Journal of Dental Sciences and Education

Review

DOI: 10.51271/JDSE-0044

Hydrogel in dentistry

Elif Tuğba Yollar

Department of Restorative Dentistry, Gülhane Faculty of Dentistry, University of Health Sciences, Ankara, Turkiye

Cite this article: Yollar ET. Hydrogel in dentistry. *J Dent Sci Educ*. 2024;2(4):109-113.

Corresponding Author: Elif Tuğba Yollar, dt.tugbaaltiparmak@gmail.com

Received: 23/09/2024 ◆ **Accepted**: 11/12/2024 ◆ **Published**: 22/12/2024

ABSTRACT

Hydrogels have a polymeric structure that can hold water in their three-dimensional networks thanks to their hydrophilic structure. Hydrogels have the capacity to hold water or biological fluids, have a structure similar to living tissues, and have the ability to swell and shrink under various effects. They have also become a popular material used in the health field due to their biocompatibility. In addition, providing the desired functionality, being recyclable and sterilizable are the positive aspects of this material. Due to these positive features, hydrogels are considered a material worth working on because they are suitable for dentistry practice. Therefore, various studies have been conducted with hydrogels due to the need for biocompatible materials in dentistry. These studies have also shown that they have found an area of use in dentistry as in the medical world and have provided useful developments. This review aims to examine the studies conducted with hydrogels in terms of dentistry.

Keywords: Smart, hydrogel, dentistry

INTRODUCTION

A hydrogel is a three-dimensional polymer network consisting of synthetic or natural materials that has a high-water content and a high degree of elasticity. They are an ideal material for a range of applications because they have a soft rubbery consistency comparable to real tissues and can hold significant amounts of water or biological fluids under physiological conditions. In order to treat or replace tissues and organs, or to interact with the biological system of living tissues, hydrogels must possess specific features, such as the required functionality, reversibility, sterilizability, and biocompatibility.[1-3]

The first synthetic hydrogel was developed by Wichterle and Lim in 1954.[4] The first use in the biomedical field dates back to the 1960s, when cross-linked polyhydroxyethyl methacrylate (PHEMA) was developed by Wichterle and Lim and later patented as a soft contact lens.[5]

Most dental applications, including the treatment of periodontitis, the restoration of endodontic pulp-dentin complexes, and general tooth regeneration, need the use of biomaterials. The potential for soft biomaterials like hydrogels to function as a matrix for encasing cells exists. To work in the tooth structure, the hydrogel must have the proper anatomical size and form.[6]

The aim of this review is to provide an overview of the use of hydrogel, a current biomaterial, in dentistry.

CLASSIFICATION OF HYDROGELS

Polymeric hydrogels can be classified depending on their preparation method, ionic charge, physical structure and cross-linking status.[7] This classification is shown schematically.

According to preparation method;

- Homopolymer hydrogels
- Copolymer hydrogels
- Multipolymer hydrogels
- IPN (interpenetrated network structure) hydrogels

According to the subgroups they contain;

- Neutral (non-ionic) hydrogels
- Ionic hydrogels

Anionic hydrogels

Cationic hydrogels

Polyampholytic hydrogels

According to their physical structure;

- Amorphous hydrogels
- Semi-crystalline hydrogels
- Hydrogen bonded hydrogels

According to cross-linking situations;

- Physically cross-linked hydrogels
- Chemically cross-linked hydrogels

By sources;

- Natural hydrogels
- Synthetic hydrogels

According to their chemical stability;

- Biodegradable hydrogels
- Non-biodegradable hydrogels

According to water content;

- Low swelling degree (20-50%)
- Medium degree of swelling (50-90%)
- High swelling degree (90-99.5%)
- Super-absorbent (>99.5%)

SMART POLYMERS

Polymers to be used in various applications must have properties that can respond to stimuli from the external environment, similar to real systems. Polymers prepared for this purpose and showing reversible physical or chemical properties by undergoing structural change as a result of any stimulus from the external environment are called "stimulus-sensitive polymers or smart polymers".[8] Stimulus-responsive hydrogels produced from polymers can be classified according to the stimulus type as follows:

- Temperature sensitive hydrogels
- pH sensitive hydrogels
- Electric field sensitive hydrogels
- Photosensitive hydrogels
- Magnetic field sensitive hydrogels

CLINICAL APPLICATION OF DIFFERENT HYDROGELS

Hydrogel scaffolds have lately been readily available in tissue engineering. They are a distinct three-dimensional (3D) network of polymers, with water serving as the liquid component. They can transfer nutrients throughout their structure and hold a lot of water and biological fluids because of their hydrophilic nature. They have biocompatibility, expected and predicted degradation patterns, are naturally crosslinked, can preserve network integrity, and have customizable mechanical properties. They become insoluble at high water concentrations as a result. Furthermore, because of their extraordinary flexibility and elasticity similar to a genuine ECM, hydrogels provide the essential cell support needed for tissue regeneration.[9-12]

Fibrin from natural hydrogels; It offers very efficient scaffolding materials that can be applied to stem cells or primary cells to regenerate adipose tissues, heart tissues, liver, ocular, nerve tissues, skin, bones, cartilage, alone or in combination with other materials. Fibrin is thus one of the most adaptable bioengineering materials with a broad range of applications to promote tissue regeneration, wound healing, and tooth regeneration.[13,14]

Chitosan, which is one of the natural hydrogels; oral administration has been found to be non-toxic.[15] Chitosan, in the form of nanoparticles and films, aids in the in situ treatment of oral mucositis and periodontal tissues with fungus using antibiotics like metronidazole and nystatin. Chitosan systems in the form of nanoparticles and films also have the advantage of being pH sensitive. The thiole-based chitosan formulation is entrapped in muco-adhesive patches to treat dental caries with sustained antibacterial drug release, preventing the growth of cariogenic Streptococcus mutans.[16]

Diniz et al.[17] developed an injectable, biodegradable scaffold made of oxidized alginate microbeads encased with gingival mesenchymal stem cells and periodontal ligament. Stem cells were introduced to alginate hydrogel in vitro. The scaffold system demonstrated strong swelling capacity as well as osteo- and adipo-differentiation.

Emdogain (EMD) is a commercially available synthetic polymer that is primarily used to repair intrabony periodontal abnormalities and to restore soft tissues. EMD's primary use is to promote the growth of new periodontal attachments for alveolar bone, periodontal ligament, and acellular cementum. EMD has the capacity to promote periodontal tissue regeneration. It is the dental biomaterial that has received the most research and is frequently utilized in surgical treatments including guided tooth tissue regeneration and root tip excision.[18]

STUDIES DONE

For doctors and researchers, the regeneration of injured or missing biological tissues is a significant problem. These biological tissues' extracellular matrix (ECM) is made up of a complex web of fibrous proteins and glycosaminoglycans that bind cells and control cellular function and interaction via a range of signals. The ECM's resident cells create and modify it on a regular basis.[19] There are still no natural or artificial biomaterials that can duplicate the ECM and replicate all of its features. However, at this time, the traditional method in tissue engineering approaches is the use of native scaffolds, such as polymeric scaffolds, ceramic scaffolds, or mixtures of multiple scaffold types loaded with suitable cells and signaling chemicals.[20]

Using an in vitro injectable three-dimensional (3D) cell distribution method, Jones et al.[21] set out to test the idea that a PEGDA-HA-based hydrogel (polyethylene glycol diacrylate-hyaluroric acid) mixed with gelatin and fibronectin could increase hDPSC survival and spread. They came to the conclusion that tailored tissue mimicking may be facilitated by an injectable scaffold with adjustable mechanical and biological components.

Han et al.[22] reported the use of an agarose hydrogel biomimetic mineralization system loaded with calcium and phosphate to induce dentin remineralization and the formation of an oriented dense parallel-packed HA layer on the dentin surface in a rabbit model in vivo. They showed how treating conditions such as erosion, abrasion and dentine hypersensitivity could have practical application.

In order to create scaffolds with the appropriate cell adhesion and angiogenesis capabilities and to assess the survival and development of dental pulp stem cells, Xia et al.[23] used self-assembled peptide hydrogels. They have developed a three-dimensional (3D) milieu that encourages stem cell adhesion and angiogenesis based on the data they collected using the functionalized self-assembly peptide scaffold. This environment has enormous promise for dental pulp tissue creation and regeneration.

In the study of Aksel et al.,[24] in which they aimed to evaluate a colloidal microgel for angiogenic and odontogenic differentiation of cells in the presence of cell-derived extracellular matrix (ECM) proteins using a 3D culture model, colloidal microgels allowed cellular organization that could improve penetration and nutrition in a full-length root canal system and concluded that the bioactivity of cell-

derived ECM proteins can be altered depending on external stimuli.

Moshaverinia et al.[25] conducted a study to develop an injectable and biodegradable scaffold based on oxidized alginate microbeads encapsulating the periodontal ligament and gingival mesenchymal stem cells and to investigate stem cell viability and osteogenic differentiation of stem cells in vitro. Alginate has been shown to be a promising candidate as a non-toxic scaffold for periodontal ligament stem cells and gingival mesenchymal stem cells. The degradation profile and swelling kinetics of the alginate hydrogel were found to be strongly dependent on the degree of oxidation, indicating its tunable chemistry and degradation rate. This study demonstrated for the first time that the immobilization of periodontal ligament stem cells and gingival mesenchymal stem cells in alginate microspheres provides a promising strategy for bone tissue engineering.

An injectable, heat-sensitive hydrogel consisting of chitosan, sodium glycerophosphate (-GP), and gelatin was created by Xu et al.[26] to stop alveolar bone loss, reduce inflammation, and promote the healing of periodontitis. The mixture underwent a sol-gel transition at body temperature. Aspirin and erythropoietin could be released from these hydrogels to cause anti-inflammatory effects and control tissue regeneration. The potentials of the hydrogel system in applications for treating periodontitis have been shown by the release profile, which suggests that the released components are non-toxic both in vitro and in vivo.

In the study of Bae et al.,[27] in which they aimed to modify zirconium dioxide (ZrO_2) with a light-curing hyaluronic acid hydrogel and then evaluate the bone regeneration potential of the modified zirconium dioxide, they suggested that surface functionalized ZrO2-5 and 7 could be used as implant materials in dental applications. They also suggested that growth and differentiation factor-5 may be useful as an effective osteogenic differentiation factor to accelerate new bone formation.

In order to address intrabony periodontal abnormalities, Yan et al.[28] prepared and evaluated an enzymatically solidified chitosan hydrogel in vivo. It was discovered that these hydrogels were highly biocompatible and biodegradable. Tan et al.[29] provided sufficient and continuous stimulation with hydrogels containing growth factors to assist the repair of periodontal tissue in a rat model. Future treatments for periodontal bone abnormalities and intermittently accelerated osteogenic orthodontic treatment may use these hydrogels instead of bone transplantation in the clinic. Additionally, it may be possible to improve the osteoconductivity of such biomaterials by combining bioactive glass nanoparticles with the heat-sensitive hydrogels.

A temperature sensitive gel has a tremendous effect on the treatment of periodontal disease. Swain et al.[30] employed moxifloxacin hydrochloride heat sensitive smart gel for subgingival application to enhance the local effect of periodontitis and extend residence time in the diseased cavity. This gel was created utilizing a mix of temperature sensitive hydrogel and gellan gum. The medicine and gel did not appear to be incompatible, and the gel maintained its antibacterial properties. Sheshala et al.[31] also created in situ gel formulations of moxifloxacin for the treatment of periodontitis using polylactic acid (poloxamer-based) and chitosan as heat-sensitive and adhesion polymers. The retention duration in the afflicted area is extended by all formulations' suitable viscosity and ease of syringe passage, according to earlier research. The pH of all formulations was neutral and did not irritate the oral mucosa.

To test their suitability for the treatment of periodontitis, Bansal et al.[32] created in situ gels containing the antibiotics metronidazole and levofloxacin for in vitro research and antimicrobial trials. No interactions between the medication and the carrier gel were seen in the studies. The duration of the drug's action can be prolonged for up to 48 hours, and the gel's high viscosity made it easier to store it in the periodontal pocket for an extended amount of time. In addition, in situ gels have more potent antibacterial properties than carrier gels. The authors therefore proposed that periodontal pockets with deep infections may be treated using the created in situ gel.

In their study of Pakzad et al.[33] for use as a biodegradable drug delivery system to be injected into periodontal pockets to allow injectable heat-sensitive chitosan/gelatin/β-glycerolphosphate hydrogel to allow sustained metronidazole release, the gelation time of chitosan/gelatin/β-glycerolphosphate was determined. and it has been shown that the gelation temperature can be adjusted by adjusting the β-glycerolphosphate and gelatin concentrations. The gel strength of chitosan/gelatin/β-glycerolphosphate increased significantly as the gelatin content increased. Results of the antibacterial activity of Chitosan/gelatin/β-glycerolphosphate-Metronidazole showed inhibition of anaerobic gram-positive *Clostridium sporogens*. Cytotoxicity testing showed that the chitosan/gelatin/β-glycerolphosphate hydrogel showed no significant toxicity and was biocompatible.

The approach of treating periodontal disease has gradually changed from resective surgical techniques to regenerative ones as we have gained a better understanding of periodontal wound healing.[34] Hydrogel-based therapeutics offer some encouraging examples in this regard. In a recent preclinical investigation, gingival mesenchymal stem cells were enclosed in alginate gelatin methacrylate (GelMA) hydrogels, which demonstrated faster wound healing in a mouse model.[35] Laboratory-produced tissue-engineered human oral mucosa equivalents (EVPOME) were employed in clinical research of intraoral grafting to assess the effectiveness in establishing a well-integrated surface epithelium. The fundamental substrate on which the cells were seeded was AlloDerm®. The clinical end-use case required a robust ECM matrix that could keep its integrity after being threaded with a needle and suture. Grafts would be surgically inserted and sutured under a flap of skin in this scenario.[36]

In their study, Struillou et al.[37] aimed to evaluate bone regeneration using a dog model with surgically induced periodontal defects for 12 weeks using a layered biomaterial consisting of a biphasic calcium phosphate (BCP) coated with a crosslinking hydrogel that acts as a polymer membrane of silated hydroxypropyl methylcellulose. They found that the hydrogel can act as an occlusive barrier promoting bone regeneration. Future clinical trials in humans are needed to confirm the results of this study.

Yan et al.'s[38] study, which investigated metronidazole (MTR)- and chlorhexidine (CHX)-loaded hydrogels as prospective

applications in intracanal medicines for root canal disinfection, evaluated the antibacterial effectiveness against *Enterococcus faecalis (E. faecalis), Streptococcus mutans (S. mutans),* and *Prevotella intermedia (P. intermedia).* Human dental pulp stem cells (hDPSCs) were also tested for biocompatibility. The viability of *E. faecalis, S. mutans,* and *P. intermedia* was dramatically decreased in vitro in MTR@gGels and CHX@gGels, according to DCT, CCK-8, CFU, and live/dead stained biofilm findings. Significant biocompatibility with hDPSCs was demonstrated by CCK-8 findings. In vivo demonstrations of the filling and removal of gGels from root canals have been made. As a result, they came to the conclusion that MTR and CHX loaded hydrogels might have a place in intracanal medications for root canal disinfection.

For the treatment of oral herpes infections HSV, Chaudhary and Verma created an oral mucosal drug delivery system for the topical and systemic delivery of acyclovir. The duration of medication activity is extended by using a temperature-sensitive gelling method, improving the bioavailability of acyclovir in the oral mucosa. Drug release studies demonstrated the sustained drug release properties of the hydrogels. All preparations showed sustained release properties. In situ injection of the medication gel formulation through the oral mucosa inhibited the first pass effect. In order to boost the bioavailability of medications, heat sensitive in situ gels offer a practical option for local and systemic delivery. It was determined that by improving patient compliance, this approach can be used to treat oral herpes infections locally.[39]

CONCLUSION

It is important that the materials used in dentistry are released over time after the drugs are applied. Hydrogels have become a focus of interest in the world of dentistry and medicine due to their ability to imitate the extracellular matrix, oscillation depending on stimulation over time and removal from the environment and have found various areas of use. Hydrogels have been the subject of various studies due to their properties. But more studies are needed regarding the effect of different materials on different cells.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Rosiak JM, Yoshii F. Hydrogels and their medical applications. *Nucl Instrum Methods Phys Res Sect*. 1999;151(1-4):56-64.
2. El-Hefian EA, Elgannoudi SE, Mainal A, Yahaya AH. Characterization of chitosan in acetic acid: rheological and thermal studies. *Turk J Chem*. 2010;34(1):47-56.
3. Khan MBH, Othman KA, Razak HM. Akil Synthesis and physicochemical investigation of chitosan-PMAA-based dual-responsive hydrogels. *J Polym Res*. 2013;20:1-8.
4. Kishida A, Ikada Y, Hydrogels for biomedical and pharmaceutical applications, Polymeric Biomaterials, Revised and Expanded. 2nd ed (Eds S. Dumitriu). Marcel Dekker, Newyork. 2002;133-145.
5. Wichterle O, Lim D. Hydrophilic gels for biological use. *Nature*. 1960;185:117-118.
6. Murray PE, Garcia-Godoy F, Hargreaves KM. Regenerative endodontics: a review of current status and a call for action. *J Endod*. 2007;33(4):377-390.
7. Swami SN. Radiation synthesis of polymeric hydrogels for swelling controlled drug release studies, Doctor of Philosophy, University of Western Sydney New South Wales, Australia. 2004.
8. Kim SJ, Park SJ, Kim SI. Properties of smart hydrogels composed of polyacrylic acid/poly(vinyl sulfonic acid) responsive to external stimuli, *Smart Mater Struct*. 2004;13(2):317-322.
9. Chang B, Ahuja N, Ma C, Liu X. Injectable scaffolds: Preparation and application in dental and craniofacial regeneration. *Mater Sci Eng R Rep*. 2017;111:1-26.
10. Fan C, WangDA. Macroporous hydrogel scaffolds for three-dimensional cell culture and tissue engineering. *Tissue Eng Part B Rev*. 2017;23(5):451-461.
11. Mantha S, Pillai S, Khayambashi P, et al. Smart hydrogels in tissue engineering and regenerative medicine. *Materials* 2019;12(20):3323.
12. Yang JM, Olanrele OS, Zhang X, Hsu CC. Fabrication of Hydrogel Materials for Biomedical Applications. In Novel Biomaterials for Regenerative Medicine; Chun HJ, Park K, Kim CH, Khang G. Eds.; Springer: Singapore, 2018;197-224.
13. Ahmed TA, Dare EV, Hincke M. Fibrin: a versatile scaffold for tissue engineering applications. *Tissue Eng Part B Rev*. 2008;14(2):199-215.
14. Riopel M, Trinder M, Wang R. Fibrin, a scaffold material for islet transplantation and pancreatic endocrine tissue engineering. *Tissue Eng Part B Rev*. 2015;21(1):34-44.
15. Soran Z, Aydın RS. Gümüşderelioğlu M. Chitosan scaffolds with BMP-6 loaded alginate microspheres for periodontal tissue engineering. *J Microencapsul*. 2012;29(8):770-780.
16. Pichayakorn W, Boonme P. Evaluation of cross-linked chitosan microparticles containing metronidazole for periodontitis treatment. *Mater Sci Eng C Mater Biol Appl*. 2013;33(3):1197-1202.
17. Diniz IM, Chen C, Ansari, S, et al. Gingival mesenchymal stem cell (GMSC) delivery system based on RGD-coupled alginate hydrogel with antimicrobial properties: a novel treatment modality for peri-implantitis. *J Prosthod*. 2016;25(2):105-115.
18. Sculean A, Windisch P, Döri F, Keglevich T, Molnár B, Gera I. Emdogain in regenerative periodontal therapy. A review of the literature. *Fogorv Szle*. 2007;100(5): 220-232.
19. Galler KM, Hartgerink JD, Cavender AC, Schmalz G, D'Souza RN. A customized self-assembling peptide hydrogel for dental pulp tissue engineering. *Tissue Eng Part A*. 2012;18(1-2):176-184.
20. Galler KM, Aulisa L, Regan KR, D'Souza RN, Hartgerink JD. Self-assembling multidomain peptide hydrogels: designed susceptibility to enzymatic cleavage allows enhanced cell migration and spreading. *J Am Chem Soc*. 2010;132(9):3217-3223.
21. Xia K, Chen Z, Chen J, et al. RGD- and VEGF-mimetic peptide epitope-functionalized self-assembling peptide hydrogels promote dentin-pulp complex regeneration. *Int J Nanomed*.2020;15:6631-6647.
22. Han M, Li QL, Cao Y, Fang H, Xia R, Zhang ZH. In vivo remineralization of dentin using an agarose hydrogel biomimetic mineralization system. *Sci Rep*. 2017;7:41955.
23. Xia K, Chen Z, Chen J, et al. RGD- and VEGF-mimetic peptide epitope-functionalized self-assembling peptide hydrogels promote dentin-pulp complex regeneration. *Int J Nanomed*.2020;15:6631-6647.
24. Aksel H, Sarkar D, Lin MH, Buck A, Huang GT. Cell-derived extracellular matrix proteins in colloidal microgel as a self-assembly hydrogel for regenerative endodontics. *J Endod*. 2022;48(4):527-534.
25. Moshaverinia A, Chen C, Akiyama K, et al. Alginate hydrogel as a promising scaffold for dental-derived stem cells: an in vitro study. *J Mater Sci Mater Med*. 2012;23(12):3041-3051.
26. Xu X, Gu Z, Chen X, et al. An injectable and thermosensitive hydrogel:

Promoting periodontal regeneration by controlled-release of aspirin and erythropoietin. *Acta Biomater.* 2019;86:235-246.

27. Bae MS, Kim JE, Lee JB, et al. ZrO2 surface chemically coated with hyaluronic acid hydrogel loading GDF-5 for osteogenesis in dentistry. *Carbohydrate Polymers*. 2013;92(1):167-175.
28. Yan XZ, van den Beucken JJ, Cai X, Yu N, Jansen JA, Yang F. Periodontal tissue regeneration using enzymatically solidified chitosan hydrogels with or without cell loading. *Tissue Eng Part A*. 2015;21(5-6):1066-1076.
29. Tan J, Zhang M, Hai Z, et al. Sustained release of two bioactive factors from supramolecular hydrogel promotes periodontal bone regeneration. *ACS Nano*. 2019;13(5):5616-5622.
30. Swain GP, Patel S, Gandhi J, Shah P. Development of moxifloxacin hydrochloride loaded *in-situ* gel for the treatment of periodontitis: *in-vitro* drug release study and antibacterial activity. *J Oral Biol Craniofac Res*. 2019;9(3):190-200.
31. Sheshala R, Quah SY, Tan GC, Meka VS, Jnanendrappa N, Sahu PS. Investigation on solution-to-gel characteristic of thermosensitive and mucoadhesive biopolymers for the development of moxifloxacin-loaded sustained release periodontal in situ gels. *Drug Deliv Transl Res*. 2019;9(2):434-443.
32. Bansal M, Mittal N, Yadav SK, et al. Periodontal thermoresponsive, mucoadhesive dual antimicrobial loaded in-situ gel for the treatment of periodontal disease: preparation, in-vitro characterization and antimicrobial study. *J Oral Biol Craniofac Res*. 2018;8(2):126-133.
33. Pakzad Y, Ganji F. Thermosensitive hydrogel for periodontal application: in vitro drug release, antibacterial activity and toxicity evaluation. *J Biomater Appl*. 2015;30(7):919-929.
34. Cho YD, Kim KH, Lee YM, Ku Y, Seol YJ. Periodontal wound healing and tissue regeneration: a narrative review. *Pharmaceuticals*. 2021;14(5):456.
35. Ansari S, Pouraghaei Sevari S, Chen C, Sarrion P, Moshaverinia A. RGD-modified alginate-gelma hydrogel sheet containing gingival mesenchymal stem cells: a unique platform for wound healing and soft tissue regeneration. *ACS Biomater Sci Eng*. 2021;7(8):3774-3782.
36. Izumi K, Neiva RF, Feinberg SE. Intraoral grafting of tissue-engineered human oral mucosa. *Int J Oral Maxillofac Implants*. 2013;28(5):e295-e303.
37. Struıllou X, Fruchet A, Rakıc M, et al. Evaluation of a hydrogel membrane on bone regeneration in furcation periodontal defects in dogs. *Dent Mater J*. 2018;37(5):825-834.
38. Yan Y, Zhou P, Lu H, et al. Potential apply of hydrogel-carried chlorhexidine and metronidazole in root canal disinfection. *Dent Mater J* 2021;40(4):986-993.
39. Chaudhary B, Verma S. Preparation and evaluation of novel in situ gels containing acyclovir for the treatment of oral herpes simplex virus infections. *Sci World J*. 2014;24:280928.