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Systematic Review

Use of Hydrogels to Regulate Orthodontic Tooth Movement in Animal Models: A Systematic Review

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Abstract: The objective of this article is to conduct a systematic review of the literature to contrast the existing evidence regarding the use of hydrogels during and after experimental orthodontic treatment in animals. An extensive search was performed through the electronic databases, Medline, Web of Science and Scopus, from December 2020 to April 2021 for in vivo animal studies. A total of 282 studies were reviewed. Eight studies were included for final revision; four studies were conducted in rats, two in rabbits, one study in mice and one study in guinea pigs. The quality assessment of the eight included studies was performed according to the ARRIVE guidelines and the risk of bias was assessed using the Center for Systematic Review of Laboratory Animal Experimentation tool; in four of the eight articles evaluated, a high risk-of-bias rating was obtained in 40% of the criteria evaluated. In the studies reviewed, the hydrogel acted as a carrier, and inhibition (post-treatment retention) or acceleration of orthodontic tooth movement was assessed according to the active substance used in each of the articles. The uses of hydrogels for transporting active substances to regulate the rate of orthodontic tooth movement remains debatable. Future studies are suggested to evaluate the feasibility of hydrogel as a transport method in humans.

Keywords: hydrogels; orthodontic tooth movement; acceleration; relapse

Citation: Montero Jiménez, O.G.; Dib Kanán, A.; Dipp Velázquez, F.A.; Aristizábal Pérez, J.F.; Moyaho Bernal, M.d.l.Á.; Salas Orozco, M.F.; Casillas Santana, M.A. Use of Hydrogels to Regulate Orthodontic Tooth Movement in Animal Models: A Systematic Review. *Appl. Sci.* **2022**, *12*, 6683. https://doi.org/10.3390/app12136683

Academic Editor: Bruno Chrcanovic

Received: 1 June 2022
Accepted: 29 June 2022
Published: 1 July 2022

1. Introduction

Orthodontic tooth movement (OTM) is a process in which the application of a force induces bone resorption on the pressure side and bone apposition on the tension side. To accelerate this process, there are currently several treatments that promote OTM, such as corticotomies [1], injection of drugs [2], use of lasers [3], mechanical vibration [4], etc., but in some cases these treatments have side effects or are considered invasive and poorly accepted by patients.

With this in mind, research has focused on developing alternatives that reduce the adverse effects of conventional appliances while being widely accepted by the orthodontic community and its patients. Therefore, the use of hydrogels as extended-release vehicles could be an alternative to solve the main problems of orthodontic treatment, such as acceleration of tooth movement and post-treatment relapse [5–7].

In 1960, Wichterle et al., first used the term "hydrogel" to describe a three-dimensional network of hydroxyethyl methacrylate (HEMA) [8–10]. Hydrogels consist of a large amount of water and a network of crosslinked polymers. The high water content provides a physical resemblance to tissues and gives hydrogels excellent biocompatibility and the ability to easily encapsulate hydrophilic drugs [11,12].

Their main property lies in their absorption capacity, which is visually manifested as a "swelling" of the material that is due to the presence of water-like groups in their molecular structure upon contact with a thermodynamically compatible solvent. Their softness and elasticity in the hydrated state depends on the hydrophilicity of the monomers and the crosslink density [13,14].

Hydrogels are currently of great importance in medicine and research. Due to their diverse properties, which are similar to those of biological tissues, many advances have been made in their applications and formulations [15]. Thus, hydrogels can serve as scaffolds that act as supports for cell growth, as materials for the encapsulation of cells, proteins, or genes, as adhesives between tissues and material surfaces, as systems that allow a reversible response to an external stimulus, and as porous membranes; as well, because of their biological compatibility, hydrogels can be designed to allow the release of a drug according to therapeutic needs, making them ideal extended-release vehicles [16].

The variety of polymers used to synthesize hydrogels provides a wide range of physicochemical properties that together allow encapsulation of bioactive molecules and a suitable profile for their release in a localized area such as the buccal mucosa, which is a desired property in orthodontic treatment acceleration [15,16].

A systematic review focusing on the use of hydrogels in orthodontic tooth movement would be of great benefit to dentists by providing up-to-date information on hydrogel as a vehicle for future use in accelerating tooth movement or anchorage after treatment. The purpose of this systematic review is to highlight the use of hydrogels during and after orthodontic treatment.

2. Materials and Methods

An electronic search was performed in databases to identify studies reporting the use of hydrogels as vehicles to accelerate orthodontic tooth movement or inhibit relapse after orthodontic treatment. Due to a lack of human studies, only animal studies were included. The search details are specified below.

2.1. Focused Question

This systematic review was done in adherence with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [17]. According to the P.I.C.O. strategy, the focused question was: "Are hydrogels an effective vehicle for drug delivery to accelerate orthodontic tooth movement or inhibit the relapse after orthodontic treatment"?

(P) Population: animal models to which orthodontic forces were applied.
(I) Interventions: the use of hydrogels to accelerate OTM or inhibit relapse.
(C) Control: groups of animals to which hydrogel was not applied.
(O) Outcome: acceleration of tooth movement or inhibition of relapse.

This protocol was registered and approved by the Comité de investigación de la Facultad de Estomatología (C.I.F.E.) de la Benemérita Universidad Autónoma de Puebla with ID number 2022039.

2.2. Search Protocol

The search was conducted through the following databases: Medline, Web of Science and Scopus. Only articles published in the English language without year restriction were included.

The main key words were a combination of: "hydrogel", "orthodontic", "OTM", "orthodontic tooth movement", "relapse", "slow release", "controlled release" and "osteoclastogenesis", aided with the proper use of Boolean operators on the format of each

database. There was an initial screening based on the title and abstract to choose the most relevant studies according to the inclusion criteria; subsequently, the full text of the selected articles was reviewed.

2.3. Inclusion and Exclusion Criteria

2.3.1. Inclusion Criteria

- All published animal studies were included.
- Articles with the main objective of evaluate the use of hydrogels as vehicles to accelerate or inhibit the rate of orthodontic tooth movement.
- All publications were considered except for those where the full-text article was not available, or the authors' affiliation or the place of publication were not specified.

2.3.2. Exclusion Criteria

- All those articles that, when talking about relapse, did so in the context of cancer or infectious process.
- All those articles that, when talking about relapse, did so in the context of the mechanical properties of dental material.
- Any article that did not have a control group.

2.4. Methods of Selection, Data Extraction, and Assessment of Risk of Bias

Due to the term "relapse" being commonly used in the context of cancer recurrence and/or infectious processes, it was necessary to use Boolean operators (NOT (cancer or infection)) to filter out all results that addressed the topic from that perspective. The authors reviewed the articles by examining the titles and abstracts of 282 identified studies. After this first review, the studies that were deemed to meet the inclusion criteria were selected for further analysis. Finally, eight articles were included, as shown in Figure 1.

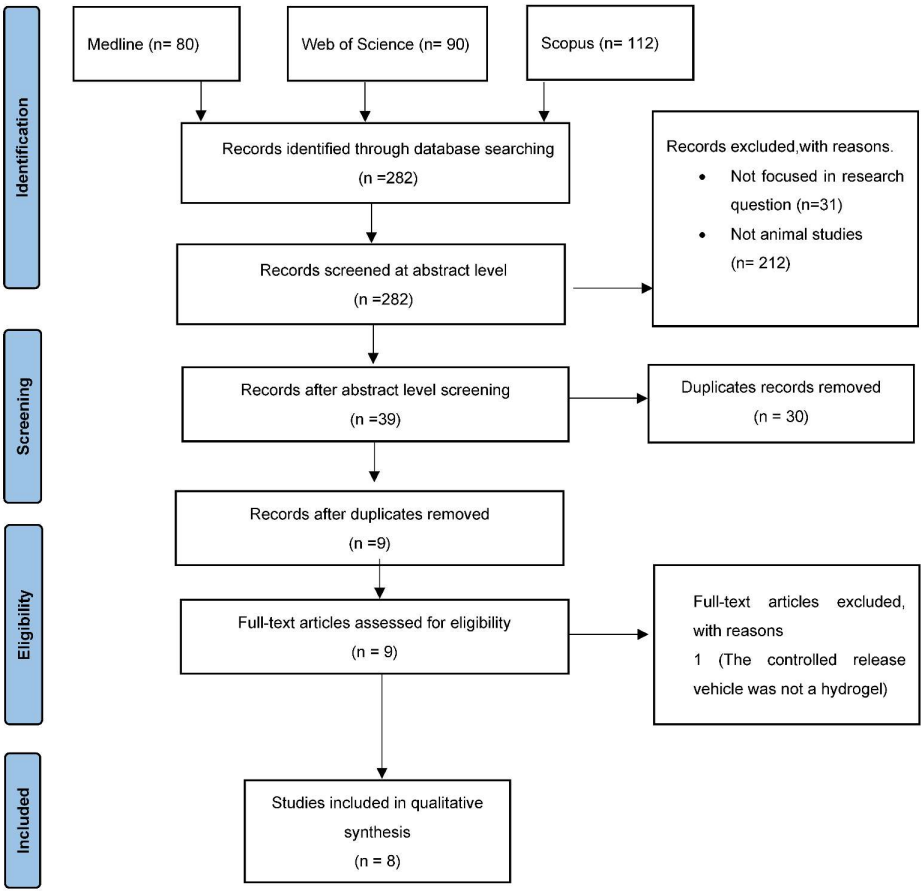

Figure 1. PRISMA flow diagram of record processing and elimination.

A quality assessment was performed according to the ARRIVE guidelines [18]. The risk of bias of the included studies was assessed using SYRCLE's risk-of-bias tool for animal studies [19]. One reviewer (O.G.M.J.) assessed basic elements to identify potential bias, which was then duplicated by a second reviewer (M.A.C.S.). Any inconsistencies were straightened out with the help of a third reviewer (M.F.S.O.).

3. Results

3.1. Selection of Studies

Eight articles in experimental animal models were included; four studies were conducted on rats [20–23], two used rabbits [24,25], one study was conducted on mice [26] and one study on guinea pigs [27], as shown in Table 1.

3.2. General Characteristics of the Studies

All studies used a hydrogel of different polymer-gelatin-based composition [20,24–27], chitosan hydrogel [20], polyethylene glycol-polycaprolactone-polyethylene glycol [21], hydroxyethyl cellulose [22], methylcellulose [23] for delivery of active substances: carbonated hydroxyapatite [24,25], curcumin [20], sclerostin [21], a formulation of RANKL [22], risedronate bisphosphonate [27], epigallocatechin [26] and parathyroid hormone [23], to accelerate orthodontic tooth movement or inhibit the post treatment relapse. Tooth movement was measured with a digital vernier or in the tomographic software depending on each article.

All eight studies were done on animal models: four on rats [20–23], two on rabbits [24,25], one on mice [26], and the last one on guinea pigs [27]. The number of animals used in the experiments of the studies ranged from 20 to 75.

Of the four studies carried out on rats, the rats weighed between 180–600 g and were 6–20 weeks old. Three of these four studies sought to accelerate orthodontic tooth movement [21–23] and one sought to inhibit the effect of orthodontic tooth movement [20].

In the studies with rabbits [24,25], the animals were 2.5–3 kg in weight and 10–12 weeks of age when evaluating the relapse of orthodontic tooth movement.

In the study with mice, they sought to prevent the recurrence of orthodontic dental movement by inhibiting the activity of the osteoclasts using 7-week-old mice [26]; in the same way as in the study carried out on guinea pigs, they used models weighing between 500 and 600 g [27].

3.3. Main Study Outcome Variables

It is important to highlight that the studies used the hydrogel only as a vehicle for drug delivery. The inhibition or acceleration of the orthodontic tooth movement was evaluated according to the active substance used in each of the studies.

Lu, Chang and Soma studies on rats show a significant increase in orthodontic tooth movement (OTM) with injectable hydrogel formulations loaded with receptor activator for nuclear factor κ B ligand (RANKL), parathyroid hormone (PTH-MC) and sclerosing protein, revealing the widening of the periodontal space on the compression side and also promoting osteoclastogenesis [21–23].

Utari et al. used a topical administration of bisphosphonate risedronate hydrogel in guinea pigs that was shown to be effective in decreasing osteoclastic activity and thus tooth relapse movement [27]. Similarly, in the two studies on rabbits by Alhasyimil et al., they found that the hydrogel was useful as a biological retainer to hinder relapse after orthodontic dental treatment [24,25]. In the study of Asefi et al. where curcumin gel was injected in rats, it showed significantly decreased bone and/or root resorption. It also reduced angiogenesis and the number of osteoclasts in the OTM field, showing to be a useful method for anchorage control [20]. Finally, the study on mice by Katsumata et al. was shown to inhibit osteoclastogenesis, giving a beneficial approach for destructive bone disease, as well as for alveolar bone anchorage control in orthodontic treatment [26], as seen in Table 2.

Table 1. General characteristics of the included studies.

Study	Study Design	Subjects of Study	Average Age	Study Groups	Duration of the Study	Primary Evaluation Methods
Asefi 2020 (Iran) [20]	Experimental (Split mouth)	40 male Wistar rats	12 weeks	Group A: Negative control. Group B: Positive control, received 0.03 cc of saline solution and apparatus. Group C: Gelatin + Curcumin, received 0.03 cc of hydrogel + apparatus. Group D: Chitosan + Curcumin, received 0.03 cc of hydrogel + apparatus.	21 days	Leaf gauge with 0.05 mm accuracy.
Lu 2019 (China) [21]	Experimental (Split mouth)	48 male Wistar rats	6 weeks	Group A: Sclerosin injection at 0.8 μg/kg. Group B: Sclerosin injection at 4 μg/kg. Group C: Sclerosin injection at 20 μg/kg.	14 days	Micro computed tomography analysis.
Chang 2019 (USA) [22]	Experimental	24 male Wistar rats	15 weeks	Group A: Orthodontic spring without microparticle formula. Group B: Orthodontic spring with placebo microparticles. Group C: Orthodontic spring with microparticles with RANKL	14 days	Micro computed tomography analysis.
Soma 2000 (Japan) [23]	Experimental	56 male Wistar rats	20 weeks	Group A: Control, treated with orthodontic force only. Group B: Orthodontic strength and local injection of vehicle dissolved in MC gel. Group C: Orthodontic force and local injection of 0.1 μg PTH dissolved in MC gel. Group D: Orthodontic force and local injection of 1 μg PTH dissolved in MC gel. Group E: Orthodontic force and local injection of 1 μg PTH dissolved in 0.9% saline. Group F: Orthodontic force and systemic injection of 1 μg PTH dissolved in MC gel. Group G: Local injection of 1 μg PTH dissolved in MC gel.	12 days	Interproximal measuring tool.
Alhasyimi 2018 (Indonesia) [24]	Experimental	45 male rabbits	10–12 weeks	Group A: Control Group B: CHA Group C: CHA-aPRF	21 days	Digital calibrator. TRAP staining
Utari 2020 (Indonesia) [27]	Experimental	75 male guinea pigs		Group A: Control Group B: Bis-CR250 (250 mmol/L) Group C: Bis-CR500 (500 mmol/L)	21 days	Histology and interproximal measuring tool.
Alhasyimi 2020 (Indonesia) [25]	Experimental	45 male rabbits	10–12 weeks	Group A: Control Group B: CHA Group C: CHA-aPRF	42 days	Histology
Katsumata 2018 (Japan) [26]	Experimental	13 male BALB/C mice	7 weeks	Group A: Control. Group B: Injected with a solution of 0.07 mg EGCG/10 mL Group C: Injected with a solution of 0.7 mg EGCG/10 mL	21 days	Micro computed tomography analysis. TRAP staining

PTH: parathyroid hormone; CHA: carbonated hydroxyapatite; EGCG: epigallocatechin gallate; RANKL: receptor activator for nuclear factor κ B ligand; aPRF: advanced platelet-rich fibrin; TRAP: tartrate-resistant acid phosphatase in osteoclasts; BALB/C: albino laboratory strain of common mouse.

Table 2. Characteristics of tooth movement in the included studies.

Study	Orthodontic Tooth Movement (OTM) Duration	Tooth Displacement Measurement	Influence on OTM Retention/Acceleration	Magnitude of OTM in the Control Groups	OTM Magnitude in the Experimental Group
Asefi 2020 (Iran) [20]	21 days	The distance between maxillary first and second molars was measured three times.	Inhibition	Control group: 0.34 mm	Group G and CH: 0.26 mm
Lu 2019 (China) [21]	14 days	It was measured between distal of the maxillary first molar to distal of the maxillary second molar.	Acceleration	Not reported	Group 4 μg/kg: 0.65 ± 0.06 mm Group 20 μg/kg: 0.72 ± 0.04 mm
Chang 2019 (USA) [22]	14 days	Intermolar distance.	Acceleration	Control group: 0.24 mm ± 0.05 mm	Placebo formulation group: 0.32 ± 0.1 RANKL formulation group: 0.55 ± 0.25
Soma 2000 (Japan) [23]	12 days	Distance between first and second molar.	Acceleration	Control group: 0.54 + 0.08 mm	1.6 times the control
Alhasyimi 2018 (Indonesia) [24]	21 days	Distance between the mesial faces of the lower incisors.	Retention	Control group: 2.45 ± 0.09 mm	Group with CHA-Aprf: 0.91 ± 0.12 mm
Utari 2020 (Indonesia) [27]	21 days	Distance between lower incisors.	Retention	Control group: 21 days: 2 mm	21 days: 0.7 mm
Alhasyimi 2020 (Indonesia) [25]	21 days	Distance between the mesial faces of the lower incisors.	Retention	Not measured	Not measured
Katsumata 2018 (Japan) [26]	21 days	Distance of maxillary right and left first molars.	Retention	Not measured	Not measured

3.4. Study Characteristics Relevant to Hydrogel Administration and Characterization

In the study of Asefi et al., they evaluated two hydrogels' formulations; the first with 4% chitosan (Sigma-Aldrich Chemie GmbH, Burlington, MA, USA) and acetic acid was prepared in a solution of double distilled water (1% v/v), the pH of which was adjusted to 6.8 with 1 N NaOH. Chitosan powder was gradually added to the solution. The pH at 7.4 led to gelation. Afterward, in the second with 10% gelatin (Sigma-Aldrich (FLUKA)), thermosensitive gelatin hydrogels were prepared to undergo gelation at physiological temperature, 1% w/v ready-made chitosan solution was added to increase mechanical properties, both loaded with 50% of their weight in curcumin (SBU Institute of Medical Drugs) [20].

Another study on rats by Lua et at. used three different concentrations of sclerostin injection (R&D systems, Minneapolis, MN, USA), 0.8 µg/kg, 4 µg/kg, or 20 µg/kg. The sclerosin was transported by a polyethylene glycol-polycaprolactone-polyethylene glycol (PECE) hydrogel [21].

In the study by Chang et al., the authors fabricated hollow porous microspheres with PLGA (poly lactic acid-co-glycolic acid) by the standard double emulsion technique, and adsorbed rat soluble RANKL onto the sterilized microspheres at a ratio of µg RANKL × 1 mg microspheres, using a concentration of 100 µg/mL RANKL in phosphate buffered saline (PBS) at room temperature for 30 min, which they lyophilized overnight to produce RANKL-PLGA microspheres. Then they embedded the RANKL-PLGA microspheres in a 10% hydroxyethyl cellulose (HEC) aqueous gel at a ratio of 1:3 (RANKL-PLGA: HEC, w/v) in PBS at room temperature to produce the RANKL-loaded hydrogel formulation [22].

Soma et al. occupied a 2% (w/v) methylcellulose hydrogel with PTH obtained by adding 4 g of methylcellulose powder (Wako Purc Chemical Industry, Osaka, Japan) to 100 mL of saline solution at a temperature of 90 to 100 °C with constant agitation, followed by the addition of synthetic PTH (Peptide InstitLtC Inc., Mino, Japan) dissolved in 0.9% saline at 2 p.g/p.L [23].

Katsumata et al. reported the use of an epigallocatechin gallate (EGCG-GL) hydrogel formulation, which was made with 100 mg of type A porcine skin gelatin (Sigma-Aldrich Co. LLC., St. Louis, MO, USA) dissolved in 5 mL of warm water at 50 °C. After cooling the solution to room temperature, 27.5 µL of N-methylmorpholine (NMM) (Nacalai Tesque Inc., Kyoto, Japan), and 0.07 or 0.7 mg EGCG (BioVerde Inc, Kyoto, Japan) and 69.2 mg 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-morpholinium chloride (DMT-MM) (Tokyo Chemical Industry Co., Tokyo, Japan) and the solution was stirred for 24 h at room temperature [26].

Utari at al. conducted their experiments on guinea pigs by topical administration of two hydrogels loaded with 400 mg Bis-CR250 and 400 mg Bis-CR500. Gelatin (G-2554P, 100286; Nitta Gelatin Inc., Osaka, Japan) was dissolved in distilled water (3% w/v) and homogenized for 3 h at 37 °C. Risedronate sodium (Cat No. 51428; Selleck Chemical, Scoresby, Australia) was added and stirred for 2 h. The mixture was cross-linked with 25% glutaraldehyde (Merck, Darmstadt, Germany) and rinsed with glycine (Merck) three times. These contained 1 mg and 1.92 mg of pure risedronate and was prepared in 5 mL of phosphate buffer solution [27].

Alhasyimi et al. fabricated a hydrogel of carbonated hydroxyapatite (CHA) and platelet-rich fibrin by adding β-type gelatin from bovine bone (Nitta Co., Osaka, Japan) to Ca $(OH)_2$ in a sodium citrate solution. In addition, 10 mL of blood was collected by venipuncture from the rabbit ear marginal vein, the fibrin clot was pressed into an advanced platelet-rich fibrin (aPRF) processing box. Then 200 µL of a PRF releaser (Osung Ltd., Houston, TX, USA) was loaded into 10 mg of CHA hydrogel to administer as an injection to the rabbits [24]

Another study by Alhasyimi et al. on rabbits also used a carbonated hydroxyapatite hydrogel (CHA); this was prepared by mixing type-β gelatin, sodium citrate and distilled water, then calcium hydroxide was added and agitated with a magnetic stirrer for 1 h. Phosphoric acid was dissolved in 50 mL of distilled water and then gently dropped into

the gelatin mixture. The sample was then pulverized and filtered through a 32 µm mesh screen [25].

In all studies, the hydrogel was administered in areas adjacent to the tooth: vestibular mucosa next to the mesial root of the first molar [20], alveolar bone on the mesial side (compression side) of the maxillary first molar [23], palatal areas to the maxillary first molar [22], sub periosteum in the mesio-palatal region [23], mesial subperiosteal area [26,27] and mesial gingival sulcus of the incisors [24,25].

Four studies [21–23,26] applied the hydrogels during orthodontic movement, one study [20], applied it immediately after the orthodontic appliance bonding and the last three studies used the hydrogel during the retention phase [24,25,27], as shown in Table 3.

3.5. Relevant Characteristics for the Application of Orthodontic Force

Eight studies used nickel– titanium (NiTi) springs. Six of them [20–23,26,27] used 0.003–0.012-inch metal ligatures to attach them to the tooth and cause orthodontic movement. In the other two studies [24,25], the spring was inserted between the brackets on a round stainless steel wire (American Orthodontics®, Sheboygan, WI, USA).

Four studies [20–23] designed their experiments by placing the orthodontic appliances between the maxillary molars and upper central incisors. Three studies [24,25,27] performed their experiments on the lower central incisors by placing the orthodontic appliances between them. One study [26] based its experiment by placing the spring between the two right and left maxillary molars.

In the study by Utari et al., after tooth movement and when the open spring was inactive, the spring was replaced with a new one, an interincisal distance of ±3 mm was maintained as a stabilization period and then topical application of the hydrogel was initiated [27]. Similarly, in the studies on rabbits, both incisors were retained by replacing the anterior wire with a 0.016 × 0.022-inch wire for retention [24,25].

The application of orthodontic forces ranged from 5–50 g measured with a force gauge and the duration of tooth movement in the studies lasted from 7–21 days.

In all eight studies, the animals were anesthetized during orthodontic appliance installation.

3.6. Evaluation of the Quality of the Included Studies

The quality assessment was performed according to the ARRIVE guidelines [9]. Individual criteria were scored for the evaluation of the quality of the studies; full percentages (100%) were recorded to the evaluation of (a) title, (b) objectives, (c) procedures, (d) experimental animals, (e) sample size, (f) assignment of animals to experimental groups, (g) experimental results, (h) statistical methods, (i) baseline data, (j) reference data, (k) numbers analyzed, (l) results and estimation, (m) interpretation/scientific implications and (n) generalization/translation. A high percentage (83%) was recorded for "(a) ethics statement"; 66% of the studies reported the "(a) Housing and agriculture and (b) funding", while only 50% fully reported the "(a) Abstract, (b) Background and (c) Adverse events". See Table 4.

3.7. Risk of Bias Assessment

The risk of bias of the eight included studies was assessed using the Systematic Review Centre for Laboratory Animal Experimentation tool, as shown in Figure 2. Four studies adequately generated and applied the allocation sequence [22,24–26]. Five studies described the selection characteristics of the animals used [21–23,25,27]. Eight studies did not adequately conceal the allocation [20–27]. Seven studies did not report how the animals were housed during the experiment [21–27]. Five studies ambiguously reported the measures used to blind the animal caretakers and investigators [20,21,23–25]. Eight studies did not report randomized selection of animals for outcome assessment [20–27]. Four studies mentioned blinding of the outcome assessor [21,23–25]. Eight studies addressed the integrity of outcome data [20–27]. One study reported on selective outcome reporting [22]. Two studies mentioned being free of other problems that could result in a high risk of bias [21,22].

Table 3. Characteristics in relation to hydrogel administration.

Author	Type of Therapy	Hydrogel	Active Agent	Dosage	Method of Administration	Frequency of Administration	Duration of Administration	OTM Result
Asefi 2020 (Iran) [20]	Retention	Chitosan and gelatin	Curcumin	0.03 cc of curcumin	Local injection	Single application	1 day	Significant decrease in bone and/or root resorption
Lu 2019 (China) [21]	Acceleration	Polyethylene glycol-polycaprolactone-poly-ethylene glycol (PECE)	Sclerosin	0.1 mL	Local injection	Single application	14 days	Improves tooth movement and osteoclastogenesis.
Chang 2019 (USA) [22]	Acceleration	Hydroxyethylcellulose	Formulation of RANKL	1 μg RANKL: 1 mg microsphere in 3 μL 10% HEC gel	Local injection	Single application	Not reported	Accelerate OTM.
Soma 2000 (Japan) [23]	Acceleration	Methylcellulose	Parathyroid hormone	0.1 and 1.0 μg/μL	Local injection	Every other day	12 days	Accelerate OTM.
Alhasyimi 2018 (Indonesia) [24]	Retention	Gelatin	Carbonated Hydroxyapatite	0.2 mL	Local injection	Every 7 days	Not reported	Reduces orthodontic relapse.
Utari 2020 (Indonesia) [27]	Retention	Gelatin	Risedronate Bisphosphonate	1.00 and 1.92 mg in 5 mL PBS	Topic	Every 3 days	14 days	Effectively reduces relapse
Alhasyimi 2020 (Indonesia) [25]	Retention	Gelatin	Carbonated Hydroxyapatite	0.2 mL of CHA	Intrasulcular injection	3 times	Day 0, 7 and 14	Helps osteoblastogenesis
Katsumata 2018 (Japan) [26]	Retention	Gelatin	Epigallocatechin	5 μL	Local injection	Single application	Not reported	Inhibits Osteoclastogenesis

PECE: polyethylene glycol-polycaprolactone-poly-ethylene glycol; RANKL: receptor activator for nuclear factor κ B ligand; HEC: hydroxyethylcellulose; OTM: orthodontic tooth movement; PBS: phosphate buffered saline; CHA: carbonated hydroxyapatite.

Table 4. Quality assessment of included studies. ARRIVE criteria.

	Asefi 2020 [20]	Lu 2019 [21]	Chang 2019 [22]	Soma 2000 [23]	Alhasyimi 2018 [24]	Utari 2020 [27]	Alhasyimi 2020 [25]	Katsumata 2018 [26]	Total
1. Title	1	1	1	1	1	1	1	1	100%
2. Summary	1	0	1	0	0	1	1	0	50%
INTRODUCTION									
3. Background	0	1	0	1	0	1	1	1	62.5%
4. Objectives	1	1	1	1	1	1	1	1	100%
METHODS									
5. Statement of Ethics	1	0	1	1	1	1	1	1	87.5%
6. Procedures	1	1	1	1	1	1	1	1	100%
7. Experimental animals	1	1	1	1	1	1	1	1	100%
8. Housing and agriculture	1	1	1	0	1	0	0	0	50%
9. Sample Size	1	1	1	1	1	1	1	1	100%
10. Assignment of animals to experimental groups	1	1	1	1	1	1	1	1	100%
11. Experimental results	1	1	1	1	1	1	1	1	100%
12. Statistical methods	1	1	1	1	1	1	1	1	100%
RESULTS									
13. Reference data	1	1	1	1	1	1	1	1	100%
14. Numbers analyzed	1	1	1	1	1	1	1	1	100%
15. Results and estimation	1	1	1	1	1	1	1	1	100%
16. Adverse events	1	1	0	1	0	0	0	0	37.5%
DISCUSSION									
17. Interpretation/scientific implications	1	1	1	1	1	1	1	1	100%
18. Generalization/Translation	1	1	1	1	1	1	1	1	100%
19. Financing	1	1	1	1	0	0	0	0	50%

Percentages of the evaluation of the quality of the studies. The number 1 indicates that the study meets the evaluation criterion and 0 indicates the absence of the evaluated criterion.

In four [20,21,24,25] of the eight articles evaluated, a rating of high risk of bias was obtained in 40% of the criteria evaluated. One article [27] had a rating of high risk of bias in 80% of the criteria evaluated.

Figure 2. Risk-of-bias summary for each of the included studies (n = 8). The green color indicates low risk of bias; the yellow color indicates an unclear risk of bias, and the red color indicates high risk of bias.

4. Discussion

Hydrogels are cross-linked three-dimensional hydrophilic polymeric networks [28] that have shown very good properties for drug loading; they are biocompatible and exhibit

swelling properties in aqueous media [29], making them a good option for use as smart carriers of active substances [11,30].

Of the eight studies included in this review, three of the studies sought to accelerate orthodontic tooth movement [21–23], while the other five studies evaluated the ability to inhibit orthodontic tooth movement after treatment had been completed, i.e., during the retention phase [20,24–27]. We observed a great diversity in the composition of the eight hydrogels used in the included studies: gelatin-based [20,24–27], chitosan hydrogel [20], polyethylene glycol-polycaprolactone-polyethylene glycol [21], hydroxyethylcellulose [22] and methylcellulose [23]. The active ingredients released by the hydrogels were equally diverse: (a) carbonated hydroxyapatite [24,25], (b) curcumin [20], (c) sclerostin [21], (d) a formulation of RANKL [22], (e) Risedronate bisphosphonate [27], (f) epigallocatechin [26] and (g) parathyroid hormone [23].

The biological effects of the drugs used in the articles included in this review are among the most important aspects to consider; although they have previously demonstrated their influence on the OTM, for the purposes of this review their effectiveness is contrasted based on how favorable their release was as a consequence of the physicochemical properties of the hydrogel synthesis materials, which is why the influence of the material on drug release will be discussed first.

4.1. Polymers

Gelatin is a protein obtained by the hydrolysis of collagen from animal bones and skin and has been used for pharmaceutical and medical applications because of its biodegradability and biocompatibility in physiological environments [31]. Utari et al. developed a gelatin hydrogel that was shown to be effective in prolonging the release of risedronate sodium by cross-linking as the gelatin hydrogel controlled the release and degradability by cross-linking through regulating the water content of the system [27]. The system was shown to be effective in prolonging the release of risedronate sodium when applied topically to a targeted area; furthermore, the hydrogel maintained the structure of the proteins during delivery and prevented their degradation or denaturation until they entered the intended area, a desirable property for possible use in clinical practice [24,25].

According to Simoni et al., one of the desirable characteristics for extended release to take place is the drying of gelatin hydrogels because it influences the conformation of the gelatin network and interactions to result in a smoother microstructure [32]. However, despite being one of the main reasons affecting drug release in this type of hydrogel, none of the articles included in this review mention the drying process.

On the other hand, Asefi et al. used two biocompatible hydrogels (4% *w/v* chitosan and 10% *w/v* gelatin); chitosan is one of the most widely used polymers in medicine. However, in the orthodontic area, this is the only report that exists regarding its use as a vehicle. They mention that, because of its sensitivity to pH and its mucoadhesive property, chitosan gels directly at physiological pH, which could favor its topical use in the oral cavity; they found no statistically significant difference between the groups of chitosan and gelatin, thus showing the importance of the active agent over the method of transport [20].

Another material used as a vehicle was a PEG derivative, which allows the hydrogel to be photo-crosslinked, providing greater mechanical stability. In particular, PEG exhibits high hydrophilicity, a bioinert structure and absence of toxic or immunogenic responses [14]. Lu et al. used a thermosensitive PEG–PCL–PEG hydrogel to transport sclerostin; this hydrogel has the ability to switch from sol–gel–sol as the temperature increases [21]. According to Chang Yang et al. the sol–gel–sol transition behavior of copolymers depends on several factors, such as the hydrophilic/hydrophobic balance in the molecular structure and the composition of the hydrogel solution. They reported that in the lower-concentration hydrogels (20% vs. 30% by weight), the drug was released faster and achieved a higher cumulative release rate (98.2%) compared to the higher-concentration hydrogel (94.6%). The effect of the amount of initial drug loading on the release profile was also investigated,

concluding that the effect of the amount of initial drug loading on the release profile was limited [33].

Of the eight included studies, two used hydrogels based on cellulose derivatives. Chang et al. created a hydroxyethylcellulose hydrogel with RANKL, their PLGA–RANKL–HEC formulation released 14% of total RANKL at day 1 and reached 82% at day 28. The use of porous PLGA microspheres minimized the initial release of RANKL for a more stable release rate. They found that embedding the microspheres in HEC gel allowed better retention of RANKL delivery, despite a slightly higher initial RANKL release, indicating a quasi-Fickian diffusion of RANKL from their RANKL formulation [22].

For their part, Soma et al., created a PTH-containing methylcellulose hydrogel, which showed a higher initial release than Chang et al. In the first 12 h of incubation, about 40% of PTH was released into the MC gel and the rest was released gradually until 72 h of incubation [23]. Because of their tunable physical properties, controllable degradability and ability to protect labile drugs from degradation, this type of hydrogels could serve as an excellent platform in which various physicochemical interactions in their matrix allow the release of encapsulated drugs to be controlled [33–38].

4.2. Biological Effects

4.2.1. Retention

Having reviewed the influence of the hydrogel synthesis material on drug release, it is important to discuss its biological effects on OTM [39]. Four of the five studies that evaluated the effect of the drug on decreasing OTM obtained positive results. In the study by Utari et al., it was observed that osteoclasts were abundant in the alveolar bone of the control group, but decreased in the Bis-CR250 and Bis-CR500 groups, which demonstrates the inhibition of the osteoclastic activity of bisphosphonates [27]; these are drugs with high affinity for calcium and are directed to areas of bone remodeling, which inhibit osteoclastic metabolism and reduce the number of these cells [40,41]. Consequently, post-treatment physiological retention is promoted. However, one of the main factors to consider is the possible adverse effects derived from the prolonged use of this type of drugs.

On the other hand, Alhasyimi et al. demonstrated that injection of CHA-aPRF can increase the expression of TGF-β1 and BMP-2 during the relapse phase of orthodontic treatment. It is important to recall that osteoblast differentiation and proliferation are known to be regulated by TGF-β1, which plays many roles in enhancing osteoblast proliferation, including recruitment of osteoblast precursors or matrix-producing osteoblasts through chemotactic attraction and prevention of osteoblast apoptosis. For its part, increased BMP-2 expression can stimulate osteoblast maturation and induce alveolar bone formation to effectively prevent relapse; in addition, it can reduce osteoclastogenesis activity through the RANKL-OPG pathway to increase bone mass [24,25].

Furthermore, in the study by Katsumata et al., they reported that EGCG decreases the RANKL/OPG ratio at the application site, which indirectly inhibits osteoclast differentiation; these authors suggest that a single injection of EGCG-GL inhibits osteoclastogenesis and thus decreases OTM [26].

However, in the study by Asefi et al., no inhibitory effect on OTM was evident [20] even though it has previously been shown that curcumin can suppress the expression of inflammatory mediators such as cyclooxygenase-2, vascular endothelial growth factor, interleukins (IL-1 β, IL-6 and IL-8), nitric oxide (NO) and prostaglandin E2 [42], which would favor the inhibition of OTM and a physiological anchoring or retention post-treatment [20].

4.2.2. Acceleration

Acceleration of OTM is one of the main objectives in recent years, since it not only determines the duration of treatment, but also reduces its possible adverse effects and is one of the most frequent requests from patients. Physiologically, the speed of tooth movement reflects the rate of bone turnover and regeneration [6].

Several active principles have been used with the aim of accelerating OTM but only three studies have used a hydrogel as a vehicle. In this sense, one of the drugs evaluated was sclerostin, previously reported to be able to inhibit osteoblast proliferation, since the expression of the SOST gene (which encodes the synthesis of sclerostin) is limited to skeletal tissue, almost exclusively to the osteocyte cell lineage, which prevents the proliferation of osteoblasts, which, in theory, could favor OTM [38,43]. This is consistent with the results obtained by Lu et al., where local injection of sclerostin into the alveolar bone on the compression side increased tooth movement and osteoclastogenesis in rats [21].

On the other hand, Soma et al. used a hydrogel loaded with PTH [23]. Parathyroid hormone (PTH) mobilizes calcium from bone by activating osteoclasts, leading to bone resorption [44]. Application of the PTH-loaded hydrogel promoted OTM acceleration up to 1.6-fold compared to the control [23], while Chang et al., in turn, found that the RANKL formulation group had significantly (129.17%) higher tooth movement ($p < 0.05$) compared to the no formulation group and 71.8% more than the placebo formulation [22]. The chemical nature of the active ingredient used to regulate OTM, the consequences at the systemic level and its possible adverse effects should be considered; however, at the moment, the results are promising and evidence that hydrogels are possibly a suitable alternative to deliver active ingredients for orthodontic purposes.

4.3. Strengths and Limitations of This Review

The most important strength of this work is the use of objective methodology based on a comprehensive strategy of data extraction from electronic resources and the verification of eligibility, selection and abstraction of information in duplicate that allowed us to contrast the most recent and important evidence on the use of hydrogels to regulate OTM. However, the heterogeneity of the included study designs, variations in animal model characteristics, evaluation periods, differences in hydrogel synthesis methodology, doses, frequency and duration of administration, as well as variations in orthodontic experimental models, made it complex to contrast the information. Nevertheless, this review demonstrates the great potential of hydrogels for future application in the field of orthodontics.

4.4. Recommendations and Future Work

Targeted and controlled release of hydrogels has revolutionized medical and dental care by improving precision and reducing side effects at the site of interest. Its use in orthodontics is relatively novel and has the potential to maximize the efficacy and quality of orthodontic treatment. For this, it is necessary to accurately understand the role of active ingredient-loaded hydrogels in OTM; however, few studies exist, so several questions remain to be answered until their eventual clinical use.

5. Conclusions

The polymers included in the synthesis of the hydrogels studied adequately incorporate the active principles without negatively influencing their biological effect; consequently, the results of the use of hydrogels as vehicles during OTM regulation is promising. However, they are still debatable. Further studies with standardized evaluation criteria would allow us to better contrast the evidence and issue recommendations for their future clinical use, particularly for orthodontic purposes and its possible topical application on the oral mucosa.

Author Contributions: Conceptualization, O.G.M.J. and M.A.C.S.; methodology, O.G.M.J. and M.A.C.S.; investigation, O.G.M.J. and M.A.C.S.; resources, A.D.K. and F.A.D.V.; data curation, M.F.S.O. and M.d.l.Á.M.B.; writing—original draft preparation, O.G.M.J. and M.A.C.S.; writing—review and editing, M.A.C.S., M.F.S.O. and J.F.A.P.; visualization, M.F.S.O. and M.A.C.S.; supervision, M.F.S.O., M.d.l.Á.M.B. and M.A.C.S.; project administration, J.F.A.P., A.D.K. and F.A.D.V.; funding acquisition, J.F.A.P., A.D.K. and F.A.D.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the institutional resources of the Benemérita Universidad Autónoma de Puebla and National Scholarships for Postgraduate Studies of Consejo Nacional de Ciencia y Tecnología (CONACyT).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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