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REVIEW ARTICLE

Applications and Perspectives of Hydrogels in Veterinary Medicine

Yang Yang[1], Congguang Cai[1], Yuxin Guo[1], Muhammad Mohsin[2], Guangwen Yin[1*] and Lei Wang[1*]

[1]College of Animal Sciences, Fujian Agriculture and Forestry University, Fuzhou, China
[2]Shantou University Medical College, Shantou, China
*Corresponding author: yinguangwen000@sina.com (G.Y.); dkwangl@fafu.edu.cn (L.W.)

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ABSTRACT

Technology transfer is an important demand for the development of veterinary medicine, and interdisciplinarity is of great significance in promoting the development of veterinary medicine. In recent years, as the star in the field of material science, hydrogel preparations have been widely used in biomedical fields and made a series of progress. Notable examples include wound management, drug delivery, and tissue engineering. However, the application of hydrogels in veterinary medicine is relatively rare, and therefore, only a few related studies have been reported. This paper reviews the classification, preparation materials, and methods of hydrogels, providing an overview of the current research status in the veterinary field. It further analyzes the potential applications of hydrogels in this area. Firstly, hydrogels demonstrate superior moisturizing properties, adequate mechanical strength, and appropriate surface microstructure and biochemical characteristics compared to traditional animal wound dressings, promoting the adhesion, proliferation, and differentiation of epidermal cells. Secondly, in the field of drug delivery, based on its unique structure and function, hydrogels have promising applications in animals for transdermal, oral and rectal mucosal administration. Lastly, in the field of animal tissue engineering, hydrogels have become a focal point of research due to their controllable physical and chemical properties, as well as their highly biomimetic characteristics that resemble the extracellular matrix of natural tissues. This review aims to enhance veterinary scholars' fundamental understanding of the advantages and applications of hydrogels and to elucidate potential future applications, thereby inspiring new research directions for the use of hydrogels in veterinary medicine.

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INTRODUCTION

Veterinary medicine is a comprehensive discipline that utilizes medicine to safeguard the health of animals and promote harmony between the global community of life and the natural environment. The development of veterinary medicine is closely linked to the progress of modern medicine. In recent years, with the context of interdisciplinary development, the research of medical materials has gained rapid growth, and a variety of nanomaterials and their derivatives have emerged (Yuan *et al*., 2021; Shi *et al*., 2022). Hydrogels are hydrophilic macromolecules with three-dimensional porous structure, flexibility, and solubility. They are formed by physical or chemical cross-linking (Zhang and Khademhosseini, 2017). Hydrogels can be used as excellent antibacterial materials, along with various antibacterial drugs for antibacterial treatment (Tang *et al*., 2023). They can also be used as dressings for skin wounds, drug delivery, and biosensors (Kesharwani *et al*., 2021; Tang *et al*., 2023). Due to their similar properties to living tissues, Hydrogels, which have a soft texture, high water-holding capacity, and good biocompatibility, have become a research hotspot nowadays (Suneetha *et al*., 2022; Usturk *et al*., 2022). The promotion of "technology transfer" from all related disciplines to veterinary medicine is one of the important needs for veterinary development, so it is important for veterinary medicine to comprehensively draw on the development of human clinical and biomedical experience.

In veterinary medicine, authors believe that hydrogels hold significant research value and promising applications in areas such as skin wound healing, drug delivery, and tissue engineering. This paper aims to provide a comprehensive overview of hydrogels and their relevant research in veterinary medicine, as well as to assess their potential applications based on existing knowledge.

Current Research Status of Hydrogels

Classification of hydrogels: Hydrogels can be classified in various ways, they can be divided based on the cross-linking method as physical cross-linking hydrogels or chemical cross-linking hydrogels; based on the source of the material used to prepare the hydrogels, they can be divided into natural, synthetic, and composite hydrogels; based on the method of preparation, they can be divided into copolymer, homopolymer, and interpenetrating network hydrogels. Additionally, They can be categorized based on the physical state of the hydrogels as solid, semisolid, and liquid hydrogels (Gyles *et al*., 2017). The physical state of hydrogels plays a crucial role in determining their biomedical applications, which will be further discussed.

Solid hydrogels: Solid hydrogels have a strongly cross-linked network structure with ionic or covalent cross-linkers and are solid at room temperature but soluble in water, buffer solutions, or biological fluids. To improve its suitability for medical applications, researchers have introduced metal nanoparticles silver, gold, zinc oxide nanoparticles, and curcumin have been used to create functional solid hydrogels for biomedical applications, especially as wound dressing scaffolds (Mohan *et al*., 2010; Nutan *et al*., 2020; Pan *et al*., 2021; Shahrousvand *et al*., 2023).

Hydrogel microneedles (HMNs) are the latest type of microneedles reported to date and have become one of the key directions in hydrogel applications in recent years. Microneedles formed from hydrogels can deliver drugs trans dermally due to their swelling properties, and they can passively extract inter-tissue fluids from the skin, which also means that they possess the potential to be used in the preparation of minimally invasive monitoring devices with biocompatibility (Turner *et al*., 2021). On the other hand, Wei *et al*. (2022) chose natural polymeric materials, chitosan, and pullulan to prepare hydrogel microneedle HFM-1, which selected CMCS-SFP/OPL hydrogels as its matrix for their swelling properties, water retention, and biocompatibility, loading with salvia miltiorrhiza. Also, HFM-1 has been verified to have good transdermal ability through a series of tests. This suggests that transdermal drug delivery through hydrogel microneedles loaded with drugs is feasible.

Semisolid hydrogels: Semisolid hydrogels, also known as adhesive hydrogels, are semisolid formulations with bioadhesive properties. These hydrogels exhibit characteristics such as wettability, stability, and high local concentration at the administration site. They also possess bioadhesive agent properties, providing long-lasting efficacy, easy application, and the ability to bypass the first-pass effect. As a result, they have become a significant focus of research in transdermal or mucosal drug delivery.

Fu *et al*. (2023) prepared a natural bio adhesive hydrogel using protocatechuic aldehyde and fish gel, which was able to regulate the immune microenvironment of diabetic wounds by modulating macrophage heterogeneity, ultimately facilitating wound healing. A hydrogel was designed based on thiourea-catechol reaction to improve adhesion and applied it to treat ulcers (Xu *et al*., 2020). Their findings demonstrated a significant reduction in ulcer index compared to sucralfate treatment in a porcine model of gastric ulcers. This effect is likely due to the hydrogel's ability to create a protective barrier on ulcer surfaces, preventing external catabolic factors from penetrating while promoting the accumulation of growth factors around the ulcer site.

Liquid hydrogels: Liquid hydrogels are typically in a liquid phase at room temperature. Still, they can self-regulate pore size and exhibit elasticity similar to that of soft tissue under specific environmental conditions. One of the key advantages of these liquid hydrogels is that they can easily incorporate a variety of substances, such as organics, inorganics, drugs, proteins, and cells, which can be easily mixed into these hydrogels. They have some particular hydrophilic molecules like -OH, -CONH, $-CONH_2$, and $-SO_3H$, which possess high hydrophilicity and can be injected into the body to target specific sites (Lin and Metters, 2006).

A novel liquid hydrogel was used to achieve efficient hemostasis in an animal model of acute mesenteric hemorrhage (Gandras *et al*., 2022). The property of those liquid hydrogels can be self-regulating to prepare a liquid hydrogel (Liu *et al*., 2024), which gels into the stomach after being consumed orally. The application of these liquid hydrogels can not only provide a new therapeutic idea for patients with dysphagia but also compensate for the disadvantage that liquid preparations are rapidly diluted after entering the stomach. Yang *et al*. (2023) developed an on-skin patch with poly aspartic acid-modified dopamine/ethyl-based ionic liquid hydrogel (PDEH), which was further embedded with silver/liquid metal (SLM) conductive layer to prepare PDEH-SLM patch was further embedded in a silver/liquid metal (SLM) conductive layer to prepare the PDEH-SLM patch. This patch can collect signals and obtain the corresponding parameters by processing and calculating by being attached to the corresponding nerve location as a stimulating/recording electrode. Ultimately, by comparing the obtained results with normal indicators, an accurate diagnosis of peripheral neuropathy can be realized.

Preparation materials of hydrogels: The biomedical applications of hydrogels are influenced by their physical state, which is determined by the nature and cross-linking structure of the constituent monomers (Gyles *et al*., 2017). These monomers can be classified into natural and synthetic materials (Table 1). Natural materials, such as polysaccharides and proteins, are macromolecular organic compounds found in biological organisms and are inherently biocompatible (Jiang *et al*., 2020). On the other hand, synthetic materials like polyethylene glycol, polyvinyl alcohol, and polyacrylamide have also been utilized. As modern materials science advances, synthetic materials are being modified to enhance their biocompatibility to meet the requirements for biomedical applications (Li *et al*., 2021a; Liu *et al*., 2021; Li *et al*., 2022a).

Table 1: Overview of hydrogel preparation materials and their characteristics.

Hydrogel preparation materials	Common materials	Source or preparation	Characteristics
Natural polymer materials	Chitosan (CS) (Hong *et al*., 2024)	A biological polysaccharide extracted from natural chitin	Electropositive
	Polydopamine (PDA) (Fiorica *et al*., 2021)	PDA is an important natural melanin analog produced by dopamine autoxidation	High viscosity; Intrinsic photothermal properties
	Gelatine(Andreazza *et al*., 2023)	Product of collagen denaturation	Beneficial for fibroblast adhesion and growth
	Agarose(Crespo-Cuevas *et al*., 2023)	Agarose is a naturally occurring water-soluble linear polysaccharide found in seaweeds	Stable thermally reversible hydrogels can be formed by physical cross-linking
	Hyaluronic acid (HA) (Xu *et al*., 2021)	A non-sulfated glycosaminoglycan present in animal tissues	Promoting granulation tissue regeneration and reepithelialization; Antiinflammatory
	Cellulose(Zainal *et al*., 2021)	Cellulose mainly derived from plant cell walls and bacteria	Modifications can be made without compromising the structural and mechanical properties.
	Alginate(Tomic *et al*., 2023)	Alginate is a natural anionic polysaccharide derived from various brown algae and bacteria	Nonimmunogenic and nonthrombotic
Synthetic polymer materials	Polyethylene glycol (PEG) (Yang and Shen, 2006; Zhao *et al*., 2011)	Gradual addition polymerization of ethylene oxide with water or ethylene glycol	PEG induces cell aggregation and fusion
	Polyvinyl alcohol (PVA)(Aslam *et al*., 2018)	Vinyl acetate is made into PVA by alcoholysis and polymerization	Film-forming property; Low protein adsorption
	Polyacrylamide (PAM) (Awasthi *et al*., 2022)	PAM is formed by free radical initiated polymerization of acrylamide (AM) monomer	PAM can effectively reduce the frictional resistance of fluids; PAM has a thickening effect in both neutral and acidic conditions
	Polylactic acid (PLA) (More *et al*., 2023)	Lactide ring opening polymerization	PLA is a biodegradable plastic with excellent anti-bacterial and anti-mold properties
	Poly (lactic-co-glycolic acid) (PLGA) (Su *et al*., 2021)	PLGA by random polymerization of lactic acid and hydroxyacetic acid	Because of its Good capsule-forming property, it is often used to prepare nanoparticles
	Polyvinyl pyrrolidone (PVP) (Luo *et al*., 2021)	PVP is obtained from the monomer vinyl pyrrolidone (NVP) by propriety polymerization, solution polymerization and other methods	Polymer surfactant
	Poloxamer(Russo and Villa, 2019)	Reaction of propylene oxide and propylene glycol to form polyoxypropylene glycol, followed by addition of ethylene oxide to form a block copolymer	Numerous compounds of this basic structure can be used as absorption enhancers

Preparation of hydrogels: Hydrogels are three-dimensional network-structured macromolecules formed by cross-linking of gel monomers. Their preparation methods can be categorized into physical cross-linking and chemical cross-linking, depending on the cross-linking method used (Figure 1). Physical cross-linking involves reversible bonding between molecules without the use of cross-linking agents, while chemical cross-linking utilizes compounds to induce chemical reactions like addition or condensation by introducing cross-linking agents. This results in the formation of covalent bonds between compounds, leading to the stability and solidity of the hydrogels (Pajic-Lijakovic *et al*., 2007; Chan *et al*., 2010).

Physical cross-linking: Physical cross-linking methods are relatively easy to prepare hydrogels with better biocompatibility, by avoiding the use of organic solvents and cross-linking agents. Physical cross-linking methods primarily include freezing-thawing, hydrogen bond forming, and interionic interaction (Luisa Pita-Lopez *et al*., 2021). The freezing-thawing method entails the creation of microcrystals within the cross-linked structure through repeated freezing and thawing cycles. For instance, during this process, polyvinyl alcohol aqueous solutions will form a hydrogel because of crystallization (Plieva *et al*., 2006). This hydrogel is spongy and has good elasticity due to its internal pore structures. The hydrogen bond forming method involves linking polymer networks through hydrogen bonding to produce hydrogels. For example, when carboxymethyl cellulose is dissolved in 0.1 M hydrochloric acid, the hydrogen ions from hydrochloric acid replace the sodium ions in the compound, leading to the formation of hydrogen bonds and, ultimately carboxymethyl cellulose hydrogels (Takigami *et al*., 2006). the interionic interaction method relies on the use of oppositely charged multivalent ions to gel aqueous solutions, as seen in examples like chitosan-glycerophosphate (Zhao *et al*., 2009) and sodium alginate-calcium salt (Chan *et al*., 2010).

Chemical cross-linking: Hydrogels formed through chemical cross-linking exhibit increased stability, insolubility in solvents, and undergo structural changes only upon cleavage of covalent cross-linking sites (Chung and Park, 2009). Consequently, hydrogels created via chemical cross-linking methods typically possess robust mechanical strength. The high mechanical properties contribute to enhanced ductility, stability, and the ability to withstand significant levels of tensile and compressive deformation. Furthermore, the enhancement of mechanical properties influences swelling resistance, self-healing capabilities, and adsorption properties (Zhuang *et al*., 2017). Chemical cross-linking methods can be categorized into two main types: graft copolymerization and chemical reagent cross-linking (Li *et al*., 2021b; Porfiryeva *et al*., 2024). generate active radicals and grafting them onto natural polymer compounds and their derivatives through chemical (initiator) or radiation methods. Chemical reagent crosslinking refers to the formation of chemical bonds between linear molecules by chemical reagents, thus creating a network structure.

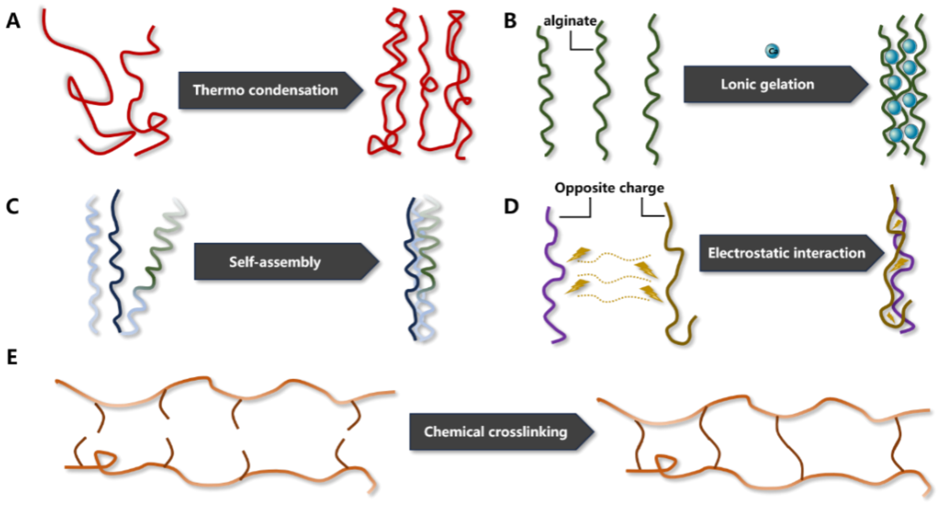

Fig. 1: Process of preparation of hydrogels through Cross-linking

Common chemical reagents used for cross-linking include glutaraldehyde (Morandim-Giannetti *et al.*, 2018; Mugnaini *et al.*, 2023), N N'-methylene bisacrylamide (Kang *et al.*, 2023) and epichlorohydrin (Salleh *et al.*, 2018; Vaid *et al.*, 2022).

Hydrogels in Veterinary Medicine: Current research on hydrogels in the global veterinary field is limited, with a primary focus on their application in companion animals. Cartilage problems are a common problem in canine orthopedic disorders. Boyer *et al.* (2020) mixed salinized hydroxypropyl methylcellulose (Si-HPMC) with salinized chitosan to prepare a hydrogel (Si-HPCH), for use in the canine cartilage defect model and started self-hardening after injected to the body. Their study demonstrated that treatment with Si-HPCH significantly promoted cartilage regeneration. It is worth mentioning that hydrogel formulations have also shown excellent efficacy in treating lameness due to equine osteoarthritis, indicating their potential in orthopedic disease treatment (da Silva Xavier *et al.*, 2021). In companion animals, corneal ulcers are a common eye disease. Research has shown that HA hydrogels, compared to HA solutions, can expedite corneal ulcer repair in dogs and cats by accelerating corneal wound closure (Williams *et al.*, 2017). This study suggested that hydrogel formulations can prolong drug residence time in the eyes, improving treatment efficacy and drug utilization and reducing administration frequency.

Additionally, hydrogel formulations have demonstrated success in nerve block (Kim *et al.*, 2023) and feline dermatologic (Santiago *et al.*, 2023) studies in recent years. Despite limited reports on hydrogels in veterinary medicine, it is undeniable that hydrogels can advance veterinary medicine and have the potential to solve veterinary clinical problems.

Hydrogel Applications in Animal Skin Wounds: Skin is the largest organ of animal organisms. However, as the first barrier the organism faces against external factors, it is also the most vulnerable organ. Skin wounds in animals are usually caused by trauma such as bites, falls, and burns. While conventional wound dressings like bandages and gauze are effective for minor exudative wounds, they often require frequent changes during application, leading to poor compliance from the animal due to pain during dressing changes. (Brumberg *et al.*, 2021). In recent years, tilapia skin has emerged as a promising wound dressing in veterinary clinical practice for treating skin wounds with positive outcomes (Choi *et al.*, 2021). When compared to traditional wound dressings, this method demonstrates superior efficacy in preventing bacterial invasion and deterring particles from adhering to the wound. However, the essence of this method is to suture the obtained exogenous skin to the wounds to minimize exposure. Despite its benefits, this technique can be complex to administer and carries the risk of immune rejection.

The ideal wound dressings should have better histocompatibility, non-toxicity, and innocuity; good moisture retention; adequate mechanical strength as well as having appropriate surface microstructure and biochemical properties to promote cell adhesion, proliferation, and differentiation (Zeng *et al.*, 2022). In recent years, hydrogels have garnered attention in wound dressing research due to their unique characteristics. Yang *et al.* (2022) prepared a starch-regulated viscous hydrogel dressing with controlled separation properties, achieving controlled adhesion and separation through the dissociative competition mechanism of polar small molecules. Another work reported that the liquid hydrogel can be leveraged for accelerated wound healing by direct injection into the skin wound, simplifying the treatment process while maintaining effectiveness (Hu *et al.*, 2022). We believe that the ease of administration and the realization of controlled adhesion and separation of hydrogels can significantly improve the compliance of animals in wound treatment and promote the application of hydrogel dressings in animal skin injuries (Figure 2).

Hydrogel Applications in Animal Drug Delivery: Hydrogels, as a drug delivery system, are mainly used in the treatment of transdermal drug delivery. Transdermal drug delivery is one of the important research directions in the treatment of dermatologic diseases. However, transdermal drug delivery is usually limited by the barrier function of the stratum corneum, which results in drugs not effectively penetrating lesions (Labouta and Schneider, 2013). Microneedles have emerged as an innovative solution to enhance drug permeability through the skin (Zhi *et al.*, 2021). It is worth mentioning that hydrogel microneedles (HMNs) have become research spotlight for microneedle preparation in recent years.

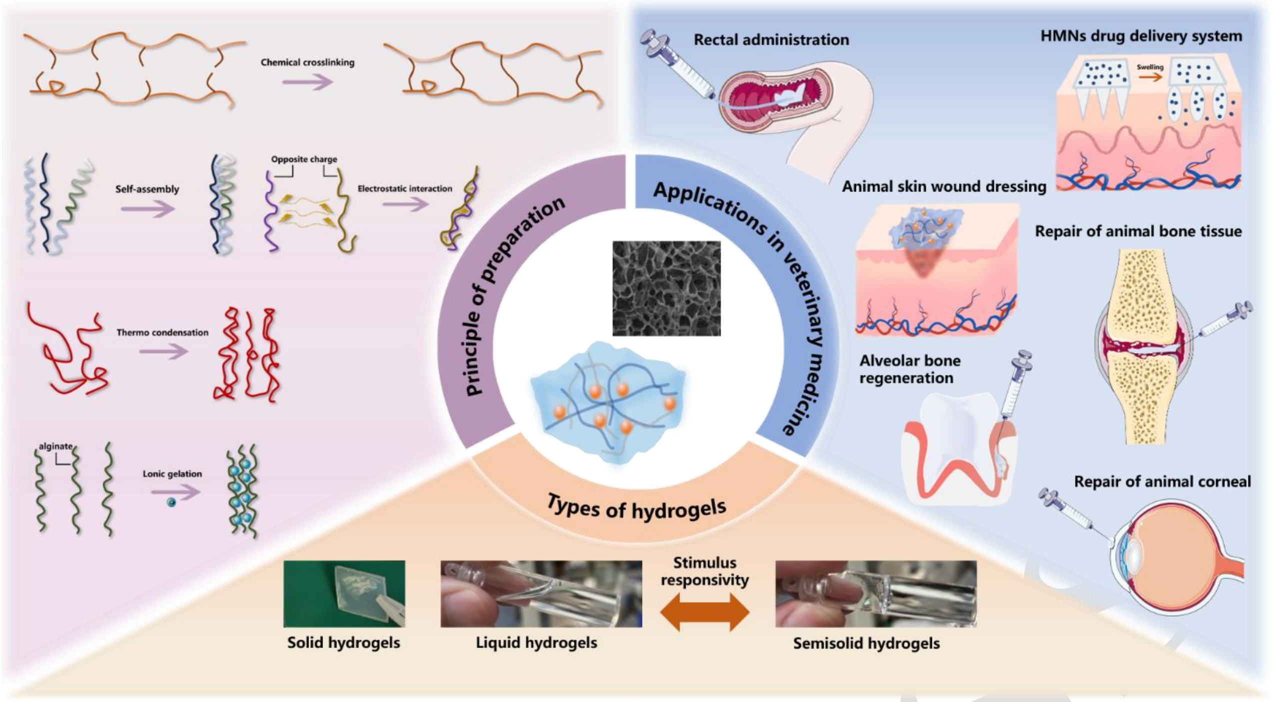

Fig. 2: Hydrogels and their applications in veterinary medicine (Principle of preparation: The principle of hydrogel formation is illustrated through six diagrams. Types of hydrogels: The physical forms of three distinct types of hydrogels are presented. Applications in veterinary medicine: The potential applications of hydrogels across various domains are demonstrated).

HMNs can be inserted into the skin to break the stratum corneum barrier effectively and then swelling after contact with the tissue fluid in the skin. Under the influence of osmosis, diffusion, and external negative pressure, the drugs are released from the internal aperture of the swelling of hydrogels as depicted in Figure 2 (Li *et al*., 2022b).

Canine and feline fungal dermatoses are among the most harmful types of dermatoses in pet clinical medicine, sometimes significantly impacting the daily behavioral activities of dogs and cats (Katiraee *et al*., 2021). The conventional treatment approach for fungal dermatoses in dogs and cats typically involves oral medication in combination with topical application of antifungal drugs (Moriello *et al*., 2017). However, traditional topical treatments present several drawbacks, including low drug bioavailability, inadequate penetration to reach skin lesions, and the potential for pets to lick the affected area. Therefore, the authors posit that HMNs hold promise for the management of fungal dermatoses in companion animals. This is supported by several factors: firstly, in comparison to traditional oral medication, HMNs can bypass the first-pass effect and enhance drug bioavailability; secondly, while traditional topical treatments rely on skin absorption, HMNs can achieve precise drug delivery by penetrating the skin's stratum corneum barrier to target disease lesions; lastly, HMNs can be applied on the surface of skin as a patch, and it can avoid pets from licking the affected area with the use of Elizabeth collar. The further application of HMNs in veterinary clinics is limited by two main reasons: the lack of mechanical strength and the significantly higher number and thickness of hairs in animals compared to humans.

In addition to transdermal drug delivery, oral administration and mucosal administration are important application directions of hydrogels (Li *et al*., 2023). Hydrogels are frequently utilized for the oral delivery of insulin, drugs, and vaccines (Yoshida *et al*., 2017; Qi *et al*., 2018; Ullah *et al*., 2023). Research has demonstrated that hydrogels effectively safeguard delivered insulin, drugs, and vaccines from degradation by stomach acids and proteases. More importantly, they can facilitate colon-targeted release of specific medications(Wang *et al*., 2023). Notably, rectal mucosal drug delivery is particularly favored by veterinarians. Compared to oral administration, rectal administration effectively reduces the risk of pet doctors being bitten. Pain management is a crucial aspect of ensuring animal welfare; however, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is often limited due to their gastrointestinal irritant properties (Bjarnason *et al*., 2018; Malkani *et al*., 2024). Consequently, the application of NSAIDs via the rectal mucosa can be an effective strategy to avoid gastrointestinal irritation. Stimuli-responsive hydrogels emerge as a promising vehicle for rectal drug delivery (Pareek *et al*., 2017). In short, a liquid hydrogel is injected into the rectum of an animal and subsequently transforms into a semi-solid hydrogel upon stimulation by temperature or pH (Figure 2). All in all, each drug delivery method has its own unique advantages and disadvantages, and the important thing is to choose the drug delivery method according to the purpose.

Hydrogel Applications in Animal Tissue Engineering: Tissue engineering has advanced significantly since 1993, when LANGER and colleagues (Langer and Vacanti, 1993) first proposed research in this field utilizing scaffolds, cells, and stimuli, tissue engineering aims to promote the growth of new tissues. Veterinarians play an important role in the transition of various studies in tissue engineering from theoretical to clinical (Brehm *et al*., 2012). Unfortunately, throughout this process, animals are usually used as models for studying tissue engineering rather than being the recipients of the benefits.

Companion animals play a family-like role in people's daily lives and have become an emotional support for pet owners. With the increasing attention paid to pet healthcare, tissue engineering has attracted the attention of veterinary scholars (Nantavisai *et al*., 2019; Purbantoro *et al*., 2024). Hydrogels have demonstrated controllable physicochemical properties and high biomimetic properties resembling natural tissue extracellular matrix. What's more, widely utilized in tissue engineering, hydrogels are considered a highly promising material for research in this field (Gomez-Florit *et al*., 2020; Talebian *et al*., 2019). Their applications span various tissues such as muscle, bone, nerve, vascular, oral, corneal, cardiac, and gastric tissues, etc. (Zhao *et al*., 2022). Despite this, research on hydrogels in pet clinical medicine remains limited, with current studies focusing on alveolar bone regeneration (Tanongpitchayes *et al*., 2022), corneal tissue (Williams *et al*., 2017), and bone tissue (Boyer *et al*., 2020; Might *et al*., 2016) (Figure 2). It is well known that animals have a large amount of daily activity and are influenced by many environmental factors. It makes the selection of tissue engineering materials in treatment more demanding, yet hydrogels offer strength and mechanical properties beyond traditional biomaterials. Looking ahead, the expanding use of hydrogels in treating veterinary diseases appears poised to be a focal point in future veterinary medicine research.

Summary and perspective: Since the previous few decades, hydrogels have emerged as a significant research topic in the field of materials science, particularly in the realm of medical materials. This paper provides a comprehensive overview of hydrogel research, covering their classification, preparation materials, methods and delving into their applications in veterinary medicine. The author also discusses potential uses in skin wound healing, drug delivery, and tissue engineering. For veterinarians, innovative research on hydrogels is greatly limited by the insufficiency of both knowledge of material science and laboratory equipment. This becomes the biggest obstacle to the further application of hydrogels in the veterinary field. Based on building an efficient sharing platform of laboratory instruments, the promotion of interdisciplinarity communication can not only accelerate the veterinarians to break the cognitive differences and improve the cross-disciplinary awareness but also supplement the insufficient experimental conditions. It is noted that veterinary medicine research lags in areas such as surgical instrument development, animal tumor diagnosis, and treatment. Therefore, veterinary scholars should conduct technology transfer and independent research by paying close attention to the research progress of hydrogels.

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REFERENCES

Yuan A, Xia F, Bian Q, et al., 2021. Ceria Nanozyme-Integrated Microneedles Reshape the Perifollicular Microenvironment for Androgenetic Alopecia Treatment. ACS Nano 15: 13759-13769.

Shi Y, Zhao J, Li H, et al., 2022. A Drug-Free, Hair Follicle Cycling Regulatable, Separable, Antibacterial Microneedle Patch for Hair Regeneration Therapy. Adv Healthc Mater 11: e2200908.

Zhang YS, Khademhosseini A, et al., 2017. Advances in engineering hydrogels. Science 356: eaaf3627.

Tang Y, Xu H, Wang X, et al., 2023. Advances in preparation and application of antibacterial hydrogels. J Nanobiotechnology 21: 300.

Kesharwani P, Bisht A, Alexander A, et al., 2021. Biomedical applications of hydrogels in drug delivery system: An update. J Drug Delivery Sci Technol 66: 102914.

Suneetha M, Rao KM, Han SS, et al., 2022. Cell/Tissue Adhesive, Self-Healable, Biocompatible, Hemostasis, and Antibacterial Hydrogel Dressings for Wound Healing Applications. Adv Mater 9: 2102369.

Usturk S, Altundag EM, Yilmaz E, et al., 2022. Pullulan/polyHEMA cryogels: Synthesis, physicochemical properties, and cell viability. J Appl Polym 139: 51822.

Gyles DA, Castro LD, Carrera Silva JO, Jr., et al., 2017. A review of the designs and prominent biomedical advances of natural and synthetic hydrogel formulations. Eur Polym J 88: 373-392.

Mohan YM, Vimala K, Thomas V, et al., 2010. Controlling of silver nanoparticles structure by hydrogel networks. J Colloid Interface Sci 342: 73-82.

Nutan B, Chandel AKS, Biswas A, et al., 2020. Gold Nanoparticle Promoted Formation and Biological Properties of Injectable Hydrogels. Biomacromolecules 21: 3782-3794.

Pan R, Liu G, Zeng Y, et al., 2021. A multi-responsive self-healing hydrogel for controlled release of curcumin†. Polym Chem 12: 2457-2463.

Shahrousvand M, Mirmasoudi SS, Pourmohammadi-Bejarpasi Z, et al., 2023. Polyacrylic acid/polyvinylpyrrolidone hydrogel wound dressing containing zinc oxide nanoparticles promote wound healing in a rat model of excision injury. Heliyon 9: e19230.

Turner JG, White LR, Estrela P, et al., 2021. Hydrogel-Forming Microneedles: Current Advancements and Future Trends. Macromol Biosci 21: e2000307.

Wei H, Liu S, Tong Z, et al., 2022. Hydrogel-based microneedles of chitosan derivatives for drug delivery. React Funct Polym 172: 105200.

Fu Y, Shi Y, Wang L, et al., 2023. All-Natural Immunomodulatory Bioadhesive Hydrogel Promotes Angiogenesis and Diabetic Wound Healing by Regulating Macrophage Heterogeneity. Adv Sci 10: e2206771.

Xu X, Xia X, Zhang K, et al., 2020. Bioadhesive hydrogels demonstrating pH-independent and ultrafast gelation promote gastric ulcer healing in pigs. Sci Transl Med 12: eaba8014.

Lin CC, Metters AT, et al., 2006. Hydrogels in controlled release formulations: Network design and mathematical modeling. Adv Drug Deliv 58: 1379-1408.

Gandras EJ, Jarrett T, Lareau R, et al., 2022. Evaluation of a Hydrogel Liquid Embolic Agent in a Porcine Mesenteric Hemorrhage Model. J Vasc Interv Radiol 33: 653-659.

Liu GW, Pickett MJ, Kuosmanen JLP, et al., 2024. Drinkable in situ-forming tough hydrogels for gastrointestinal therapeutics. Nat Mater DOI: 10.1038/s41563-41024-01811-41565.

Yang G, Hu Y, Guo W, et al., 2023. Tunable Hydrogel Electronics for Diagnosis of Peripheral Neuropathy. Adv Mater e2308831.

Jiang Y, Wang Y, Li Q, et al., 2020. Natural Polymer-based Stimuli-responsive Hydrogels. Curr Med Chem 27: 2631-2657.

Li Z, Xu W, Wang X, et al., 2021a. Fabrication of PVA/PAAm IPN hydrogel with high adhesion and enhanced mechanical properties for body sensors and antibacterial activity. Eur Polym 146: 110253.

Liu S, Jiang T, Guo R, et al., 2021. Injectable and Degradable PEG Hydrogel with Antibacterial Performance for Promoting Wound Healing. ACS Appl Bio Mater 4: 2769-2780.

Li Y, Yang K, Wang Z, et al., 2022a. Rapid In Situ Deposition of Iron-Chelated Polydopamine Coating on the Polyacrylamide Hydrogel Dressings for Combined Photothermal and Chemodynamic Therapy of Skin Wound Infection. ACS Appl Bio Mater DOI: 10.1021/acsabm.1022c00602.

Pajic-Lijakovic I, Plavsic M, Bugarski B, et al., 2007. Ca-alginate hydrogel mechanical transformations - The influence on yeast cell growth dynamics. J Biotechnol 129: 446-452.

Chan ES, Yim ZH, Phan SH, et al., 2010. Encapsulation of herbal aqueous extract through absorption with ca-alginate hydrogel beads. Food Bioprod Process 88: 195-201.

Luisa Pita-Lopez M, Fletes-Vargas G, Espinosa-Andrews H, et al., 2021. Physically cross-linked chitosan-based hydrogels for tissue engineering applications: A state-of-the-art review. Eur Polym 145: 110176.

Plieva FM, Karlsson M, Aguilar MR, et al., 2006. Pore structure of macroporous monolithic cryogels prepared from poly(vinyl alcohol). J Appl Polym 100: 1057-1066.

Takigami M, Amada H, Nagasawa N. Preparation and properties of CMC gel. in Joint Symposia of the Materials-Research-Society-of-Japan. 2006. Nihon Univ, Tokyo, JAPAN.

Zhao Q, Ji Q, Xing K, et al., 2009. Preparation and characteristics of novel porous hydrogel films based on chitosan and glycerophosphate. Carbohyd Polym 76: 410-416.

Chung HJ, Park TG, et al., 2009. Self-assembled and nanostructured hydrogels for drug delivery and tissue engineering. Nano Today 4: 429-437.

Zhuang Y, Yu F, Ma J, et al., 2017. Enhanced adsorption removal of antibiotics from aqueous solutions by modified alginate/graphene double network porous hydrogel. J Colloid Interface Sci 507: 250-259.

Li B, Wang Y, Wang Z, et al., 2021b. Preparation and Properties of Hydrogels Based on Lignosulfonate and Its Efficiency of Drug Delivery. Chemistryselect 6: 8213-8218.

Porfiryeva NN, Zlotver I, Pinhas MD, et al., 2024. Mucus-Mimicking Mucin-Based Hydrogels By Tandem Chemical And Physical Crosslinking. Macromol biosci 21: e2400028-e2400028.

Morandim-Giannetti AdA, Rubio SR, Nogueira RF, et al., 2018. Characterization of PVA/glutaraldehyde hydrogels obtained using Central Composite Rotatable Design (CCRD). J Biomed Mater Res B Appl Biomater 106: 1558-1566.

Mugnaini G, Gelli R, Mori L, et al., 2023. How to Cross-Link Gelatin: The Effect of Glutaraldehyde and Glyceraldehyde on the Hydrogel Properties. ACS Appl Polym Mater 5: 9192-9202.

Kang M, Cheng Y, Hu Y, et al., 2023. Self-healing poly(acrylic acid) hydrogels fabricated by hydrogen bonding and Fe3+ ion cross-linking for cartilage tissue engineering. Front Mater Sci 17: 230655

Salleh KM, Zakaria S, Sajab MS, et al., 2018. Chemically crosslinked hydrogel and its driving force towards superabsorbent behaviour. Int J Biol Macromol 118: 1422-1430.

Vaid KV, Nikhil ND, Jindal R, et al., 2022. Microwave-Assisted Synthesis of Guar-Gum and Carboxymethyl Cellulose-Based Hydrogel for Efficient Removal of Crystal Violet and Brilliant Green Dyes. Chemistryselect 7: e202203138.

Boyer C, Rethore G, Weiss P, et al., 2020. A Self-Setting Hydrogel of Silylated Chitosan and Cellulose for the Repair of Osteochondral Defects: From in vitro Characterization to Preclinical Evaluation in Dogs. Front Bioeng Biotechnol 8: 23.

Da Silva Xavier AA, Da Rosa PP, Mackmill LdB, et al., 2021. An assessment of the effectiveness of hyaluronic acid and polyacrylamide hydrogel in horses with osteoarthritis: Systematic review and network meta-analysis. Res Vet Sci 134: 42-50.

Williams DL, Wirostko BM, Gum G, et al., 2017. Topical Cross-Linked HA-Based Hydrogel Accelerates Closure of Corneal Epithelial Defects and Repair of Stromal Ulceration in Companion Animals. Invest Ophthalmol Vis Sci 58: 4616-4622.

Kim J, Kim D, Shin D, et al., 2023. Effect of temperature-responsive hydrogel on femoral and sciatic nerve blocks using bupivacaine in Beagle dogs. Vet Med Sci 9: 91-97.

Santiago MG, Da Silva CD, Souza BM, et al., 2023. Topical hydrophilic gel with itraconazole-loaded polymeric nanomicelles improves wound healing in the treatment of feline sporotrichosis. Int J Pharm 634: 122619.

Brumberg V, Astrelina T, Malivanova T, et al., 2021. Modern Wound Dressings: Hydrogel Dressings. Biomedicines 9: 1235.

Choi C, Linder T, Kirby A, et al., 2021. Use of a tilapia skin xenograft for management of a large bite wound in a dog. Can Vet J 62: 1071-1076.

Zeng Q, Qi X, Shi G, et al., 2022. Wound Dressing: From Nanomaterials to Diagnostic Dressings and Healing Evaluations. Acs Nano 16: 1708-1733.

Yang M, Fei X, Tian J, et al., 2022. A starch-regulated adhesive hydrogel dressing with controllable separation properties for painless dressing change. J Mater Chem B 10: 6026-6037.

Hu T, Wu G-P, Bu H, et al., 2022. An injectable, adhesive, and self-healable composite hydrogel wound dressing with excellent antibacterial activity. Chem Eng J 450: 138201.

Labouta HI, Schneider M, et al., 2013. Interaction of inorganic nanoparticles with the skin barrier: current status and critical review. Nanomedicine 9: 39-54.

Zhi D, Yang T, Zhang T, et al., 2021. Microneedles for gene and drug delivery in skin cancer therapy. J Control Release 335: 158-177.

Li X, Zhao Z, Zhang M, et al., 2022b. Research progress of microneedles in the treatment of melanoma. J Control Release 348: 631-647.

Katiraee F, Kosari YK, Soltani M, et al., 2021. Molecular identification and antifungal susceptibility patterns of dermatophytes isolated from companion animals with clinical symptoms of dermatophytosis. J Vet Res 65: 175-182.

Moriello KA, Coyner K, Paterson S, et al., 2017. Diagnosis and treatment of dermatophytosis in dogs and cats. Clinical Consensus Guidelines of the World Association for Veterinary Dermatology. Vet Dermatol 28: 266-e268.

Li XR, Chen AQ, Liu Y, et al., 2023. Preparation and rectal administration of hydroxybutyl chitosan/graphene oxide composite thermosensitive hydrogel. Reactive & Functional Polymers 189: DOI10.1016/j.reactfunctpolym.2023.105608.

Yoshida M, Kamei N, Muto K, et al., 2017. Complexation hydrogels as potential carriers in oral vaccine delivery systems. Eur J Pharm Biopharm 112: 138-142.

Qi X, Yuan Y, Zhang J, et al., 2018. Oral Administration of Salecan-Based Hydrogels for Controlled Insulin Delivery. J Agric Food Chem 66: 10479-10489.

Ullah I, Farooq AS, Naz I, et al., 2023. Fabrication of Polymeric Hydrogels Containing Esomeprazole for Oral Delivery: In Vitro and In Vivo Pharmacokinetic Characterization. Polymers (Basel) 15: 1798.

Wang D, Wang W, Wang P, et al., 2023. Research progress of colon-targeted oral hydrogel system based on natural polysaccharides. Int J Pharm 643: 123222.

Bjarnason I, Scarpignato C, Holmgren E, et al., 2018. Mechanisms of Damage to the Gastrointestinal Tract From Nonsteroidal Anti-Inflammatory Drugs. Gastroenterology 154: 500-514.

Malkani R, Paramasivam S, Wolfensohn S, et al., 2024. How does chronic pain impact the lives of dogs: an investigation of factors that are associated with pain using the Animal Welfare Assessment Grid. Front Vet Sci 11: 1374858.

Pareek A, Maheshwari S, Cherlo S, et al., 2017. Modeling drug release through stimuli responsive polymer hydrogels. International Journal of Pharmaceutics 532: 502-510.

Langer R, Vacanti JP, et al., 1993. Tissue engineering. Science 260: 920-926.

Gomez-Florit M, Pardo A, Domingues RMA, et al., 2020. Natural-Based Hydrogels for Tissue Engineering Applications. Molecules 25: 5858.

Brehm W, Burk J, Delling U, et al., 2012. Stem cell-based tissue engineering in veterinary orthopaedics. Cell Tissue Res 347: 677-688.

Nantavisai S, Egusa H, Osathanon T, et al., 2019. Mesenchymal stem cell-based bone tissue engineering for veterinary practice. Heliyon 5: e02808.

Purbantoro SD, Taephatthanasagon T, Purwaningrum M, et al., 2024. Trends of regenerative tissue engineering for oral and maxillofacial reconstruction in veterinary medicine. Front Vet Sci 11: 1325559.

Talebian S, Mehrali M, Taebnia N, et al., 2019. Self-Healing Hydrogels: The Next Paradigm Shift in Tissue Engineering? Adv Sci 6: 1801664.

Zhao Y, Song S, Ren X, et al., 2022. Supramolecular Adhesive Hydrogels for Tissue Engineering Applications. Chem Rev 122: 5604-5640.

Tanongpitchayes K, Randorn C, Lamkhao S, et al., 2022. Effectiveness of a Nanohydroxyapatite-Based Hydrogel on Alveolar Bone Regeneration in Post-Extraction Sockets of Dogs with Naturally Occurring Periodontitis. Vet Sci 9: 7.

Might KR, Martinez SA, Karin N, et al., 2016. The effect of lysophosphatidic acid using a hydrogel or collagen sponge carrier on bone healing in dogs. Vet Comp Orthop Traumatol 29: 306-313.

Hong F, Qiu P, Wang Y, et al., 2024. Chitosan-based hydrogels: From preparation to applications, a review. Food Chem X 21: 101095.

Fiorica C, Palumbo FS, Pitarresi G, et al., 2021. Ciprofloxacin releasing gellan gum/polydopamine based hydrogels with near infrared activated photothermal properties. Int J Pharm 610: 121231.

Andreazza R, Morales A, Pieniz S, et al., 2023. Gelatin-Based Hydrogels: Potential Biomaterials for Remediation. Polymers 15: 1026.

Crespo-Cuevas V, Ferguson VL, Vernerey F, et al., 2023. Poroviscoelasto-plasticity of agarose-based hydrogels. Soft Matter 19: 790-806.

Xu Q, Torres JE, Hakim M, et al., 2021. Collagen- and hyaluronic acid-based hydrogels and their biomedical applications. Mater Sci Eng R Rep 146: 100641.

Zainal SH, Mohd NH, Suhaili N, et al., 2021. Preparation of cellulose-based hydrogel: a review. Journal of Materials Research and Technology-Jmr&T 10: 935-952.

Tomic SL, Babic Radic MM, Vukovic JS, et al., 2023. Alginate-Based Hydrogels and Scaffolds for Biomedical Applications. Mar Drugs 21: 177.

Yang J, Shen MH, et al., 2006. Polyethylene glycol-mediated cell fusion. Methods Mol Biol 325: 59-66.

Zhao WY, Xiong HY, Yuan Q, et al., 2011. In vitro effects of polyethylene glycol in University of Wisconsin preservation solution on human red blood cell aggregation and hemorheology. Clin Hemorheol Microcirc 47: 177-185.

Aslam M, Kalyar MA, Raza ZA, et al., 2018. Polyvinyl alcohol: A review of research status and use of polyvinyl alcohol based nanocomposites. Polymer Engineering and Science 58: 2119-2132.

Awasthi S, Gaur JK, Bobji MS, et al., 2022. Nanoparticle-reinforced polyacrylamide hydrogel composites for clinical applications: a review. Journal of Materials Science 57: 8041-8063.

More N, Avhad M, Utekar S, et al., 2023. Polylactic acid (PLA) membrane-significance, synthesis, and applications: a review. Polymer Bulletin 80: 1117-1153.

Su Y, Zhang B, Sun R, et al., 2021. PLGA-based biodegradable microspheres in drug delivery: recent advances in research and application. Drug Deliv 28: 1397-1418.

Luo Y, Hong Y, Shen L, et al., 2021. Multifunctional Role of Polyvinylpyrrolidone in Pharmaceutical Formulations. AAPS PharmSciTech 22: 34.

Russo E, Villa C, et al., 2019. Poloxamer Hydrogels for Biomedical Applications. Pharmaceutics 11: 671.