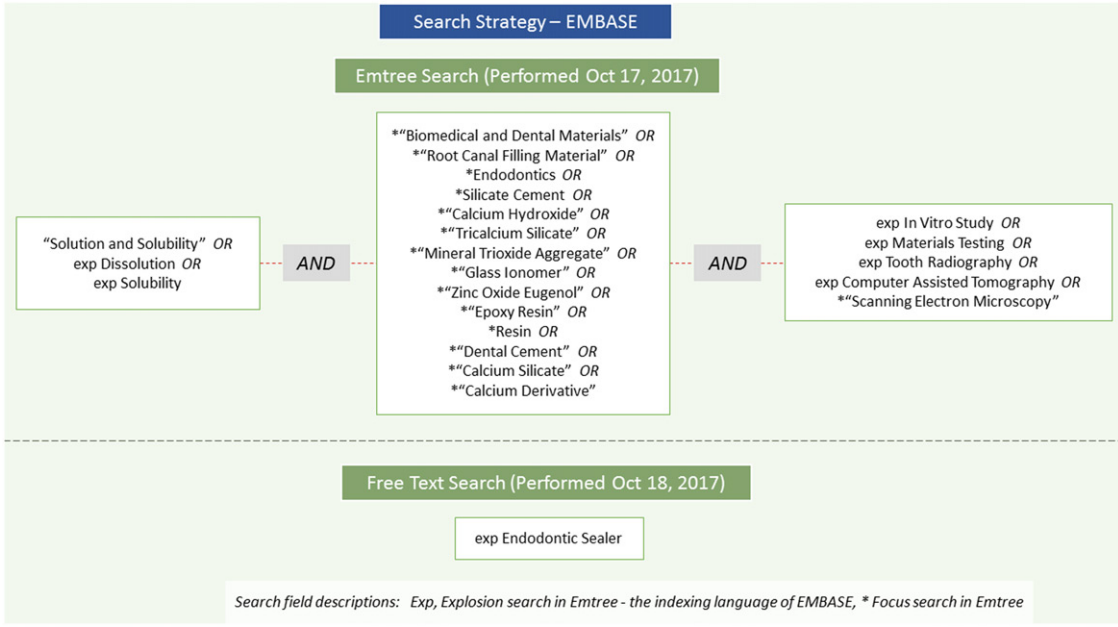

Figure 2. Search strategy used in the Embase database.

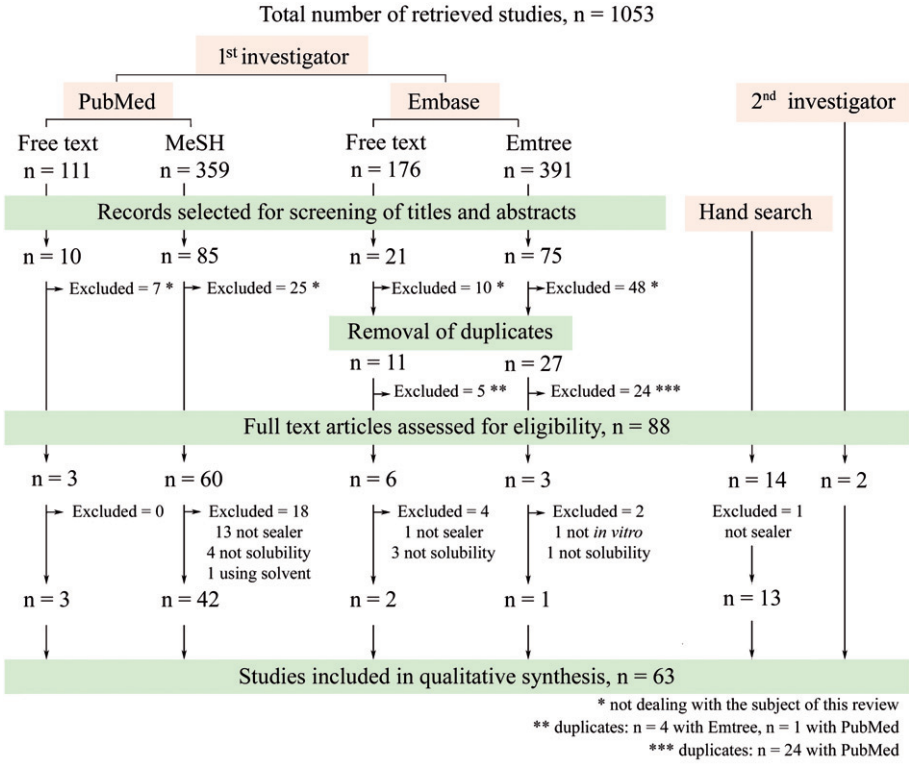

Figure 3. Workflow used for the selection of studies: reasons for exclusion and retention of articles in this review.

independently by the two investigators (AR and ARB) according to the above-mentioned eligibility criteria.

Data collection process

Data collection, extraction and analysis were performed independently, in duplicate, by the same two investigators using pilot forms with data items, described in detail below. For each article, information regarding the method details, study design and quality (according to the modified CONSORT checklist) was gathered. A third investigator (LB) was consulted in case of a difference of opinion.

Evidence criteria (Table 1) were framed beforehand by all the investigators and were based on the aims of the review. In short, the evidence criteria focused on the quality of reporting methods and results, the use of test parameters that are relevant to the clinical situation, testing of current

Table 1. Levels of evidence and criteria for evidence synthesis applied to the classification of the solubility studies included in this review.

Level of evidence[a,b]	Criteria
High	1. Low risk of bias (randomization, allocation concealment, blinding, account of outcome data, complete reporting of results) 2. Sufficient number of samples ($n \geq 10$) 3. Sufficient detailed explanation of the procedure to permit replication 4. Presence of control group(s) 5. Inclusion of all types of commonly used endodontic sealers 6. Inclusion of at least five of the following parameters: a. Surface area of sealer exposed to testing b. Specimen design c. Moment of immersion, in relation to setting of the sealer d. Type of immersion media e. Quantity of immersion media f. Duration of immersion g. Renewal of immersion media h. Test addresses water uptake
Moderate	1. If any of the above-mentioned criteria are not met 2. If the study does not have deficits as mentioned in the low level of evidence
Low	1. Insufficient ($n < 10$)[a] or unclear sample size 2. Methods not described in sufficient detail to permit replication[b]

[a]Studies including less than 10 samples per group were classified as low evidence, despite following the recommended standard norms, due to lack of statistical power.
[b]In principle it would be enough to refer to the standard norms, which describe in details the mixing ratio of test materials, sample size, specimen fabrication, recommend setting prior to immersion, demoulding of specimens, moment and duration of immersion, quantity and type of immersion media, temperature and humidity conditions. However, if a particular standard was mentioned but discrepancies to the standard were noticed in the study methodology, the missing information in the article could not reliability be retrieved from the standard and the study was classified as low evidence.

endodontic sealers and estimation of time-dependent sealer dissolution.

Data items

Data pertaining to the following variables were extracted: relevant parameters (according to our evidence criteria, Table 1); solubility test and sealer types used; sample size; details permitting study replicability; presence of control group; specimen design and number of surfaces exposed to the solution; type, quantity and renewal of immersion media; moment and duration of immersion; address of water uptake and time-dependent dissolution. Additional methodological details such as desiccation, moment of weight measurement and moment of demoulding were registered. Moreover, the data items as per the modified CONSORT checklist were recorded separately.

Risk of bias in individual studies

Data items pertaining to the quality of reporting according to the modified CONSORT checklist allowed assessing the risk of bias for the individual studies (*i.e.* presence of randomization, allocation concealment, blinding, account of outcome data, complete reporting of results).

Synthesis of results

The data items in the pilot forms were then compared to the predefined evidence criteria (Table 1) to classify the studies accordingly as low, moderate or high.

Risk of bias across studies

The risk of bias across studies was not applicable due to the differing nature of the studies with regard to the methods and materials tested.

Results

Study selection

A flowchart demonstrating the process of study selection is presented in Figure 3. The electronic search in PubMed retrieved 470 articles (111 in free text search and 359 in medical subject heading [MeSH] search), out of which 95 (10 from free text search and 85 from MeSH search) studies were screened for their titles and abstracts. After going through the abstracts, 32 studies (7 from free text and 25 from MeSH searches) were excluded, as they did not cover the subject of the study. From Embase, 567 records were retrieved (176 in the free text and 391 articles in Emtree searches); 96 records had their titles and abstracts screened and 58 studies were excluded. Further 29 articles were excluded after assessment for duplicates, which was done in two steps: (i) common articles with PubMed and (ii) common articles between Emtree and free text searches in Embase. Full-text versions of the remaining 63 articles from PubMed and 9 from the Embase searches were assessed for eligibility. Further 14 studies from hand search and 2 additional studies identified from the search made by the second investigator were also assessed for eligibility. Finally, from the 88 studies assessed in full, 63 studies that dealt specifically with the assessment of solubility of endodontic sealers were retained and subjected to qualitative review. Articles that either dealt with the solubility of endodontic cements for other applications, *e.g.* root-end fillings or repair of perforations, or those that did not investigate solubility but exclusively used other assessments such as release of ions or dimensional change measurements were excluded.

Table 2. Overview of the 63 selected articles investigating solubility of endodontic sealers, classified according to the method used, specimen size, type of immersion media and duration of immersion.

Solubility method	Additional methods[b]	Specimen design	Immersion media	Immersion duration
Based on *ISO 6876 or ANSI/ ADA Specification no. 57 (n = 40)*	**Dimensional change test *(n = 19)*** Barros et al. [64]	**Cylindrical, *Ø smaller than standard (n = 30)*** Azadi et al. [63]	**Water *(n = 60)*** Amoroso-Silva et al. [60]	**Short (≤ 7 days) *(n = 43)*** Amoroso-Silva et al. [60]
Arias-Moliz et al. [62]	Carvalho-Júnior et al. [65]	Borges et al. [32]	Arias-Moliz et al. [62]	Arias-Moliz et al. [62]
Ashraf et al. [69]	Carvalho-Júnior et al. [84]	Borges et al. [80]	Ashraf et al. [69]	Ashraf et al. [69]
Azadi et al. [63]	Duarte et al. [67]	Carvalho-Júnior et al. [84]	Azadi et al. [63]	Azadi et al. [63]
Barros et al. [64]	Flores et al. [c][40]	Camargo et al. [37]	Barros et al. [64]	Barros et al. [64]
Borges et al. [32]	Garrido et al. [68]	Cañadas et al. [83]	Borges et al. [32]	Borges et al. [32]
Borges et al. [80]	Kazemi et al. [28]	Collares et al. [66]	Borges et al. [80]	Borges et al. [80]
Camargo et al. [37]	Lee et al. [72]	Donnelly et al. [39]	Camargo et al. [37]	Camargo et al. [37]
Cañadas et al. [83]	Lim et al. [44]	Faria-Júnior et al. [13]	Cañadas et al. [83]	Cañadas et al. [83]
Carvalho-Júnior et al. [65]	Marín-Bauza et al. [c][47]	Flores et al. [40]	Carvalho-Júnior et al. [65]	Carvalho-Júnior et al. [65]
Carvalho-Júnior et al. [84]	Marín-Bauza et al. [c][48]	Gandolfi et al. [38]	Carvalho-Júnior et al. [84]	Carvalho-Júnior et al. [84]
Duarte et al. [67]	Resende et al. [c][52]	Gandolfi et al. [21]	Collares et al. [66]	Collares et al. [66]
Flores et al. [40]	Rosa et al. [31]	Garrido et al. [68]	Donnelly et al. [39]	Duarte et al. [67]
Fonzi et al. [41]	Segato et al. [c][76]	He et al. [42]	Duarte et al. [67]	Faria-Júnior et al. [13]
Garcia et al. [36]	Sousa-Neto et al. [77]	Kaplan et al. [43]	Ersahan and Aydin [33]	Flores et al. [40]
Garrido et al. [68]	Viapiana et al. [78]	Marín-Bauza et al. [47]	Faria-Júnior et al. [13]	Gandolfi et al. [38]
Lee et al. [72]	Versiani et al. [c][58]	Marín-Bauza et al. [48]	Flores et al. [40]	Gandolfi et al. [21]
Lim et al. [44]	Versiani et al. [c][35]	Mathias-Júnior et al. [30]	Fonzi et al. [41]	Garcia et al. [36]
Marciano et al. [45]	Zhou et al. [61]	McComb and Smith [49]	Gandolfi et al. [38]	Garrido et al. [68]
Marciano et al. [46]	**Microscopy/scanning electron microscopy *(n = 9)***	McMichen et al. [73]	Gandolfi et al. [21]	He et al. [42]
Marín-Bauza et al. [47]	Borges et al. [c][32]	Portella et al. [51]	Garcia et al. [36]	Higginbotham [70]
Marín-Bauza et al. [48]	Flores et al. [c][40]	Resende et al. [52]	Garrido et al. [68]	Kuga et al. [71]
Mathias-Júnior et al. [30]	Gandolfi et al. [c][38]	Rosa et al. [31]	He et al. [42]	Lee et al. [72]
Prüllage et al. [34]	Kaplan et al. [43]	Schäfer et al. [75]	Higginbotham [70]	Marciano et al. [45]
Poggio et al. [74]	Marciano et al. [c][46]	Silva et al. [59]	Kaplan et al. [43]	Marciano et al. [46]
Resende et al. [52]	Marín-Bauza et al. [c][47]	Siboni et al. [14]	Kazemi et al. [28]	Marín-Bauza et al. [47]
Ruiz-Linares et al. [53]	Portella et al. [c][51]	Versiani et al. [35]	Kuga et al. [71]	Marín-Bauza et al. [48]
Schäfer and Zandbiglari [29]	Siboni et al. [c][14]	Viapiana et al. [78]	Lee et al. [72]	Mathias-Júnior et al. [30]
Schäfer et al. [75]	Versiani et al. [c][35]	Vitti et al. [79]	Lim et al. [44]	McComb and Smith [49]
Silva et al. [54]	**Energy dispersive X-ray spectroscopy *(n = 8)*** Borges et al. [c][32]	Vitti et al. [81]	Marciano et al. [45]	Ono and Matsumoto [50]
Segato et al. [c][76]	Gandolfi et al. [c][38]	**Cylindrical, standard Ø *(n = 28)*** Amoroso-Silva et al. [60]	Marciano et al. [46]	Resende et al. [52]
Song et al. [57]	Gandolfi et al. [c][21]	Arias-Moliz et al. [62]	Marín-Bauza et al. [47]	Ruiz-Linares et al. [53]
Sonntag et al. [85]	Marciano et al. [c][46]	Ashraf et al. [69]	Marín-Bauza et al. [48]	Siboni et al. [14]
Sousa-Neto et al. [77]	Portella et al. [c][51]	Barros et al. [64]	Mathias-Júnior et al. [30]	Silva et al. [54]
Versiani et al. [58]	Segato et al. c76] Siboni et al. [c][14]	Carvalho-Júnior et al. [65]	McMichen et al. [73]	Silva et al. [55]
Versiani et al. [35]	Versiani et al. [c][35]	Carvalho-Júnior et al. [d][84]	McComb and Smith [49]	Song et al. [57]
Viapiana et al. [78]	**Spectrometry/atomic absorption spectrometry *(n = 10)***	Duarte et al. [67]	Ono and Matsumoto [50]	Sonntag et al. [85]
Vitti et al. [79]	Borges et al. [32]	Ersahan and Aydin [33]	Poggio et al. [74]	Sousa-Neto et al. [77]
Vitti et al. [81]	Carvalho-Júnior et al. [c][84]	Fonzi et al. [41]	Higginbotham [70],	Versiani et al. [58]
Wang et al. [82]	Flores et al. [c][40]	Garcia et al. [36]	Portella et al. [51]	Versiani et al. [35]
Zhou et al. [61]	Kuga et al. [71]	Grga et al. [22]	Prüllage et al. [34]	Viapiana et al. [78]
Based on ISO 4049 *(n = 4)*	Marciano et al. [c][46]	Kuga et al. [71]	Resende et al. [52]	Zhou et al. [61]
Collares et al. [66]	Marín Bauza et al. [c][47]	Lee et al. [72]	Rosa et al. [31]	Ørstavik [23]
Donnelly et al. [39]	Marín Bauza et al. [c][48]	Lim et al. [44]	Ruiz-Linares et al. [53]	**Intermediate (8–30 days) *(n = 13)*** Carvalho-Júnior et al. [f][84]
Ersahan and Aydin [33]	Mathias-Júnior et al. [c][30]	Marciano et al. [45]	Schäfer and Zandbiglari [29]	Donnelly et al. [39]
Siboni et al. [14]	Resende et al. [c][52]	Marciano et al. [46]	Schäfer et al. [75]	Ersahan and Aydin [33] Grga et al. [22]
Other gravimetric methods *(n = 18)* Amoroso-Silva et al. [60]	Versiani et al. [c][58]	Poggio et al. [74]	Segato et al. [76]	Lim et al. [44]
Faria-Júnior et al. [13]		Prüllage et al. [34]	Siboni et al. [14]	Marín-Bauza et al. [f][48]
Gandolfi et al. [38]		Ruiz-Linares et al. [53]	Silva et al. [54]	Portella et al. [51]
Gandolfi et al. [21]		Schäfer and Zandbiglari [29]	Silva et al. [59]	Prüllage et al. [34]
Grga et al. [22]		Silva et al. [54]	Simões et al. [56]	Schäfer and Zandbiglari [29]
He et al. [42]		Simões et al. [56]	Song et al. [57]	Schäfer et al. [75]
Higginbotham [70]		Song et al. [57]	Sonntag et al. [85]	Silva et al. [59]
Kaplan et al. [43]		Sonntag et al. [85]	Sousa-Neto et al. [77]	Vitti et al. [a][79]
Kazemi et al. [28]		Sousa-Neto et al. [77]	Versiani et al. [58]	Vitti et al. [b][81]
Kuga et al. [71]		Versiani et al. [58]	Versiani et al. [35]	**Long (> 30 days) *(n = 7)***
McMichen et al. [73]		Zhou et al. [61]	Viapiana et al. [78]	Kaplan et al. [43]
Simões et al. [a][56]		Ørstavik [23]	Vitti et al. [79]	Kazemi et al. [28]
McComb and Smith [a][49]		**Cylindrical, Ø not specified *(n = 2)*** Higginbotham [70]	Vitti et al. [81]	McMichen et al. [73]
Ono and Matsumoto [50]		Ono and Matsumoto [50]	Zhou et al. [61]	Poggio et al. [74]
Portella et al. [51]		**Other designs *(n = 3)***	Ørstavik [23]	Rosa et al. [31]
Rosa et al. [31]		Kazemi et al. [28]	**Simulated body fluid/ phosphate buffered saline/ acidic solution *(n = 9)*** Gandolfi et al. [e][38]	Segato et al. [76]
Silva et al. [59]		Silva et al. [55]	Gandolfi et al. [e][21]	Simões et al. [56]
Ørstavik [23]		Segato et al. [76]	Grga et al. [22]	**Unspecified (*n* = 2)** Fonzi

(*continued*)

Table 2. Continued.

Solubility method	Additional methods[b]	Specimen design	Immersion media	Immersion duration
High-resolution micro-CT ***(n = 1)*** Silva et al. [55]		**Unspecified (*n* = 2)** Fonzi et al. [41] Wang et al. [82]	Higgginbotham e Portella et al. [e][51] Prüllage et al. [e][34] Rosa et al. [e][31] Schäfer and Zandbiglari [e][29] Silva et al. [55] **Unspecified (*n* = 1)** Wang et al. [82]	et al. [41] Wang et al. [82]

[a]Studies according to Specification 8 ADA.
[b]All studies with tests added to solubility tests.
[c]All studies with more than one additional tests.
[d]Study using different specimen sizes ($n = 1$).
[e]Studies with other immersion media besides water ($n = 7$).
[f]Studies with additional duration for other tests ($n = 2$).
[g]Ø.

Study characteristics

An overview of the information extracted from the studies is shown in Table 2.

Results of individual studies

No study could be assigned a high level of evidence. Eleven [14,21,28–36] of the 63 studies showed moderate level of evidence (Tables 3 and 4). The remaining 52 studies [13,22,23,37–85] demonstrated low quality of evidence with respect to the proposed research question (Table 5). The reasons for classification as low level of evidence were either too low number of samples, unclear information about the sample size and/or insufficient details to allow reproducibility. Very few moderate studies (Table 3) employed some of the parameters that we consider relevant, *e.g.* examining time-dependent dissolution of current endodontic sealers.

Risk of bias within studies

The quality of the studies assessed according to the modified CONSORT checklist (Table 4) did not provide a very encouraging picture, and it was seen that even moderate studies lacked many important factors related to reducing the risk of bias (such as sample size calculation, randomization, allocation, account of outcome data, complete reporting of results). None of the studies mentioned confidence interval while reporting the results. Blinding was reported in only two of the moderate studies [32,35]. Moreover, a number of studies did not mention a control group [14,31]. A low risk of bias was not found in any of the individual studies (Table 4).

Discussion

Summary of evidence

Only a few studies showed careful design and reported enough details to allow replicability. It is noteworthy to mention that a few of the studies [22,53,55,83] were classified as low due to small sample size, in spite of having sufficient details pertaining to reproducibility.

Many of the reviewed studies did not employ the methodological parameters that are considered relevant to the clinical situation according to the prespecified evidence criteria. Therefore, it is difficult to directly interpret the results of these *in vitro* studies or to relate the limited time-dependent dissolution data of available endodontic sealers to the clinical scenario.

The study by Silva et al. [55], other than demonstrating good design and details to allow reproducibility, included several relevant parameters from the evidence criteria. However, due to a small sample size and consequently lack of statistical power, it was also assigned a low level of evidence.

Adherence to international solubility standards

Most of the studies included in this review report to be based on international solubility standards (ISO or ANSI/ADA). However, many studies fail to provide a clear picture of how strictly they adhered to the international standards. Currently, the ISO 6876 [16,17] and the ANSI/ADA specification no. 57 [18] are frequently utilized (Table SI, Supplementary information). These standards propose using the residue method, *i.e.* estimating the difference in sealer weight before and after 24 h of immersion in water [61,73,74]. Modifications of the standard methods have been undertaken in individual studies, for example, by direct measurement of the sealer mass before and after immersion in water [22,29,52,75]. Additionally, the assessment of solubility and water sorption of resin-based and other hydrophilic (*e.g.* calcium silicate) sealers with significant water uptake have been based on the ISO 4049:2009 standard [19], as ISO 6876 [16,17] and ANSI/ADA specification no. 57 [18] do not apply to these hydrophilic sealers [66]. According to ISO 4049:2009, weight gain from the immersion of sealers in water for 7 days is recorded as water sorption, while weight loss from subsequently dehydrating the specimens to constant mass is registered as solubility (Tables SI and SII, Supplementary information). Taken together, even though studies refer to the use of standard tests, variation in the described methodology is a common feature.

Among the main limitations of the standard tests are the large surface area of the specimens (*i.e.* much larger than the surface area of extruded sealers in the clinical scenario), the

Table 3. Studies with moderate quality of evidence along with reasons for such classification ($n = 11$).

			Relevant parameters					
Moderate level study	Control group	Sealers not tested	Specimen dimension and design	Moment of immersion	Immersion media and quantity	Time-dependent dissolution	Renewal of immersion	Addresses water uptake
Borges et al. [32]	Yes	Zinc oxide	7.7 mm ×1.5 mm cylinder	3 × setting time	Water, 7.5 mL	7 days	No	No
Ersahan and Aydin [33]	Yes	Zinc oxide	20 mm ×1.6 mm cylinder	3 × setting time	Water, 20 mL	14 days	No	Yes
Gandolfi et al. [21]	Yes	Zinc oxide and calcium hydroxide	8 mm ×1.6 mm cylinder	70% of final setting time	Water, 20 mL	1 day (solubility)	After 3 h, 24 h (solubility)	Yes
Garcia et al. [36]	Yes	Zinc oxide and calcium hydroxide	20 mm ×1.5 mm cylinder	3 × setting time	Water, 50 mL	7 days	No	No
Kazemi et al. [28]	Yes	Calcium silicate and calcium hydroxide	15 mm on each side of 1mm pipettes	40 min after mixing	Water, volume unclear	180 days	No	Yes
Mathias-Júnior et al. [30]	Yes	Calcium silicate, calcium hydroxide and zinc oxide	7.75 mm ×1.5 mm cylinder	3 × setting time	Water, 7.5 mL	7 days	No	No
Prüllage et al. [34]	Yes	Calcium hydroxide and zinc oxide	20 mm ×1.6 mm cylinder	24 h	Water, PBS, 160 mL	28 days	No	No
Rosa et al. [31]	No	Calcium silicate	3 mm ×2 mm cylinder	Unclear	Water and Simulated body fluid, 2 mL	90 days	Every 15 days	No
Schäfer and Zandbiglari [29]	Yes	Calcium silicate	20 mm ×1.6 mm cylinder	24 h	Water and Artificial saliva, 160 mL	28 days	After 1 day and then weekly	No
Siboni et al. [14]	No	Calcium hydroxide	8 mm ×1.6 mm cylinder	50% of final setting time	Water, 20 mL	7 days	No	Yes
Versiani et al. [35]	Yes	All except zinc oxide	7.75 mm ×1.5 mm cylinder	3 × setting time	Water, 7.5 mL	7 days	No	No

These studies describe enough details to allow replication and use $n \geq 10$ specimens per group.

type of immersion media (water, which differs from oral fluids) and the short testing period (which does not give any indication of the stability of the fully hardened sealer). Additionally, the ISO 6876:2001/2012 [16,17] or the ANSI/ADA specification no. 57 (2000) [18], which only evaluate the solubility of water-soluble components, may underestimate the results for certain sealers due to loss of eluate by volatilization [78]. Only four studies from the moderate category in this systematic review had taken water uptake into consideration during the solubility testing of the sealers [14,21,28,33]. Notably, the use of micro CT was employed in one study as an alternate methodology to exclude the influence and role of free water from the solubility analysis [55].

The reviewed studies rarely included methods or design parameters that were considered relevant as per our criteria. Although we are aware that the *in vitro* studies do not aim to reproduce the situation in the clinic, it would be desirable if these parameters were incorporated to closer simulate the clinical scenario. A number of parameters, as included in our data items, influence the outcome of the solubility studies, namely, the type of sealer used, the type of immersion media, the quantity of solution, the duration and moment of immersion of sealers, and the sealer surface area (Tables 2 and 3), as discussed in detail below.

Type of endodontic sealers

Only a few studies investigated the solubility of newer water-based materials such as the calcium silicate sealers (Table 3). The standard solubility test may not be the appropriate choice for these materials, which show different composition and behaviour than the cements for which the standard tests were originally developed [20]. ISO 6876 and its modified versions adopted in various studies [22] fail to effectively address water uptake by the hydrophilic sealers, which in turn may influence the measurement of solubility [23,28,78]. For resin-based sealers, mainly investigated using ISO 4049:2009 [19] to address the issue of water uptake [33], problems such as differential water uptake by similar composition of sealers are still encountered due to the difference in the extent of polymerization [39].

Only six of the moderate studies were conducted on the calcium silicate-based sealers [14,21,32–34,36]. Additionally, calcium silicates show reduced solubility (as formation of calcium phosphate deposits can increase their mass and fill porosities) in the presence of body fluids [14,21]. However, not many studies included in this review employed body fluids as an immersion media for calcium silicate-based cements (Table 3). Only one solubility study by Prüllage et al. [34] from the moderate category used calcium silicates in

Table 4. Assessment of moderate studies according to the modified CONSORT checklist.

	Checklist item	Study												
		Borges et al. [32]	Ersahan and Aydin [33]	Gandolfi et al. [21]	Garcia et al. [36]	Kazemi et al. [28]	Mathias-Júnior et al. [30]	Prüllage et al. [34]	Rosa et al. [31]	Schäfer and Zandbiglari [29]	Siboni et al. [14]	Versiani et al. [35]
1	**Structured abstract**	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
2a	**Scientific background**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2b	**Specific objectives**	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
3	**Method intervention**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	**Method outcomes**	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
5	**Sample size**	No	No	No	No	No	No	No	No	No	No	No
6	**Randomization sequence generation**	No	No	No	No	No	No	No	No	No	No	No
7	**Allocation concealment**	No	No	No	No	No	No	No	No	No	No	No
8	**Implementation**	No	No	No	No	No	No	No	No	No	No	No
9	**Blinding**	Yes	No	No	No	No	No	No	No	No	No	Yes
10	**Statistical methods**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	**Result outcomes and estimation**	No	No	No	No	No	No	No	No	No	No	No
12	**Trial limitations**	No	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Yes
13	**Funding**	No	Yes	No	No	No	No	No	Yes	No	No	No
14	**Protocol**	No	No	No	No	No	No	No	No	No	No	No

Table 5. Studies with low quality of evidence along with the given reasons ($n = 52$).

Low sample size ($n < 10$ specimens) ($n = 27$)	Insufficient details provided to permit replication ($n = 25$)
Amoroso-Silva et al. [60]	Arias-Moliz et al. [62][b]
Ashraf et al. [69]	Azadi et al. [63]
Borges et al. [80]	Barros et al. [64][b]
Camargo et al. [37]	Collares et al. [66][b]
Cañadas et al. [83]	Donnelly et al. [39]
Carvalho-Júnior et al. [65]	Duarte et al. [67][a]
Carvalho-Júnior et al. [84]	Fonzi et al. [41][a]
Faria-Júnior et al. [13]	Gandolfi et al. [38]
Flores et al. [40]	Garrido et al. [68][b]
Grga et al. [22]	Higginbotham [70][b]
He et al. [42]	Kuga et al. [71]
Kaplan et al. [43]	Lee et al. [72][a]
Lim et al. [44]	McComb and Smith [49][a]
Marciano et al. [45]	McMichen et al. [73]
Marciano et al. [46]	Ono and Matsumoto [50][a]
Marín-Bauza et al. [47]	Poggio et al. [74]
Marín-Bauza et al. [48]	Schäfer et al. [75][b]
Portella et al. [51]	Segato et al. [76][b]
Resende et al. [52]	Silva et al. [59][a]
Ruiz-Linares et al. [53]	Sonntag et al. [85][a]
Silva et al. [54]	Sousa-Neto et al. [77][a]
Silva et al. [55]	Viapiana et al. [78]
Simões et al. [56]	Vitti et al. [79]
Song et al. [57]	Vitti et al. [81]
Versiani et al. [58]	Wang et al. [82][b]
Zhou et al. [61]	
Ørstavik [23]	

[a]Studies with low sample size as well.
[b]Studies in which sample size is unclear or not mentioned.

combination with a body fluid as an immersion media. A study by Siboni et al. [14] demonstrated the apatite-forming ability of calcium silicates in the presence of body fluid using ESEM-EDX (environmental scanning electron microscopy coupled with energy dispersive X-ray analysis) and micro-Raman spectroscopy; yet, solubility testing in the same study just used water as the immersion media. Current endodontic sealers, in particular, the hydrophilic calcium silicate-based materials, should be included in future studies.

Type and quantity of immersion media

Considerable criticism has been encountered regarding the use of water as an immersion medium for solubility tests, despite it being recommended in the ISO and ADA standards. Among alternate media, the use of acidic solutions and artificial saliva have been proposed [29,70]. More recently, simulated body fluids such as Hank's balanced salt solution (HBSS) [22], phosphate-buffered saline (PBS) [34,55], and synthetic tissue fluid (STF) [31] have been utilized in solubility studies (Table 3). On the one hand, the use of saline or buffered media can affect dissimilar materials differently, *e.g.* dissociation of calcium hydroxide cements is more sensitive to the constitution, quantity and buffer of the media. On the other hand, sealer solubility can vary according to the type and pH of the immersion media, as observed in acidic solutions for zinc oxide and glass ionomer sealers [29]. Therefore, the assessment of sealer solubility needs to include acidic media apart from water. This is relevant as the pH in the periapical region is acidic when inflammation is present.

Another important aspect is the quantity of liquid used in solubility studies, which consequently influences the concentration gradient involved in ion extraction. Different quantities ranging from 2 mL [31] to 160 mL have been used in various studies [29,34]. However, it is very difficult to estimate an amount that is relevant for the clinical reality due to variations in the gradient concentration and transport from the periapical region. There are a few studies that advocate renewal of the immersion solution after a certain period, for example, weekly [22,29,75] or every 15 days [31]. Most studies, however, do not employ such renewal. Only three of the moderate studies had employed renewal of immersion media [21,29,31]. A study from the moderate category, undertaken by Prüllage et al. [34], employed new samples for each time period; however, renewal of immersion media for long observation periods was not performed. To summarize, it is desirable to include a simulated body fluid in realistic quantities in future *in vitro* solubility studies.

Duration and moment of immersion

There are only a few published studies on long-term dissolution of endodontic sealers. The duration of immersion of sealer samples in various solubility studies varies from a few hours (15–128 h) [42,61], days (7–45 days) [58,81], or months (2–6 months) [28,31,56]. Nevertheless, in most of the studies, including those based on ISO 6876:2001 [16], evaluation is performed after 24 h. This idea has been supported by the observation of increasing solubility of sealers over a period of 28 days [28,29,31,43,76]. Although the greatest dimensional changes in sealers take place within the first 4 weeks, some sealers have been reported to display changes even up to 48 weeks [86]. In this review, only 4 moderate studies included observation periods of 28 days or more [28,29,31,34] (Table 3).

Other than the duration, the moment of immersion is also relevant for solubility studies [43]. A common approach is to allow different times for the initial setting of the sealer samples before they are immersed, or to allow setting of the sealer in unrealistic conditions [33]. Thus, the results of standard tests cannot be correlated to the actual *in vivo* conditions, in which immediate contact with fluids may take place [43]. To the best of our knowledge, limited research involved immersion of endodontic sealers immediately after mixing, allowing no time for setting, in order to simulate the clinical situation [55]. This approach should be encouraged in future studies as it comes closest to the reality.

Sealer surface area and design of samples

Most of the solubility studies have utilized sealer samples prepared in moulds of specific sizes conforming to the ISO/ADA recommendations. A reduction in the size of the sealer sample has been suggested as an attempt to reduce the surface area of material exposed to the immersion medium [84]. However, complete immersion of samples, as is done in the standard solubility tests, does not actually take place *in vivo*, where only a small portion of the sealer comes in contact with periapical fluids, *e.g.* in cases of apical extrusion of sealer [43]. With this in mind, other authors have utilized filled roots of extracted human teeth [55] or acrylic teeth with root-end fillings [87] for solubility testing.

Additionally, variability amongst studies with respect to the surfaces of sealer exposed to immersion exists based on whether the mould was retained [29,34] during immersion or not [14,35,60,69]. In future solubility studies, it would be appropriate to reproduce sealer volume and surface area that reflect the clinical situation.

Limitations of this study

An inherent limitation of this systematic review is that only papers published or available online were included, thus excluding grey literature, unpublished findings or personal communications. Additionally, it was not possible to assess the risk of bias across individual studies.

It could be argued that classifying studies as low evidence due to low sample size is not reasonable because these studies have actually followed the existing international standard recommendations. However, these international standards differ from the recently recommended CONSORT guidelines for reporting *in vitro* studies on dental materials [26]. Furthermore, a vast majority of the low evidence studies with low sample size demonstrated relatively large statistical dispersion. An increased sample size would definitely have improved the confidence intervals of the reported results of these studies.

Future perspectives

Further alternative, low-cost *in vitro* methods that correlate with the clinical scenario are needed to estimate the dissolution of endodontic sealers. Additionally, there is a dire need to conduct and report studies using consensus guidelines and detailed methodology to allow replication, and at the same time, provide low risk of bias.

Final remarks

Within the limitation of this review, we conclude that existing *in vitro* studies on the solubility of endodontic sealers do not demonstrate a high quality of evidence. Most of these studies do not comply with the modified CONSORT guidelines for reporting *in vitro* studies nor do they employ relevant parameters prespecified in our evidence criteria. Only few studies estimate time-dependent dissolution and include current endodontic sealers. Altogether, data obtained from the *in vitro* solubility studies on endodontic sealers are difficult to apply to a clinical context.

Disclosure statement

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