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Original Article

Evaluation of Nickel Ion Release in Orthodontic Archwires: A Narrative Synthesis of In Vitro and In Vivo Research

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Abstract

Nickel-based orthodontic archwires, particularly nickel-titanium (NiTi) and stainless steel (SS), remain essential in fixed orthodontic therapy because of their favorable mechanical behavior. Nevertheless, concerns persist regarding nickel-associated hypersensitivity, cytotoxic effects, and ion release. This review examines recent evidence on nickel release from orthodontic devices, expanding upon earlier systematic reviews by incorporating both in vitro and in vivo investigations conducted under various conditions. Literature searches were performed in Web of Science, PubMed, and Scopus to identify studies that assessed the relationship between environmental factors and nickel ion release from archwires containing nickel. Current findings indicate that ion release occurs mainly during the early treatment phase but remains well below toxic thresholds. Influencing factors include pH variation, corrosion processes, treatment duration, and oral environmental conditions. However, most studies have been short-term and confined to either in vitro or in vivo settings, rarely combining both. To establish stronger causal evidence, continuous in vivo monitoring of nickel release is required, alongside further studies into long-term health implications. Collaborative efforts involving clinicians, researchers, and regulatory organizations are necessary to establish evidence-based recommendations for orthodontic material selection, focusing on minimizing nickel exposure and prioritizing patient safety.

Key words: Nickel release, Nickel-containing archwires, Orthodontic appliances, In vitro, In vivo, Artificial saliva

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Introduction

Excessive exposure to nickel can cause multiple health risks [1]. Fatalities have been reported from nickel carbonyl exposure, and by the 1930s, nickel was widely acknowledged as a cause of contact dermatitis. Occupational studies also noted elevated risks of lung and nasal cancers in nickel-exposed workers [2, 3]. In 2008, nickel was named the "Allergen of the Year" by Gillette [4], with dermatologists highlighting the increasing prevalence of nickel sensitivity. This recognition intensified research into nickel's effects on human health [5]. The International Agency for Research on Cancer (IARC) currently classifies nickel as a Group 1 carcinogen; however, no conclusive evidence links nickel released from orthodontic devices to carcinogenesis in patients [6].

The majority of global nickel output is directed toward the production of stainless steel and nickel-based alloys [7], with widespread use in medical devices, particularly orthodontic archwires. These wires are critical for controlled tooth movement and are considered a cornerstone of fixed orthodontic treatment [8]. Although newer technologies and materials have expanded available options, no single wire type is optimal for every treatment phase [9]. The most common wires in practice remain NiTi alloys (sometimes modified with copper) and SS.

NiTi wires often contain more than 50% nickel, whereas copper–NiTi variants generally include less than 50%. In contrast, stainless steel wires contain only about 8% nickel [10–12]. SS wires are easier to manipulate and less likely to provoke hypersensitivity compared to NiTi. Their chromium content (12–13%) allows the formation of a protective chromium oxide film, limiting corrosion by restricting oxygen diffusion into the alloy [13]. Nonetheless, SS wires are relatively stiff with reduced elasticity, leading to a greater need for adjustments throughout treatment [14, 15].

Conversely, NiTi wires are valued for their elasticity, superelastic behavior, and shape-memory properties. They can return to their original form after deformation at lower temperatures but may undergo irreversible changes if exposed to high heat [16]. Despite these advantages, the high nickel content raises biocompatibility concerns, as nickel has been associated with cytotoxic, allergenic, and potentially mutagenic effects [17].

During extended treatment, variations in pH and fluoride levels can compromise both titanium-based and stainless steel wires. The corrosive nature of orthodontic appliances is well documented; however, limited information exists regarding the systemic impact of corrosion by-products on patient health. Evidence indicates that ion release does occur during treatment but at concentrations far below daily dietary intake levels. Nonetheless, more clinically oriented research is required to fully assess these effects [18, 19]. Nickel hypersensitivity is among the most common concerns, with female patients showing higher sensitization rates than males, as reported by Zigante *et al.* [11, 20, 21].

The introduction of NiTi alloys into orthodontics initially raised questions about their safety. Wever *et al.* [22] addressed these by conducting both in vitro and in vivo evaluations of NiTi alloy biocompatibility. Their findings demonstrated that NiTi wires exhibit good resistance to corrosion and minimal ion release, confirming short-term safety in clinical use. More recent studies over the past decade consistently report that nickel ion release from orthodontic components, including brackets, generally remains below toxic thresholds and often declines after an initial peak [23].

Allergic responses to nickel from orthodontic alloys

The previously cited findings do not suggest that nickel ions released from NiTi wires are free of adverse consequences. In fact, similar to type IV delayed hypersensitivity, nickel exposure in orthodontics can provoke immune-mediated reactions [24, 25]. This mechanism involves two distinct phases: first, sensitization, where immune cells identify nickel ions and generate memory T-cells; second, elicitation, where re-exposure leads to cytokine release and subsequent inflammation. Clinically, this often appears as contact dermatitis outside the mouth, with signs ranging from erythema and swelling to more severe oral lesions such as ulceration. Apart from nickel, elements like chromium, cobalt, copper, silver, and titanium may also trigger similar reactions [11]. Beyond local manifestations, systemic and extra-oral effects of nickel ion exposure from orthodontic devices have also been documented, as highlighted in the review by Di Spirito *et al.* [26].

Recent years have seen an increase in studies on ion release during orthodontic therapy. Although the concentrations detected are markedly lower than dietary nickel intake, the interactions between alloy composition, oral environment, and patient-specific susceptibility remain incompletely understood [27–29]. Nickel, however, continues to be recognized as the leading cause of contact dermatitis related to metals, accounting for more hypersensitivity reactions than all other metals combined [30].

Effect of saliva and environmental conditions on nickel release

The oral environment significantly influences nickel ion release during orthodontic treatment. Fixed appliances such as brackets, wires, and bands are continuously exposed to varying pH levels, dietary influences, temperature changes, mechanical stress, and corrosion processes [31]. Multiple investigations [29, 32, 33] have simulated oral conditions by immersing nickel-containing archwires in artificial saliva for periods corresponding to treatment timelines. Results consistently show measurable increases in nickel levels in saliva and serum shortly after appliance placement [34]. Even so, most studies agree that these concentrations remain far below toxic limits, and notably, permissible thresholds in drinking water are much higher than the nickel concentrations reported in oral fluids [35].

A protective factor is the presence of passive oxide layers, especially from chromium and titanium, which act as barriers against corrosion. However, such films may deteriorate through wear, polishing, or acidic conditions, increasing ion release [13]. Surface coatings on appliances have been investigated as an additional strategy to suppress nickel release [36, 37].

Interestingly, external influences beyond intraoral chemistry have also been implicated. Studies [38, 39] show that radiofrequency exposure from mobile phones may accelerate nickel ion release from orthodontic wires. Mortazavi *et al.* [38] suggest expanding research to include emissions from devices such as Wi-Fi routers. Rajendran *et al.* [39] reported that using earphones during phone calls reduced the effect, implying that proximity to electronic devices may influence ion release kinetics.

Two comprehensive reviews by Mikulewicz and Chojnacka (2009 and 2010) [31, 35] summarized evidence from both in vitro and in vivo studies. They concluded that, in the short term, orthodontic appliances do not release nickel at toxic levels, though long-term data were lacking at that time. More recently, a meta-analysis by Imani *et al.* [40] confirmed that small amounts of nickel are released, potentially inducing tolerance during the early phases of therapy. Still, the authors emphasized the need for larger, ethnically diverse cohorts and improved control of salivary variables to strengthen conclusions.

This review, therefore, aims to trace how current knowledge about nickel ion release has progressed since earlier evaluations, to highlight gaps that remain, and to provide recommendations for future investigations. To achieve this, the literature is organized into two categories—**in vitro** and **in vivo** studies—examining how environmental and material-related factors influence nickel release from orthodontic wires.

Scope and Sources of Reviewed Literature

This narrative review focuses on nickel ion release from two widely used orthodontic alloys: stainless steel (SS) and nickel-titanium (NiTi). These include CrNi SS wires, martensitic-active heat-activated (thermodynamic) NiTi and CuNiTi wires, and austenitic-active superelastic NiTi.

A targeted search strategy was applied to capture a wide range of relevant studies, without adhering to a strict systematic review protocol. The databases consulted were PubMed, Scopus, and Web of Science. Search terms included: *"nickel ion release"*, *"nickel content dynamics"*, *"stainless steel orthodontic archwires"*, *"nickel-titanium archwires"*, *"in vivo"*, and *"in vitro"*.

Inclusion criteria were as follows:

(a) studies investigating SS or NiTi wires;

(b) studies evaluating nickel ion release either in vivo or in vitro;

(c) studies analyzing environmental or chemical factors affecting nickel release.

Papers not meeting these standards were excluded (Figure 1). This flexible but structured approach ensured the review remained focused on clinically relevant findings, while offering contextual synthesis and critical evaluation of evidence concerning nickel ion dynamics in orthodontic appliances.

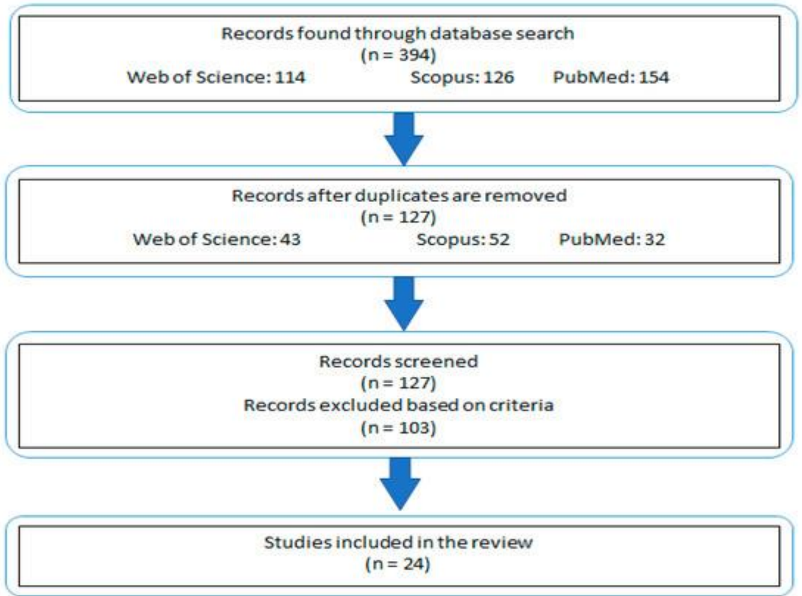

Figure 1. Flow diagram showing criteria for study inclusion and exclusion

Key Findings from the Literature

To quantify the release of metallic ions, analytical techniques such as atomic absorption spectrometry (AAS) and atomic emission spectroscopy (AES) are most frequently applied, as both enable detection in very small sample volumes. Surface characterization is commonly performed using scanning electron microscopy with energy-dispersive spectroscopy (SEM/EDS), which provides insight into elemental composition as well as morphological alterations in localized regions of the materials under study.

In Vitro investigations of nickel-releasing archwires

The majority of in vitro research relies on artificial saliva solutions to replicate the oral environment. **Table 1** summarizes the formulations of artificial saliva used across the included studies.

Several works explore how immersion in artificial saliva influences ion discharge from nickel-based archwires over time. For instance, Cioffi *et al.* [41] tested pseudoelastic NiTi wires under simulated physiological conditions and fluoridated solutions, assessing both stress effects and environmental exposure. They observed no nickel release during the stress-driven austenite–martensite phase transition, implying NiTi's surface resists transformation stresses. However, long-term fluoride exposure elevated ion release, leading the authors to call for further exploration of fluoride's short-term impact.

Expanding this focus, Pastor *et al.* [42] evaluated popular orthodontic wires immersed in different mouthwashes. Their results demonstrated increased nickel discharge in these conditions, with potential implications for hypersensitive patients. They suggested caution when prescribing mouthwashes during fixed appliance therapy.

Similarly, Mirjalili *et al.* [18] immersed wires in artificial saliva to analyze corrosion behavior, employing potentiodynamic and potentiostatic polarization methods. Findings showed that NiTi resisted pitting in artificial saliva, whereas stainless steel exhibited only slight improvements. Fluoride media did not worsen artificial crevice conditions, but pre-passivation treatment reduced pitting susceptibility in both alloys exposed to fluoride.

Didovic *et al.* [43] assessed NiTi wires alongside stainless steel brackets, bands, and ligatures. Distinct surface morphologies were noted, linked to manufacturing processes. In their initial condition, stainless steel bands and brackets already showed pitting. Immersion produced adhesive coatings on brackets and ligatures, though no protective oxide films were evident. Salt precipitation (mainly KCl) was also observed. Notably, stainless steel bands released significantly more ions than other parts, attributed to welding during production. Surface roughness, however, did not correlate with ion release.

Ganidis *et al.* [44] compared stainless steel (SS), NiTi, and CuNiTi wires immersed in artificial saliva. After 30 days, the eluates contained higher levels of chromium and nickel, particularly under acidic conditions (pH 3.5), where the greatest release was seen. Despite this, measured levels never exceeded normal daily dietary intake.

Laird *et al.* [45] investigated five types of wires in buffers with varying pH. Nickel release generally rose over time but decreased with higher pH. Coated wires showed lower overall ion emission compared to uncoated ones.

In another study, Osmani *et al.* [46] examined six wire types—NiTi, coated NiTi, SS, nickel-free SS, CoCr, and Ti–Mo (TMA)—immersed in artificial saliva. Results indicated NiTi discharged higher nickel and titanium compared to coated NiTi. Standard SS released more Fe, Cr, and Ni than nickel-free SS. CoCr released high cobalt but less Cr, Ni, and Mo compared to the Mo and Ti levels seen in TMA. Overall, lower ion release occurred at neutral pH (6.6) and in hypoallergenic wires compared to conventional alloys.

Al-Jammal *et al.* [47] further evaluated NiCr alloys in artificial saliva at different pH levels, using AAS for quantification. The greatest Ni and Cr release occurred at pH 2.5 regardless of immersion period, with nickel levels consistently higher than chromium. The authors concluded that ion release is highly pH-dependent, with acidic conditions accelerating nickel discharge.

To compare two materials directly, Chikhale *et al.* [48] immersed TMA and NiTi wires in artificial saliva. NiTi showed higher nickel release, while TMA produced more titanium ions. Nevertheless, all levels were well within safety margins.

Aiswareya *et al.* [29] evaluated ion release from NiTi and SS wires combined with SS and ceramic brackets. Using flame atomic absorption spectrometry (FAAS), they quantified nickel and chromium ions and assessed cytotoxicity on HeLa cells. SS brackets combined with wires showed significantly greater nickel and chromium release, although no major differences were observed between the wires themselves.

Kao *et al.* [49] studied how saliva pH influenced fluoride-related corrosion extracts of SS and heat-activated NiTi wires on U2OS osteosarcoma cells. Their results indicated fluoride agents could increase cytotoxic potential, highlighting clinical concerns.

Senkutvan *et al.* [33] analyzed four wire types (NiTi, SS, CuNiTi, ion-implanted NiTi) in artificial saliva. They reported that nickel discharge diminished over time, remained below allergic thresholds, and concluded that, despite ion release under acidic conditions, the wires were clinically safe.

Table 1. Composition of artificial saliva formulations reported in the studies included in this review

Artificial Saliva Components	Citations
Phosphate-buffered saline (PBS), pH 4.6; PBS with 0.001% NaF, pH 4.8; PBS with 0.01% NaF, pH 5; PBS with 0.1% NaF, pH 5.6	[41]
Sodium chloride (0.844 mg), Potassium chloride (1.2 mg), Anhydrous calcium chloride (0.146 mg), Magnesium chloride hexahydrate (0.052 mg), Potassium phosphate dibasic (0.34 mg), 70% Sorbitol solution (60 mg), Methyl paraben (2 mg), Hydroxyethyl cellulose (3.5 mg)	[48], [30], [17]
Sodium chloride (0.4 g), Potassium chloride (1.21 g), Sodium hypophosphate (0.78 g), Sodium sulfide (0.005 g), Urea (1 g), Distilled and deionized water (1000 mL)	[33], [29]
Neutral solution: Calcium (1.5 mM), Phosphorus (0.9 mM), Tris buffer (20 mM), Potassium chloride (150 mM), pH 7.0; Acidic solution: Calcium (2 mM), Phosphorus (2 mM), Acetate buffer (74 mM), pH 4.3	[32]
Potassium chloride (0.4 g), Sodium chloride (0.4 g), Calcium chloride dihydrate (0.906 g), Sodium dihydrogen phosphate dihydrate (0.69 g), Sodium sulfide nonahydrate (0.005 g), Urea (1 g)	[18]
Sodium chloride (0.84 mg/100 mL), Potassium chloride (1.2 mg/100 mL), Magnesium chloride (0.052 mg/100 mL), Calcium chloride (0.146 mg/100 mL), Potassium dihydrogen phosphate (0.34 mg/100 mL), 70% Sorbitol solution (60 mL), Hydroxyethyl cellulose (3.5 mg/100 mL)	[49]
Potassium chloride (1.5 g/L), Sodium bicarbonate (1.5 g/L), Potassium thiocyanate (0.5 g/L), Lactic acid (0.9 g/L)	[37], [43], [46]
Dipotassium phosphate (7.69 g), Monopotassium phosphate (2.46 g), Sodium chloride (5.3 g), Potassium chloride (9.3 g), Distilled water (1000 mL)	[47]

Sodium chloride (NaCl); potassium chloride (KCl); sodium dihydrogen phosphate (NaH_2PO_4); water (H_2O); sodium sulfide (Na_2S); urea ($CO(NH_2)_2$); calcium chloride ($CaCl_2$); sodium bicarbonate ($NaHCO_3$); potassium thiocyanate (KSCN).

Saliva in the mouth is highly dynamic, unlike the static conditions of most in vitro systems, which is a critical factor to consider. To better replicate oral conditions, Mikulewicz *et al.* [50] designed a thermostatically controlled glass device that maintained a constant flow of artificial saliva while testing stainless steel (SS) wires. Their results confirmed that the total nickel released remained far below toxic thresholds, supporting the biocompatibility of SS wires.

Another factor impacting ion liberation from nickel-based wires is patients' daily use of oral care products. Jamilian *et al.* [30] compared nickel and chromium ion release from SS and round NiTi wires immersed in Oral B®, OrthoKin®, and artificial saliva. They observed that ion release increased progressively with time, with artificial saliva producing the lowest values. They also noted that SS released ions more gradually than NiTi.

In a related experiment, Mirhashemi *et al.* [51] tested the effect of different mouth rinses and reported that Listerine caused the highest ion release, whereas Oral B® yielded the lowest.

Zubaidy and Hamdany [52] assessed the effect of magnetically treated water (MTW) on SS archwires. Their results showed that MTW substantially reduced nickel release compared with mouthwash exposure, suggesting that MTW could be a safer adjunct during orthodontic therapy.

Beyond hygiene products, certain dietary components may also influence corrosion. Erwansyah *et al.* [53] showed that extract from snake fruit (Salacca zalacca), particularly at 300 ppm, decreased nickel ion release from SS wires, implying a protective action.

Table 2 summarizes the key characteristics of the in vitro studies reviewed, including wire materials, manufacturers, types of ions analyzed, immersion duration, and post-exposure assessment methods.

Since clinicians must also choose wire geometry, Azizi *et al.* [17] explored whether the cross-sectional shape influences metal release. Their comparison of round and rectangular NiTi wires revealed that rectangular wires released significantly more ions, especially within the first hour of exposure to artificial saliva. This indicates that wire shape can alter corrosion dynamics.

Although most experiments report ion release values within safe ranges, it remains essential to determine their biological impact. Dugo *et al.* [54] addressed this by testing the cytotoxicity of eluates from NiTi and SS appliances (archwires, bands, brackets, ligatures) on four human cell lines: oral epithelial (CAL 27), hepatic (HepG2), colon (CaCo-2), and gastric (AGS). They observed strong adverse effects on CAL 27 cells at all concentrations, while CaCo-2 showed the greatest resistance. Reactive oxygen species (ROS) were induced in AGS and HepG2 cells, although the highest ion concentrations reduced ROS production compared with lower concentrations. Some eluates containing Cr, Mn, and Al displayed minor DNA damage and weak genotoxic effects, though these were within tolerable levels. Statistical analysis indicated that Fe, Cr, Mn, and Al were the main contributors to cytotoxicity, with Mn and Cr linked to hydroxyl radical formation and DNA breaks, while Fe and Ni drove ROS production.

More recently, Thiyagarajan *et al.* [55] employed electrochemical methods to quantify nickel release from NiTi, SS, and CuNiTi archwires exposed to artificial saliva for three days. They determined that NiTi and CuNiTi exhibited higher resistance to corrosion than SS, with nickel ion release being negligible overall.

In Vivo studies of ni-containing archwires

The in vivo investigations included in this review examined nickel-containing wires used clinically for varying treatment durations (7 days to 18 months). The studies are organized here according to the maximum period of use, ending with two reports analyzing release kinetics statistically. **Table 3** outlines the archwire composition, brands, ions assessed, exposure times, and analytical techniques used post-treatment.

Nickel release and its potential to trigger allergic reactions remain a central concern in orthodontics. Ghazal *et al.* [56] studied surface changes and ion release in superelastic and heat-activated NiTi wires. After 30 days in the mouth, both groups released comparable nickel levels, although superelastic wires showed greater surface roughening. Interestingly, once re-immersed in artificial saliva, previously used wires released fewer ions, suggesting that nickel liberation may decrease with clinical wear.

Ibañez *et al.* [57] examined ion release dynamics and salivary pH changes in patients with heat-activated NiTi and SS wires. Their results indicated that metal ion release peaked within clinically acceptable limits. Salivary pH dropped to acidic levels after three months but returned to alkaline after six months, suggesting that while orthodontic devices temporarily alter oral conditions, physiological adaptation occurs over time.

Almasry *et al.* [58] monitored nickel discharge from thermoactive round NiTi wires during the initial two months of clinical application. They detected a modest rise in nickel release but confirmed that concentrations stayed within permissible safety margins. These findings support the conclusion that although nickel is released during orthodontic therapy, the levels are typically not hazardous.

Bass *et al.* [59], in a 1993 study, explored the relationship between orthodontic appliances (SS and NiTi wires) and nickel hypersensitivity, particularly in individuals with prior sensitivity. Among 29 subjects, five (all female) tested positive for nickel reactivity before treatment, and two more developed sensitivity while under treatment. Their results showed that nickel-related allergies occur more often in women and that orthodontic devices, while not significantly impacting overall oral health, may trigger sensitivity in certain cases.

Lages *et al.* [60] broadened the scope by analyzing salivary metal levels, including nickel, in patients fitted with either metallic or esthetic orthodontic appliances (SS brackets with heat-activated NiTi wires). In their retrospective study, no meaningful differences in salivary nickel were found between patients with metallic appliances and controls, or between esthetic appliances and controls. Nonetheless, the choice of appliance material was shown to play a significant role in nickel ion concentration, highlighting the importance of selecting appropriate components.

Amini *et al.* [61] conducted a comparative test involving patients wearing fixed orthodontic appliances and their siblings of the same gender who were not undergoing orthodontic therapy. Appliances included NiTi and SS wires, with SS brackets and bands. Saliva samples from patients were compared with their siblings' samples as controls. The study found nickel content was significantly higher in the treatment group, while chromium levels showed no notable difference. Despite inherent limitations of in vivo work, the authors concluded that fixed orthodontic systems increase salivary metal ion content.

Table 2. Summary of nickel-containing wires and in vitro testing approaches. NiTi; coated NiTi; CuNiTi; SS; NiCr; Ni-free SS; TiMo; CoCr; TMA; days (d); inches (in).

Wire Composition	Product Name and Supplier	Ions Examined	Testing Environment	Test Duration	Evaluation Methods	Source
NiTi	Nitinol N Memory-Metalle 0.5 × 0.5 mm, Nitinol S Memory-Metalle foil 0.05 and 1 mm (GmbH, Weil am Rhein, Germany); Sentalloy standard 0.46 × 0.46 mm, Neo Sentalloy standard 0.46 × 0.63 mm (GAC International Inc., Bohemia, NY, USA)	Ni	Artificial saliva (with/without fluoride)	7 d	Thin-layer activation, X-ray photoelectron analysis	[41]
NiTi	NiTi archwires, round 0.020 in, rectangular 0.016 × 0.016 in (Ortho Technology, Tampa, FL, USA)	Ni, Ti	Artificial saliva	1 h, 24 h, 7 d, 21 d	Plasma atomic emission spectrometry	[17]
NiTi, TiMo	NiTi archwire 17 × 25 in, TMA archwire 17 × 25 in (Modern Orthodontics, Ludhiana, India)	Ni, Ti	Artificial saliva	90 d	Atomic absorption analysis	[48]
SS, NiTi, TiMo	Stainless Steel (American Orthodontics, Sheboygan, WI, USA); NiTi (Neo Sentalloy, GAC, West Columbia, USA); TiMo (Beta	Ni, Ti	Various mouthwashes (unspecified brands)	1 d, 4 d, 7 d, 14 d	Plasma mass spectrometry, Electron microscopy scanning	[42]

	Blue, Highland Metals, Bangkok, Thailand)					
NiTi, CuNiTi	NiTi Memory Wire 0.016 in, Damon Optimal-Force Cu Ni-Ti 0.016 in, Tanzo Cu NiTi 0.016 in (American Orthodontics); Flexy NiTi Cu 0.016 in (Orthometric)	Ni, Cu	Neutral and acidic solutions	7 d	Graphite furnace absorption spectrometry, Plasma atomic emission spectrometry	[32]
NiTi, Coated NiTi, SS, Ni-free SS, CoCr, TMA	BioForce Sentalloy, High Aesthetic (Dentsply GAC, New York, NY, USA); Remanium, Noninium, Elgiloy, Rematitan Special (Dentaurum, Ispringen, Germany)	Ni, Ti	Artificial saliva	3 d, 7 d, 14 d, 28 d	Plasma mass spectrometry	[46]
NiTi, CuNiTi, SS	N/A	Ni	Artificial saliva	3 d	Cyclic voltammetry, Impedance spectroscopy, Tafel polarization	[55]
NiTi, Esthetic wires, SS	NiTi 0.019 × 0.025 in (Ormco, Glendora, CA, USA); FLI wire 0.019 × 0.025 in (Rocky Mountain Orthodontics, Denver, CO, USA); Iconix 0.019 × 0.025 in (American Orthodontics, Sheboygan, WI, USA); Bio-Active RC 0.019 × 0.025 in (GC Orthodontics, TOMY Inc., Fuchu City, Tokyo); SS 0.019 × 0.025 in (3M Unitek, St. Paul, MN, USA)	Ni, Cr	Buffer solutions (pH 4, 5.5, 7)	4 wks, 13 wks	Plasma mass spectrometry	[45]
NiTi, SS	Rematitan® LITE ideal arches 0.43 × 0.64 mm (Dentaurum, PA, USA)	Fe, Ni, Cr, Mn, Al, Ti, Cu	Artificial saliva	3 d, 7 d, 14 d	Energy dispersive spectroscopy with electron microscopy, Plasma mass spectrometry	[43]
NiTi, SS	Wire SS Upper 016 Form III 0.016 × 0.016, Wire NiTi Form I Upper 016 0.016 × 0.016, Tanzo® Copper Nickel Titanium Low Wire Upper 016 0.016 × 0.016, Tru-Arch® UM 0.016 × 0.016, Tru-Arch® CuNiTi 35 °C UL 0.016 × 0.022 (Ormco)	Ni, Mn, Cr, Mo, Ti	Artificial saliva	7 d, 30 d	Plasma optical emission spectrometry	[44]
NiTi, SS	SS (Fe-18Cr-8Ni) 0.010/0.014/0.016 × 0.022 in, Heat-activated Nitinol 0.016/0.016 × 0.022 in (3M Unitek, Monrovia, CA, USA)	Ni, Ti, Cr	Artificial saliva	1 h, 24 h	Atomic absorption spectrometry	[49]

NiTi, SS	NiTi 0.016 × 0.022 in, Stainless Steel 0.016 × 0.022 in (American Orthodontics, Sheboygan, WI, USA); Ion-implanted NiTi 0.016 × 0.022 in (GAC International, Bohemia, NY, USA); Copper NiTi 0.016 × 0.022 in (Ormco)	Ni	Artificial saliva	7 d, 14 d, 21 d	Atomic absorption spectrometry	[33]
NiTi, SS	SS rectangular archwires 0.017 × 0.025 in, NiTi rectangular archwires 0.017 × 0.025 in (Ormco)	Ni, Cr	Artificial saliva	7 d, 14 d, 1 mo	Flame atomic absorption analysis	[29]
NiTi, SS	Nitinol 0.4 mm (Dentaurum, Germany); SS304 0.4 mm (Tiger Ortho, Boston, MA, USA)	Ni, Ti, Cr, Mo, Mn	Fusayama–Meyer solution	N/A	Potentiodynamic/potentiostatic polarization, X-ray energy dispersive analysis, Atomic adsorption spectrometry	[18]
NiTi, SS	SS 0.018 in diameter, NiTi 0.018 in diameter (American Orthodontics, Sheboygan, WI, USA)	Ni, Cr	Oral B®, Orthokin®, Artificial saliva (SaliLube®, Sinphar Pharmaceutical Co., Ltd., Taipei, Taiwan)	1 h, 6 h, 24 h, 7 d	Atomic absorption spectrometry	[30]
NiTi, SS	N/A	Ni, Cr	Oral B®, Oral B® 3D White Luxe, Listerine, Listerine Advanced White	1 h, 6 h, 24 h, 168 h	Atomic absorption spectrometry	[51]
SS	N/A	Ni, Cr	Snakefruit extract (Salacca zalacca)	24 h	Atomic absorption spectrophotometry	[50]
SS	SS archwires 0.016 × 0.022 in (Dentaurum, Germany)	Ni	Magnetically treated water, OrthoKin®	24 h, 2 wks, 4 wks	Electron microscopy scanning, Atomic absorption analysis	[52]
NiCr (alloy)	N/A	Ni, Cr	Artificial saliva	12 d, 24 d, 36 d	Atomic absorption spectrometry	[47]

Table 3. Summary of nickel-containing wires and in vivo analytical approaches.NiTi; coated NiTi; CuNiTi; SS; NiCr

Wire Composition	Product Name and Supplier	Ions Examined	Testing Environment	Test Duration	Analytical Techniques	Source
NiTi	NiTi Force I® 0.019 × 0.025 in, Therma-Ti Lite® 0.019 × 0.025 in (American Orthodontics, Sheboygan, WI, USA)	Ni	Oral cavity	1 mo	Electron microscopy scanning, Atomic force microscopy, Atomic absorption spectrometry	[56]
NiTi, CuNiTi	Superelastic (austenitic) NiTi 0.016 × 0.022 in, Heat-activated NiTi 0.016 × 0.022 in, Heat-activated CuNiTi 0.016 × 0.022 in	Ni	Oral cavity	6 wks, 8 wks	X-ray energy dispersive analysis, Dynamic simulation modeling	[62]
NiTi, Rh-coated NiTi, SS	Heat-activated Nitinol archwire (Abzil, São José do Rio Preto, SP, Brazil), Rhodium polymer-coated	Ni, Cr, Fe, Cu	Oral cavity	1–6 mo	Total reflection X-ray fluorescence	[60]

	heat-activated Nitinol 0.014 in (BioActive, Crystal 3D, São Carlos, SP, Brazil)					
NiTi, SS	N/A	N/A	Oral cavity	3 mo	Nickel patch testing, Gingival health index, Plaque accumulation index, Intraoral imaging	[59]
NiTi, SS	Ni–Ti heat-activated wires 0.016 in, Stainless steel wires 0.016 × 0.022 in (3M™ Unitek™ mark)	Ni, Ti	Oral cavity	1 mo	Plasma optical emission spectroscopy, Scanning electron microscopy	[57]
NiTi, SS	Round thermoactive archwires 0.016 in (Equire Thermo-Aktive, Dentaurum, Germany)	Ni	Oral cavity	7 d, 1 mo, 2 mo	Atomic absorption spectrometry	[58]
NiTi, SS	Stainless steel CrNi, Superelastic (austenitic) NiTi, Thermodynamic heat-activated NiTi, Thermodynamic heat-activated CuNiTi, TriTanium™, Bio-active™	Ni	Oral cavity	6 wks, 8 wks	Electron microscopy with energy dispersive spectroscopy, Dynamic simulation modeling	[63]
NiTi, SS	Pre-adjusted Roth stainless steel brackets 0.018 in (Discovery, Dentaurum, Pforzheim, Germany), Stainless steel orthodontic bands (Unitek/3M, Monrovia, CA, USA), Nitinol (Ormco Corporation, Orange, CA, USA), Stainless steel archwires (Remantium; Dentaurum)	Ni, Cr	Oral cavity	12–18 mo	Atomic absorption spectrometry	[61]

To better understand nickel release over time, statistical studies [62, 63] examined how intraoral use affects wire composition and provided guidelines on clinical use duration.

In 2019, [62] evaluated austenitic NiTi, heat-activated NiTi, and heat-activated CuNiTi wires. Samples were divided into four groups: sterilized as-received (S0), as-received (S1), used intraorally for ≤6 weeks (S2), and used for >8 weeks (S3). Nickel distribution was examined across different regions of the wires. For global (overall) measurements, no significant changes were found between S0 and S1, or between S1 and the used groups. However, localized measurements showed statistically significant differences between S1, S2, and S3. Using these data, the authors developed a model describing nickel release dynamics, though they stressed that this model is approximate and clinical judgment should account for individual patient variability.

Expanding this, the 2025 study [63] assessed the same alloys, with the addition of SS and multi-force wires. Wires were grouped as as-received, used ≤6 weeks, and used >8 weeks. The results revealed that each wire type had a distinct pattern of nickel release depending on composition and oral exposure. SS-CrNi, HA-NiTi-Cu, and TriTanium™ demonstrated high stability and were considered suitable for long-term use, whereas superelastic NiTi, HA-NiTi (without copper), and Bio-Active™ showed greater nickel release and were suggested for short- to medium-term applications. The authors reiterated that these conclusions provide general guidance, but patient-specific conditions should direct clinical decisions.

Collectively, these studies show that nickel-containing orthodontic devices do release ions and can contribute to hypersensitivity, particularly in females. Nonetheless, concentrations usually remain below toxic thresholds. Factors such as appliance design, surface roughness, treatment time, and alloy type determine the extent of release. Although nickel allergy remains a clinical concern, careful material choice and periodic monitoring reduce risk and ensure safe treatment outcomes.

In summary, variables such as fluoride exposure, pH changes, immersion or treatment time, salivary flow dynamics, oral care products, dietary agents, and wire geometry all significantly affect nickel release. Understanding these factors is key to maintaining safety and guiding orthodontic material selection.

Insights from Published Research

A total of 24 studies, most of which were conducted in recent years, collectively outline how nickel is released from orthodontic components containing this element, especially nickel–titanium (NiTi) archwires (with or without copper) and stainless steel (SS) wires. These two alloys remain the most frequently employed in fixed orthodontics and have important consequences for both compatibility with biological systems and patient well-being. Over time, scholarly attention has shifted from early worries regarding the safety of NiTi alloys toward a more refined view that considers the various factors regulating nickel discharge under laboratory and clinical conditions.

Short-term biocompatibility of NiTi alloys

One of the earliest influential contributions was from Wever *et al.* [22], who demonstrated through combined laboratory and clinical evaluations that NiTi wires show low toxicity, little tendency to provoke immune reactions, and high resistance to corrosion, thereby making them acceptable for dental use. These findings were later reinforced by Kovac *et al.* [64], who observed that the ion release from NiTi archwires and SS brackets remained well under established daily intake limits even after long exposure. An interesting point raised in their work was that nickel concentrations were higher in surface debris than in artificial saliva, pointing to the localized risks of plaque or food remnants enriched with metal particles. Matusiewicz [65], in a review, emphasized this further, noting that corrosion in the oral setting—real or simulated—can generate particulate matter, which may accumulate over time, particularly in patients with less-than-optimal oral hygiene.

In vitro results largely confirm that the levels of metals, including nickel, are too low to be considered harmful. Yet, these controlled settings cannot fully mimic the diversity of oral conditions across patients. For this reason, in vivo studies are critical. They generally confirm that nickel-releasing wires emit ions within safe limits but can, in some individuals (notably females), trigger allergic responses. Thus, careful selection of materials and ongoing observation are key to maintaining safety during treatment.

Effect of fluorides, pH, and salivary factors

Fluoride has been consistently shown to alter nickel ion dynamics. Both Cioffi *et al.* [40] and Mirjalili *et al.* [18] reported that NiTi wires, although stable under mechanical stress, released significantly more ions after extended exposure to fluoride-rich environments. Given that fluoride toothpastes and rinses are routinely recommended, this finding is clinically significant. Kao *et al.* [49] also noted that fluoride at low pH can produce corrosive extracts with cytotoxic properties, urging caution with acidic fluoride solutions in patients using NiTi wires. Interestingly, Zubaidy and Hamdany [52] showed that magnetically treated water may reduce fluoride-induced corrosion and ion release.

The complexity of saliva further complicates predictions. Mikulewicz *et al.* [50] designed a thermostatic model simulating oral conditions and confirmed that SS archwires discharged nickel below toxic thresholds, highlighting the value of simulating natural conditions in lab studies. Additional findings from Senkutvan *et al.* [33] and Ibañez *et al.* [57] demonstrated that while acidic conditions initially elevate nickel levels, the concentrations gradually decline and remain clinically acceptable, suggesting an adaptive balance in the oral cavity. Osmani *et al.* [46] reported that more alkaline environments reduce ion release, confirming that acidic pH promotes greater metal liberation **(Figure 2)**.

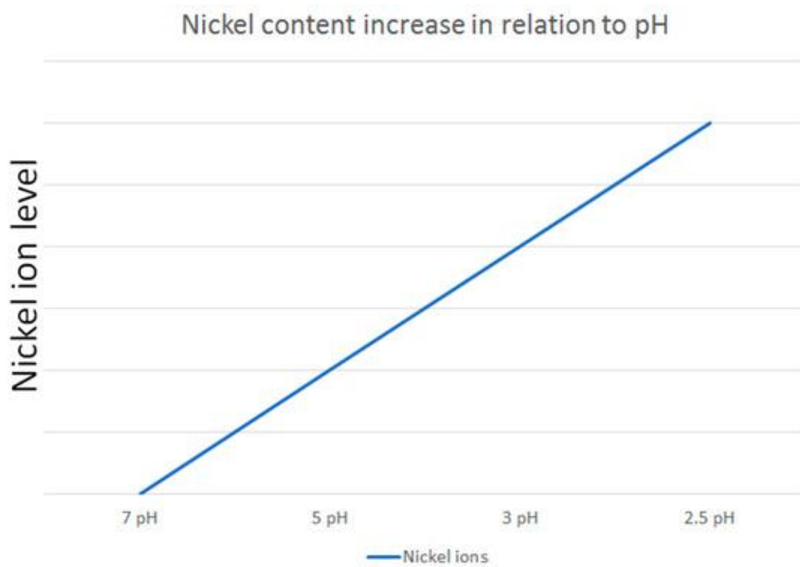

Figure 2. Illustration of nickel ion release trends under different pH values, derived from the reviewed literature

Impact of surface features, wire geometry, and material choice

The physical surface and geometry of wires strongly influence their behavior. Didovic *et al.* [42] and Aiswareya *et al.* [29] observed that rougher surfaces and certain fabrication processes increased ion release, with SS bands producing more ions than NiTi due to welding methods. Azizi *et al.* [17] showed that rectangular NiTi wires discharged more ions than round ones, suggesting that wire form should be factored into decisions for patients prone to nickel allergy.

Material choice remains a decisive factor. Lages *et al.* [60] found little difference in nickel levels between patients with metallic appliances and those with esthetic devices, indicating that esthetic substitutes may be viable for individuals sensitive to nickel. Conversely, Bass *et al.* [59] emphasized that nickel allergy is more common in females and can be triggered or worsened during orthodontic care, highlighting the importance of both individualized material selection and continuous monitoring.

Clinical implications and future perspectives

The predictive frameworks proposed in studies [62, 63] may offer orthodontists useful guidance for anticipating nickel release behavior and customizing treatment to each patient's sensitivity profile. Drawing from these works and the broader reviewed evidence, the following clinical recommendations are suggested for different wire types:

- **Stainless Steel CrNi (chromium–nickel alloy):** Appropriate for extended use, as nickel output stabilizes after the initial adjustment phase, making it suitable for treatments lasting several months.
- **Superelastic NiTi:** Best employed for short-term phases of about 4–6 weeks, since ion release peaks early and provides steady forces, but prolonged use could elevate sensitization risk.
- **Heat-Activated NiTi (without Cu):** Recommended for up to 6–8 weeks due to higher early release levels; beyond this period, replacement is advisable to ensure stable exposure.
- **Heat-Activated NiTi (with Cu):** Reliable for long-term treatment exceeding several months, as its nickel release curve plateaus, reducing the chance of excessive ion accumulation.
- **TriTanium™:** Well suited for multi-month treatments, given that nickel levels gradually stabilize with time, ensuring sustained safety.
- **Bio-Active™:** Effective for short to medium phases (roughly 4–6 weeks) because of its higher early release supporting initial forces, though replacement is preferable for longer treatment duration.

Overall, nickel discharge is strongly influenced by multiple factors: fluoride intake, pH conditions, duration of exposure, saliva behavior, oral hygiene products, dietary influences, and wire geometry. These aspects collectively determine clinical safety and should guide orthodontic material selection.

Future investigations should prioritize long-term **in vivo** work to clarify cumulative exposure effects throughout orthodontic therapy. Research into new corrosion-resistant alloys with reduced ion release would further safeguard patients. Promising avenues include studying the protective action of natural extracts (e.g., snake fruit [53]) and refining surface modifications like pre-passivation [18] to minimize nickel emission.

Concluding Observations

This review, by its design, has inherent limitations and should not be seen as universally applicable. The weight of evidence, however, consistently shows that nickel-based wires release ions under both laboratory and clinical conditions. Although typical levels remain under toxic thresholds and pose no immediate systemic risk, the possibility of sensitization or allergy in previously unaffected individuals calls for caution. Factors such as oral pH, salivary dynamics, wire geometry, patient hygiene, diet, and existing sensitivities must all be weighed when selecting materials. While short-term use of SS and NiTi is generally safe, ongoing monitoring is needed to detect adverse reactions. Evidence on long-term exposure, especially studies bridging in vitro and in vivo, is still limited and requires expansion to refine safety guidelines.

To better establish cause–effect relationships, **in vivo** monitoring of nickel (Ni) and chromium (Cr) release is critical. Beyond total concentration, assessment should extend to speciation—chemical form, oxidation state, and organometallic complexes. Improvements in trace element analysis enabling species-level detection at subnanogram to picogram scales will be key.

Finally, coordinated efforts across clinicians, researchers, and regulatory authorities are essential to frame robust, evidence-based standards for material use in orthodontics. These initiatives should center patient safety while addressing the potential risks from metal ion release.

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