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REVIEW ARTICLE

Natural Polymer-Based Microspheres for Anti-Inflammatory Drug Delivery: Materials, Characterization, and Therapeutic Applications

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SUMMARY

Microsphere-based drug delivery systems have gained considerable attention in pharmaceutical research due to their ability to provide controlled, targeted, and sustained release of therapeutic agents while minimizing systemic side effects. In particular, microspheres formulated from natural polymers such as chitosan, sodium alginate, pectin, and gelatin have emerged as promising carriers for anti-inflammatory therapy owing to their biocompatibility, biodegradability, low toxicity, and responsiveness to physiological stimuli. This review comprehensively discusses the role of natural polymer-based microspheres in inflammatory drug delivery, focusing on polymer characteristics, preparation methods, release and delivery mechanisms, and routes of administration. Their anti-inflammatory performance is summarized across in vitro models, mainly lipopolysaccharide-stimulated macrophages and chondrocytes challenged with cytokines or oxidative stress, and in vivo models, mainly carrageenan-induced paw edema, experimental arthritis/osteoarthritis, tendinopathy, and wound-healing models, whereas disease-specific osteoarthritis models such as monosodium iodoacetate-induced osteoarthritis have rarely been used. Preclinical evidence, which is still dominated by in vitro studies, suggests that these systems are capable of enhancing drug stability, prolonging residence time at the inflamed site, modulating inflammatory mediators such as TNF-α, IL-1β, and IL-6, and improving overall therapeutic efficacy compared with free drugs. Despite these advantages, challenges related to polymer variability, mechanical stability, release precision, and large-scale production remain. In addition, head-to-head comparisons between polymers under matched conditions and standardized, disease-specific in vivo models are still lacking. Future advancements in polymer modification, hybrid polymer systems, and advanced fabrication technologies are expected to further optimize natural polymer-based microspheres, supporting their potential application in personalized and long-term inflammatory therapy.

Keywords: *Microspheres, natural polymer, inflammation*

Antiinflamatuar İlaçların Taşınması İçin Doğal Polimer Bazlı Mikroküreler: Malzemeler, Karakterizasyon ve Terapötik Uygulamalar

ÖZ

Mikroküre tabanlı ilaç taşıma sistemleri, terapötik ajanların kontrollü, hedefe yönelik ve uzun süreli salımını sağlarken sistemik yan etkileri en aza indirme yetenekleri nedeniyle farmasötik araştırmalarda önemli ölçüde ilgi görmüştür. Özellikle kitosan, sodyum aljinat, pektin ve jelatin gibi doğal polimerlerden formüle edilen mikroküreler; biyouyumlulukları, biyobozunurlukları, düşük toksisiteleri ve fizyolojik uyaranlara duyarlılıkları sayesinde anti-inflamatuvar tedavi için umut verici taşıyıcılar olarak öne çıkmaktadır. Bu derleme, doğal polimer bazlı mikrokürelerin inflamatuvar ilaç taşınmasındaki rolünü kapsamlı bir şekilde ele almakta; polimer özellikleri, hazırlama yöntemleri, salım ve taşıma mekanizmaları ile uygulama yollarına odaklanmaktadır. Antiinflamatuvar performansları, başlıca lipopolisakkarit (LPS) ile uyarılmış makrofajlar ile sitokin veya oksidatif stresle uyarılmış kondrositlerden oluşan in vitro modeller ve başlıca karragenan kaynaklı ayak ödemi, deneysel artrit/osteoartrit, tendinopati ve yara iyileşmesi modellerinden oluşan in vivo modeller üzerinden özetlenmektedir; monosodyum iyodoasetat ile oluşturulan osteoartrit gibi hastalığa özgü modeller ise nadiren kullanılmıştır. Henüz büyük ölçüde in vitro çalışmalara dayanan preklinik bulgular, bu sistemlerin ilaç stabilitesini artırabildiğini, inflamasyon bölgesinde kalış süresini uzatabildiğini, TNF-α, IL-1β ve IL-6 gibi inflamatuvar mediyatörleri modüle edebildiğini ve serbest ilaçlara kıyasla genel terapötik etkinliği iyileştirdiğini düşündürmektedir. Bununla birlikte, polimer değişkenliği, mekanik stabilite, salım hassasiyeti ve büyük ölçekli üretimle ilgili zorluklar halen mevcuttur. Ayrıca, polimerlerin eşleştirilmiş koşullar altında doğrudan karşılaştırıldığı çalışmalar ve standartlaştırılmış, hastalığa özgü in vivo modeller hâlâ eksiktir. Gelecekte polimer modifikasyonu, hibrit polimer sistemleri ve gelişmiş üretim teknolojilerindeki ilerlemelerin, doğal polimer bazlı mikrokürelerin daha da optimize edilmesini sağlayarak kişiselleştirilmiş ve uzun dönemli inflamatuvar tedavilerde kullanım potansiyelini desteklemesi beklenmektedir.

Anahtar Kelimeler: *Mikroküreler, doğal polimerler, inflamasyon*

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INTRODUCTION

Microspheres are small spherical particles ranging from 1 to 1000 micrometers. They are widely used in the pharmaceutical field, especially as drug delivery systems designed to enhance therapeutic effectiveness and reduce side effects (Virmani & Gupta, 2017). Microsphere technology allows for controlled, targeted, and sustained drug release, enabling the concentration of drugs in the bloodstream to be maintained within the therapeutic range for a longer duration (Jain, 2000). The physical and chemical characteristics of microspheres, including particle size, porosity, and the kind of polymer employed, significantly influence the drug release profile of this system.

Microspheres are used not only as drug delivery systems but also in diagnostics, tissue engineering, and cell-based therapy, making them a promising technology for developing biomedical products. Several natural and synthetic polymers such as gelatin, chitosan, Poly(lactic-co-glycolic acid), and ethyl cellulose are used depending on the purpose, biodegradability, and biological compatibility. Owing to their flexibility and wide range of applications, microspheres remain a focus of research in modern drug delivery systems. Microspheres offer several advantages over conventional drug delivery systems, including controlled and targeted release, prolonged therapeutic effect, and reduced dosing frequency (Adepu & Ramakrishna, 2021). They protect unstable drugs from degradation, enhancing stability and bioavailability (Sinha & Trehan, 2005). Additionally, microspheres enable tissue-specific delivery, minimize side effects, improve patient compliance, and allow flexible release profiles like immediate, delayed, or sustained release.

Inflammation is a complex and tightly regulated biological response to tissue injury, infection, or harmful stimuli, characterized by vascular dilation, increased permeability, leukocyte recruitment, and the release of pro-inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), prostaglandins, and reactive oxygen species (Kumar, Abbas, Fausto, & Aster, 2010; Medzhitov, 2008). Recognition of pathogen- or damage-associated molecular patterns by pattern recognition receptors activates nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling, promoting the expression of inflammatory mediators, whereas resolution requires attenuation of these pathways and activation of pro-resolving mechanisms (Kumar et al., 2010; Medzhitov, 2008). Although acute inflammation is protective and self-limiting, persistent inflammation contributes to chronic disorders such as osteoarthritis, rheumatoid arthritis, inflammatory bowel disease, and chronic pulmonary diseases (Medzhitov, 2008). Effective treatment therefore requires maintaining therapeutic concentrations at inflamed tissues while minimizing systemic exposure and adverse effects (Hu, Wang, Zhang, & Kapilevich, 2023).

Microspheres offer a suitable drug delivery platform for inflammatory conditions because they can encapsulate and protect therapeutic agents from premature degradation while providing controlled, sustained, and potentially site-specific release (Adepu & Ramakrishna, 2021; Varde & Pack, 2004). Drug release from microspheres is governed by matrix characteristics and may occur through diffusion, polymer swelling, erosion or degradation, and, depending on the formulation, a combination of these mechanisms (Fu & Kao, 2010; Siepmann & Siepmann, 2008). Accordingly, release kinetics may follow zero-order, first-order, Higuchi, or other empirical models, depending on the dominant release mechanism and physicochemical properties of the matrix (Costa & Sousa Lobo, 2001; Higuchi, 1963; Ritger & Peppas, 1987). Natural polymers such as alginate, chitosan, gelatin, and pectin further support this approach because of their biocompatibility, biodegradability, low toxicity, and ability to undergo environmentally responsive swelling, degradation, or ionic interactions (Dash, Chiellini, Ottenbrite, & Chiellini, 2011; Lee & Mooney, 2012; Munarin, Tanzi, & Petrini, 2012;

Young, Wong, Tabata, & Mikos, 2005). These properties can prolong drug residence at the target site and modulate release rates, thereby potentially reducing dosing frequency and systemic toxicity (Agnihotri, Mallikarjuna, & Aminabhavi, 2004; Hu et al., 2023). Thus, natural polymer-based microspheres represent a rational platform for improving the therapeutic efficacy and safety of anti-inflammatory drug delivery (Hariyadi & Islam, 2020; Hu et al., 2023; Lee & Mooney, 2012).

Compared with synthetic polymers, natural polymers additionally offer a high capacity for bioactive loading and bioadhesive interaction with the mucosa, which enhances the absorption efficiency of anti-inflammatory drugs at the target site (Dutta, Dutta, & Tripathi, 2004), while some natural polymers further contribute an intrinsic anti-inflammatory activity that acts synergistically with the carried drug (Sinha & Kumria, 2001).

LITERATURE SEARCH STRATEGY

This narrative review was based on a literature search of PubMed, ScienceDirect, Scopus, and Google Scholar for articles published between 2000 and 2026, supplemented by seminal earlier publications and textbooks on inflammation biology and drug-release theory identified from the reference lists of the retrieved articles. The search combined the following keywords using Boolean operators: ("microsphere*" OR "microparticle*" OR "microbead*") AND ("chitosan" OR "alginate" OR "pectin" OR "gelatin" OR "natural polymer*") AND ("anti-inflammatory" OR "inflammation" OR "osteoarthritis" OR "arthritis" OR "controlled release").

Studies were included if they (i) described microspheres or microparticles prepared predominantly from chitosan, alginate, pectin, or gelatin; (ii) reported at least one physicochemical characteristic (particle size, morphology, drug loading (DL), encapsulation efficiency (EE), or release profile) and/or an anti-inflammatory outcome *in vitro* or *in vivo*; and (iii) were published in English or, for selected formulation studies in Indonesian pharmaceutical journals, in Indonesian with an English abstract. Studies were excluded if they concerned nanoparticles without a microsphere component, used a synthetic polymer as the main matrix (except for the natural–synthetic comparison in Table 7.), were conference abstracts without full text, or did not report extractable formulation or efficacy data. Titles and abstracts were screened first, followed by full-text assessment, and the relevant data were extracted into Tables 1–6.

TYPES OF NATURAL POLYMERS FOR MICROSPHERES IN PHARMACEUTICAL APPLICATIONS

Chitosan

Chitosan is a natural polysaccharide composed of repeating units of β-(1→4)-D-glucosamine and N-acetyl-D-glucosamine, obtained through the partial deacetylation of chitin. Its structure is characterized by the presence of free amino groups ($–NH_2$) on the glucosamine units, which distinguish chitosan from chitin and confer a unique cationic nature under acidic conditions due to protonation to $–NH_3^+$. The degree of deacetylation (DD) and molecular weight are the key structural parameters that govern the physicochemical properties of chitosan, including solubility, viscosity, surface charge density, and interaction capability with other molecules. The amino and hydroxyl functional groups along the chitosan backbone enable extensive hydrogen bonding, electrostatic interactions, and crosslinking with oppositely charged agents or polymers. This structural versatility imparts chitosan with strong bioadhesive properties, chemical modifiability, and the ability to form three-dimensional polymeric networks, making it highly suitable as a matrix material for various drug delivery systems, particularly natural polymer-based microspheres (Dash et al., 2011; Rinaudo, 2006).

Chitosan exhibits notable stability, making it a highly promising natural polymer for microsphere-based drug delivery systems. One of its key advantages lies in its ability to form stable polymeric

matrices under a wide range of physical and chemical conditions. Chitosan can maintain structural integrity at physiological pH, particularly in acidic to neutral environments, which renders it suitable for both oral and localized drug delivery applications (Rinaudo, 2006). Its relatively high thermal stability also allows formulation processes to be conducted without significant degradation of the polymer backbone. Moreover, the inherent ability of chitosan to spontaneously form films and hydrogels enhances its capacity to protect encapsulated drugs from premature degradation caused by enzymatic activity or harsh gastrointestinal conditions (Dash et al., 2011). Consequently, the stability of chitosan within microsphere systems not only prolongs drug release but also improves the shelf life of the formulation, supporting its suitability for long-term pharmaceutical use.

Beyond stability, chitosan plays a pivotal role in microsphere formation due to its cationic nature, arising from protonated amino groups ($-NH_3^+$) along the polymer backbone that enable strong electrostatic interactions with anionic crosslinkers and negatively charged drug molecules. Microsphere characteristics are strongly influenced by intrinsic chitosan properties, including degree of deacetylation, molecular weight, solution pH, and the type and concentration of crosslinking agents, all of which govern polymer chain entanglement and network density. Common fabrication methods for chitosan-based microspheres include ionic gelation with sodium tripolyphosphate (TPP), emulsification–crosslinking using agents such as glutaraldehyde or genipin, spray drying, and polyelectrolyte complexation with anionic polymers such as alginate or pectin. From a characterization perspective, increasing chitosan concentration or molecular weight generally increases solution viscosity, resulting in larger droplet formation during emulsification or atomization and yielding microspheres with increased particle size and more spherical, compact morphology. Strong polymer–drug electrostatic interactions contribute to high EE and improved DL, particularly for hydrophilic or negatively charged compounds. Furthermore, the dense yet swellable chitosan matrix supports controlled and sustained drug release through diffusion, polymer relaxation, and gradual biodegradation. Owing to its biocompatibility, biodegradability, and intrinsic bioadhesive and immunomodulatory properties, chitosan-based microspheres have been extensively validated as effective carriers for pharmaceutical applications, including controlled drug delivery systems for chronic inflammatory therapy (Agnihotri et al., 2004; Dash et al., 2011; Rinaudo, 2006).

Table 1. Chitosan microspheres characterization

No	Polymer	Active pharmaceutical ingredient	Preparation method	Particle size	Drug loading (DL)	Encapsulation efficiency (EE)	Reference
1	Chitosan-Alginate	Quercetin	Complex coacervation	Not reported	Not reported	>80%	Frent et al., 2022
2	Chitosan-Carrageenan	Retinol (vitamin A), L-ascorbic acid (vitamin C), and α-tocopherol (vitamin E)	W/O emulsion	50–70 μm	Not reported	Not reported	Lewicka et al., 2021
3	Chitosan	Methyl orange	Microfluidic	440 μm	Not reported	Not reported	Zhai, Bai, Zhu, Wang, & Luo, 2018

Sodium alginate

Sodium alginate is a natural polysaccharide-based polymer extracted from the cell walls of brown algae, widely utilized in microsphere formulations due to its physicochemical properties that enhance the stability and efficiency of drug delivery systems. One of the key advantages of sodium alginate lies in its ability to form ionic gels through interactions with divalent cations,

particularly calcium (Ca^{2+}), enabling the formation of microspheres with controlled morphology and particle size (Lee & Mooney, 2012). Alginate, particularly in the form of sodium alginate, is a natural polymer that plays a critical role in microsphere formation due to its anionic polysaccharide nature, which enables rapid hydrogel network formation through ionic crosslinking with divalent cations, especially Ca^{2+}. This gelation mechanism is commonly referred to as the *egg-box* model, in which specific interactions between guluronate blocks (G-blocks) and calcium ions generate a stable three-dimensional matrix. The gelation characteristics of alginate—including polymer concentration, solution viscosity, type and concentration of cations, and curing time—directly influence droplet formation and the densification of microsphere structures. Consequently, alginate is widely processed using methods such as ionotropic gelation (external gelation via dripping, aerosolization, or prilling), emulsification–gelation, spray drying, and electrospraying, each offering different levels of control over particle size and homogeneity. Among these, ionotropic gelation is the most commonly applied technique because it operates under mild conditions, avoids the use of organic solvents, and is suitable for sensitive bioactive compounds, making alginate highly compatible for microsphere-based pharmaceutical and biomedical drug delivery systems (Hariyadi & Islam, 2020; Lee & Mooney, 2012).

From a characterization perspective, alginate plays a crucial role in determining particle size, morphology, EE, DL capacity, and release profile. Increasing alginate concentration generally increases solution viscosity, which can influence droplet formation and consequently particle size during microsphere preparation. The physicochemical properties of alginate, including molecular weight, composition, and crosslinking conditions, also affect the structural characteristics and performance of alginate-based delivery systems (Lee & Mooney, 2012).

Crosslinking density is another important determinant of microsphere structure and drug release. Increasing Ca^{2+} concentration or extending gelation can produce a more highly crosslinked alginate network, which may restrict molecular diffusion and thereby modify drug retention and release kinetics (Lee & Mooney, 2012). However, the effects on EE and DL are formulation-dependent and should therefore be interpreted according to the specific drug–polymer system rather than generalized across all alginate microspheres.

The dense and hydrophilic alginate network can support controlled drug release through diffusion and matrix-related relaxation processes. For example, diclofenac sodium-loaded alginate microspheres incorporated into a thermosensitive chitosan hydrogel demonstrated sustained drug release for up to 5 days in vitro, with the combined system showing enhanced anti-inflammatory efficacy in a rabbit model of experimental rheumatoid arthritis (Qi et al., 2016).

In the context of inflammatory therapy, alginate is attractive because of its biocompatibility and established utility in drug-delivery and tissue-engineering applications (Lee & Mooney, 2012). In addition, alginate-based composite microcapsules have been investigated for wound-healing applications, including systems capable of sustained delivery of bioactive agents such as vascular endothelial growth factor (VEGF) (Yang, Ding, Yang, Shang, & Zhao, 2023).

Thus, alginate functions not only as a microsphere-forming matrix but also as an important determinant of the physicochemical and release characteristics of drug-delivery systems (Lee & Mooney, 2012; Qi et al., 2016).

Table 2. Alginate microspheres characterization

No	Polymer	Active pharmaceutical ingredient	Preparation method	Particle size	Drug loading (DL)	Encapsulation efficiency (EE)	Reference
1	Alginate	Aceclofenac	Ionotropic gelation	600–1200 µm	Not reported	86–97%	Prasad, Setty, Gupta, Devanna, & Rama Devi, 2011
2	Alginate	Ovalbumin (protein)	Ionic aerosolization ($CaCl_2$)	12–22 µm	Not reported	53–63%	Utama, Hendradi, & Hariyadi, 2013
3	Alginate	Metformin HCl	Ionic aerosolization	1.82–2.97 µm	5.09–15.09%	30.53–48.35%	Hariyadi, Rosita, & Rosadi, 2019
4	Alginate	Quercetin	Aerosolization + Ca^{2+} crosslinking	<2 µm	<6%	74–93%	Kalalo et al., 2022
5	Alginate	Quercetin	Ionotropic gelation	~200 µm	Not reported	82.71 ± 4.11%	Chen, Wu, Wu, & Jiao, 2025
6	Alginate	None (blank microspheres)	Emulsion method	<65.88 µm	Not reported	Not reported	Uyen, Hamid, Tram, & Ahmad, 2020

Pectin

Pectin is a natural polysaccharide that has been widely utilized as a polymer matrix for microspheres in drug delivery systems due to its structural features and physicochemical properties that support the formation of controlled-release systems. Structurally, pectin is mainly composed of linear chains of α-(1→4)-D-galacturonic acid with varying degrees of esterification, which determine its gelation behavior and molecular weight; the molecular weight of pectin generally ranges from several tens to hundreds of kilodaltons, depending on its source and extraction method. Pectin is derived from plant cell walls, particularly citrus peels and apple pomace, and is therefore biodegradable, biocompatible, and safe for pharmaceutical applications. One of the major advantages of pectin is its ability to form gels via an ionotropic gelation mechanism in the presence of divalent cations such as Ca^{2+}, enabling microsphere formation under mild conditions without the use of organic solvents or high temperatures. In addition, pectin is hydrophilic and bioresponsive to pH changes as well as enzymatic degradation by colonic microflora, making it highly suitable for targeted drug delivery systems, particularly for drug release in the colon. Numerous studies have demonstrated that pectin-based microspheres can provide controlled drug release profiles, enhance the stability of encapsulated active compounds, and reduce the risk of irritation and systemic toxicity, positioning pectin as a promising and sustainable natural polymer for the development of microspheres in pharmaceutical and biomedical applications (Munarin et al., 2012).

As a natural polymer, pectin also exerts a significant influence on the characterization of microspheres, including particle size, morphology, EE, DL, and release behavior. Pectin concentration and degree of esterification are key factors governing solution viscosity and gelation capacity; increasing pectin concentration generally leads to the formation of larger droplets during microsphere preparation, thereby increasing particle size. From a morphological perspective, pectin is capable of forming microspheres with relatively spherical shapes and smooth surfaces, particularly when ionotropic gelation with Ca^{2+} occurs rapidly and uniformly, whereas imbalances in the pectin-to-cation ratio or suboptimal drying conditions may result in porous surfaces and less homogeneous structures. Ionic interactions between the carboxyl groups of pectin and divalent cations produce a compact gel matrix, contributing to relatively high EE by limiting drug diffusion out of the microspheres during gelation, although DL remains dependent on the drug-to-polymer ratio and drug solubility within the hydrophilic pectin matrix. In terms of release behavior, pectin-based microspheres typically exhibit

controlled to sustained drug release profiles governed by diffusion and enzymatic degradation mediated by colonic microflora, which is particularly advantageous for colon-targeted drug delivery. Commonly employed methods for preparing pectin microspheres include ionotropic gelation (using $CaCl_2$), emulsification–gelation, spray drying, and combinations of pectin with other polymers such as chitosan or alginate to enhance structural stability and release control (Liu, Fishman, Kost, & Hicks, 2003; Munarin et al., 2012). Pectin plays an important role in inflammatory drug delivery owing to its biocompatibility, pH responsiveness, and susceptibility to enzymatic degradation by colonic microflora, enabling controlled and site-specific drug release at inflamed tissues. For example, Ramasamy, Ruttala, Shanmugam, and Umadevi (2013) demonstrated that Eudragit-coated pectin microspheres loaded with aceclofenac achieved colon-targeted delivery and produced significant anti-inflammatory effects in arthritis models, confirming their suitability for chronic inflammation management. In another study, Jing et al. (2023) reported that pectin–oligochitosan–based microspheres for quercetin delivery markedly reduced inflammatory mediators and alleviated colitis symptoms in vivo, highlighting the effectiveness of pectin-based systems for targeted inflammatory therapy.

Table 3. Pectin microspheres characterization

No	Polymer	Active pharmaceutical ingredient	Preparation method	Particle size	Drug loading (DL)	Encapsulation efficiency (EE)	Reference
1	LM Pectin	Sulfasalazine	Ionotropic gelation (Ca^{2+})	200–800 µm	Not reported	65–82%	Costas, Pera, Gómez López, Mechetti, & Castro, 2012
2	LM pectin–alginate	Repaglinide	Dual ionic crosslinking (Ca^{2+})	150–400 µm	Not reported	70–85%	Awasthi et al., 2017
3	Amidated pectin ± PAA, PVP, PEG, or aristoflex	5-Aminosalicylate	Ionotropic gelation (Ca^{2+})	820–1830 µm (dry: 820–1030; wet: 1470–1830)	Not reported	Not reported	Wójcik-Pastuszka, Potempa, & Musiał, 2020
4	Pectin–chitosan (coated)	5-Aminosalicylate	Ionotropic gelation + polyelectrolyte coating	300–600 µm	Not reported	>80%	Ribeiro et al., 2014
5	LM & HM pectin	Ellagic acid–lysine salt (EALYS)	Ionic gelation + solvent casting (microgel/film)	Not reported	10% (w/w)	Not reported*	Ortenzi et al., 2021
6	LM amidated pectin	Anthocyanins (Hibiscus sabdariffa extract)	Double emulsion + ionotropic gelation (Ca^{2+}): dripping-extrusion or atomization	D50 78–1100 µm	Not reported	67.9–93.9%	Moura, Berling, Germer, Alvim, & Hubinger, 2018

*Ortenzi et al. (2021) reported a release of approximately 50–60% rather than EE. LM, low-methoxyl; HM, high-methoxyl; PAA, poly(acrylic acid); PVP, polyvinylpyrrolidone; PEG, polyethylene glycol

Gelatin

Gelatin is a natural polymer obtained from the partial hydrolysis of collagen, the primary structural protein present in animal connective tissues such as bovine and porcine skin and bones (Gómez-Guillén, Giménez, López-Caballero, & Montero, 2011). Structurally, gelatin is a linear polypeptide polymer with a molecular weight ranging from approximately 15 to 250 kDa. Its amino acid composition provides free carboxyl, amino, and hydroxyl groups that can participate in chemical interactions and crosslinking reactions (Gullapalli & Mazzitelli, 2017). Based on its

isoelectric point, gelatin is classified into type A (acid-processed) and type B (alkali-processed) gelatin, with differences in surface charge that significantly influence gelation behavior and drug–polymer interactions. The main advantages of gelatin as a microsphere-forming polymer include its excellent biocompatibility, biodegradability, non-toxicity, and ability to form gels and films under mild processing conditions, making it particularly suitable for the encapsulation of sensitive drugs and biomolecules. Furthermore, the structural similarity of gelatin to components of the extracellular matrix contributes to its favorable biological acceptance, supporting its extensive use in pharmaceutical and biomedical applications, including drug delivery and tissue engineering (Gómez-Guillén et al., 2011).

As a microsphere matrix, gelatin plays a crucial role in the formation of stable drug delivery carriers through fabrication methods such as emulsification–crosslinking, coacervation, and spray drying, often combined with crosslinking agents such as glutaraldehyde or genipin to improve mechanical stability and control degradation rates (Dinarvand, Mahmoodi, & Farboud, 2004). Gelatin concentration and molecular weight strongly influence microsphere characteristics; higher concentrations generally increase solution viscosity, resulting in larger particle sizes and more spherical morphologies with relatively smooth surfaces. Interactions between gelatin functional groups and encapsulated drugs contribute to favorable EE and DL, particularly for hydrophilic drugs and therapeutic biomolecules. In terms of release behavior, gelatin-based microspheres typically exhibit controlled to sustained drug release profiles governed by diffusion, matrix swelling, and enzymatic degradation of the gelatin network. These properties render gelatin especially suitable for inflammatory drug delivery, as they enable prolonged local drug retention, reduced dosing frequency, and minimized systemic exposure. Several studies have demonstrated that gelatin-based microspheres loaded with anti-inflammatory agents or bioactive proteins effectively suppress inflammatory mediators and promote tissue repair in inflammatory models, highlighting that gelatin functions not only as a passive carrier but also as a functional polymer that enhances the therapeutic performance of microsphere-based systems for chronic inflammatory conditions (Jin et al., 2022; Mao et al., 2024).

Table 4. Gelatin microspheres characterization

No	Polymer	Active pharmaceutical ingredient	Preparation method	Particle size	Drug loading (DL)	Encapsulation efficiency (EE)	Reference
1	Gelatin	Diclofenac sodium	Emulsification/ crosslinking	37–46 μm	9.8–26.7% (w/w)	EE 88.4–91.6%; encapsulation 81.3–88.7%	Saravanan, Bhaskar, Maharajan, & Pillai, 2011
2	Gelatin	Diclofenac sodium	Emulsification + glutaraldehyde crosslinking	67.8 μm	23.4%	93.6%*	Karthikeyan et al., 2012
3	Gelatin (glutaraldehyde-crosslinked)	Lactic acid	Water-in-oil emulsion + glutaraldehyde crosslinking	18–54 μm	23–63%	Not reported	Dinarvand et al., 2004

RELEASE MECHANISMS AND KINETICS OF NATURAL POLYMER MICROSPHERES

Drug release from natural polymer microspheres is governed by three principal and often concurrent mechanisms: diffusion of the dissolved drug through the hydrated polymer network, swelling and relaxation of the polymer chains, and erosion or degradation of the matrix (Fu & Kao, 2010; Siepmann & Siepmann, 2008). In diffusion-controlled systems, water penetrates the microsphere and dissolves the drug, which then diffuses out along its concentration gradient; the release rate is determined by particle size, ma-

trix density (degree of crosslinking), drug solubility, and drug–polymer interactions. Because the diffusion path length increases with particle radius, smaller microspheres with a larger specific surface area generally release their cargo faster than larger particles prepared from the same formulation (Siepmann & Siepmann, 2008; Varde & Pack, 2004).

Swelling-controlled release is particularly relevant to hydrophilic polysaccharide and protein matrices. On contact with aqueous media, chitosan, alginate, pectin, and gelatin networks absorb water and their chains relax, which enlarges the mesh size and progressively increases drug mobility; release is then governed by the relative rates of water penetration, chain relaxation, and drug diffusion (Siepmann & Siepmann, 2008). For ionically crosslinked alginate and low-methoxyl pectin microspheres, swelling depends strongly on the release medium: in phosphate-buffered saline or other media containing monovalent cations, the Ca^{2+} ions in the egg-box junctions are progressively exchanged for Na^{+} and sequestered by phosphate or citrate, which loosens the network and accelerates swelling, disintegration, and drug release, whereas the network remains comparatively compact under acidic conditions (Bajpai & Sharma, 2004; Lee & Mooney, 2012; Munarin et al., 2012). For chitosan, protonation of the amino groups at acidic pH increases swelling and drug release, while ionic or covalent crosslinking (e.g., with tripolyphosphate, glutaraldehyde, or genipin) restricts chain relaxation and slows release (Agnihotri et al., 2004).

Erosion- and degradation-controlled release occurs when the matrix itself is dissolved or cleaved. Gelatin microspheres are degraded by proteases such as collagenases and matrix metalloproteinases, so that the release of entrapped drugs and proteins can be coupled to the enzymatic activity of the surrounding tissue, and the degradation rate can be tuned through the type and degree of crosslinking (Park, Hart, Rolauffs, Stegemann, & Annamalai, 2020; Young et al., 2005). Chitosan is degraded mainly by lysozyme at a rate that depends on its degree of deacetylation (Dash et al., 2011), and pectin is depolymerized by the pectinolytic enzymes of the colonic microflora (Munarin et al., 2012; Sinha & Kumria, 2001). In contrast, ionically crosslinked alginate is not enzymatically degraded in mammals; its gels erode instead through the gradual loss of crosslinking cations described above (Lee & Mooney, 2012). In most natural polymer microspheres these processes overlap, and the dominant mechanism can shift during the course of release.

Many natural polymer microspheres also show an initial burst release, which arises from drug adsorbed on or located close to the particle surface and from rapid hydration of the outer matrix layer. A pronounced burst wastes part of the dose and transiently raises local drug concentrations; it is commonly reduced by increasing the crosslinking density, applying polyelectrolyte coatings (e.g., chitosan on alginate or pectin), or blending polymers (Huang & Brazel, 2001). To identify the dominant release mechanism, release data are usually fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models (Costa & Sousa Lobo, 2001; Higuchi, 1963). In the Korsmeyer–Peppas equation ($M_t/M\infty = kt^n$), the release exponent n indicates the transport mechanism; for spherical particles, $n \leq 0.43$ indicates Fickian diffusion, $0.43 < n < 0.85$ indicates anomalous (non-Fickian) transport combining diffusion and polymer relaxation, and $n \geq 0.85$ indicates case-II, relaxation- or erosion-controlled transport (Ritger & Peppas, 1987; Siepmann & Siepmann, 2008). Several of the studies summarized in Tables 1–5 describe release only qualitatively (e.g., "sustained" or "slow" release); reporting kinetic parameters together with the composition of the release medium would allow a more meaningful comparison between polymers.

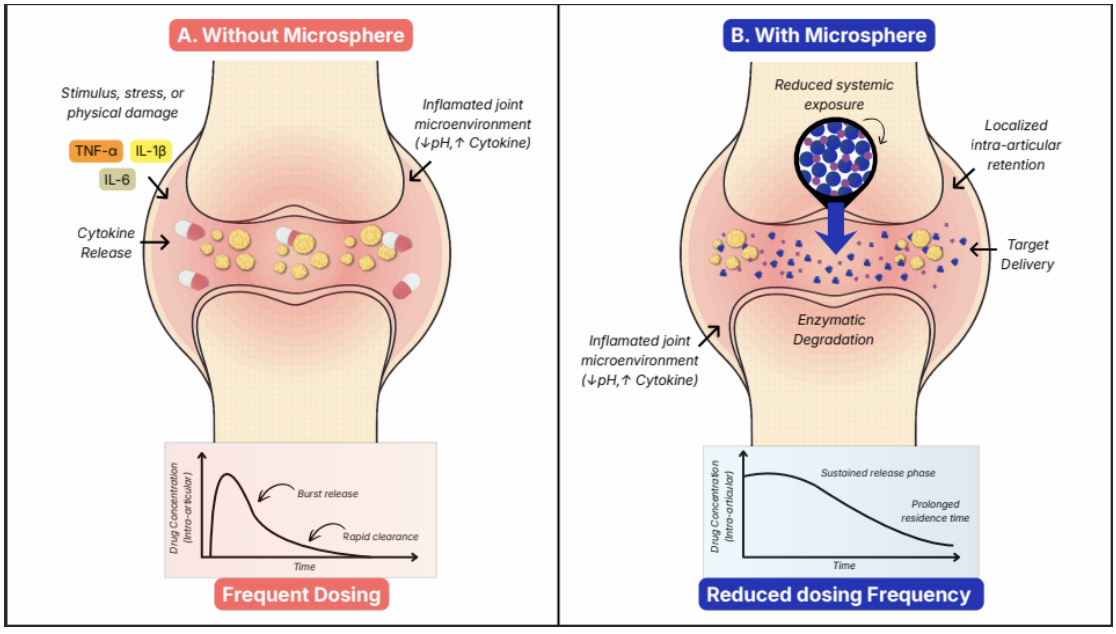

Figure 1. Schematic of microsphere-based drug delivery encapsulating an active compound, enabling controlled release, targeted delivery, and improved bioavailability for sustained anti-inflammatory therapy with reduced dosing frequency

The mechanistic advantages of natural polymer-based microspheres for anti-inflammatory delivery derive from the properties of the four polymers described above, namely sodium alginate, chitosan, gelatin, and pectin (Lee & Mooney, 2012; Li et al., 2018). These polymers can form gel-like matrices that encapsulate bioactive compounds, protect them from enzymatic or oxidative degradation, and enable sustained release at sites of inflammation (Vaidya, Jain, Agrawal, & Jain, 2015).

Many natural polymer systems are responsive to environmental stimuli, such as pH or enzymatic activity, which is particularly beneficial in inflamed tissues where such conditions are altered. This allows for site-specific drug release, improving therapeutic efficacy and reducing systemic side effects (Jing et al., 2023). Furthermore, several of these polymers possess mucoadhesive properties, which enhance drug residence time at the target site and promote absorption (Sahu, Jain, & Shukla, 2020).

For example, gelatin–polyvinyl alcohol microspheres have demonstrated controlled and sustained release of growth factors such as BMP-2 and VEGF, supporting osteogenic and angiogenic differentiation in tissue-regeneration applications (Platania, Loukelis, & Chatzinikolaidou, 2026). In another study, pectin/oligochitosan microspheres were developed for colon-specific controlled release of quercetin, with potential application in the treatment of inflammatory bowel disease (Jing et al., 2023).

MECHANISM OF ANTI-INFLAMMATORY ACTION

While the preceding section outlines how natural polymer-based microspheres control the release and delivery of therapeutic agents, it is equally important to distinguish this drug-delivery mechanism from the mechanism by which the encapsulated active agents actually exert their anti-inflammatory effects once released at the target site.

Many of the active agents loaded into natural polymer microspheres act by interrupting specific steps of the inflammatory cascade outlined in the Introduction. Non-steroidal anti-inflammatory drugs such

as diclofenac and aceclofenac inhibit cyclooxygenase (COX-1/COX-2) enzymes, thereby suppressing prostaglandin E2 (PGE2) synthesis and reducing the pain, swelling, and vasodilation associated with acute inflammation; diclofenac inhibits COX-mediated prostaglandin production directly, while aceclofenac is enzymatically converted into diclofenac and 4′-hydroxydiclofenac, its active cyclooxygenase-inhibiting metabolites (Gan, 2010; Yamazaki et al., 1997). Polyphenolic compounds such as curcumin and quercetin act through a different route: curcumin has been reported to suppress activation of the nuclear factor-κB (NF-κB) signaling pathway and downstream mitogen-activated protein kinase (MAPK) cascades, reducing the transcription and release of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, and lowering inducible nitric oxide synthase (iNOS) and COX-2 expression (Hewlings & Kalman, 2017; Shishodia, 2013); quercetin modulates similar NF-κB and MAPK-related pathways, reducing the same panel of pro-inflammatory mediators (Li et al., 2016; Xu et al., 2025), and has additionally been shown to protect chondrocytes from IL-1β-induced apoptosis via inactivation of the p38 MAPK pathway, a mechanism directly relevant to osteoarthritis-related inflammation (Wang et al., 2021). These compounds additionally scavenge reactive oxygen species generated during the oxidative burst of activated macrophages and chondrocytes, limiting secondary tissue damage. Growth factors and cytokines delivered via microspheres act through yet another route. IL-4 and IL-13 can exert anti-inflammatory effects in cartilage, and IL-4 may also promote macrophage polarization toward a reparative M2 phenotype. In a microsphere-based delivery study, IL-4- and IL-13-loaded gelatin microspheres reduced nitric oxide production by activated chondrocytes by approximately 65–80% within three days, whereas IL-10-loaded microspheres produced only a marginal effect under the tested conditions (Park et al., 2020). Hepatocyte growth factor delivered via gelatin microspheres has similarly been reported to reduce inflammatory markers including iNOS and IL-1β in tenocyte-based inflammatory models (Han et al., 2024). Together, these agent-specific mechanisms shift the local tissue environment from a catabolic, pro-inflammatory state toward a pro-resolving one.

The polymeric matrix itself primarily functions as a delivery platform that protects the active agent from premature degradation, concentrates it at the inflamed site, and sustains its local concentration above the effective therapeutic threshold for a prolonged period; however, natural polymers should not necessarily be considered completely pharmacologically inert, since their molecular weight, purity, degree of chemical modification, and particulate form may themselves influence cellular and immune responses. The therapeutic benefit observed in the in vitro and in vivo studies summarized in Tables 5 and 6 therefore reflects the combined contribution of two distinct mechanisms: the material mechanism of the polymer matrix, which governs where and how fast the drug is released, and the pharmacological mechanism of the encapsulated agent, which determines which specific step of the inflammatory cascade is ultimately suppressed.

DELIVERY ROUTES FOR INFLAMMATORY THERAPY

Microspheres as drug delivery systems have been extensively developed for targeting inflammatory therapy via various administration routes, including oral, intravenous, intramuscular, and intra-articular routes. The oral route is the primary choice due to ease of administration and patient compliance, although it faces challenges such as enzymatic degradation and gastric pH that can reduce drug bioavailability (Sharma, Sharma, & Jain, 2016). Meanwhile, intravenous and intramuscular routes enable rapid and controlled drug distribution to target tissues but require invasive techniques and carry risks of systemic side effects (Bebarta et al., 2017). The intra-articular route has gained increasing attention, particularly for treating joint inflammation such as osteoarthritis and

rheumatoid arthritis, due to its ability to deliver drugs directly to the inflamed site at high concentrations while minimizing systemic exposure (Qi et al., 2016). Microspheres used for this route are often modified with natural polymers to enhance biocompatibility, stability, and controlled drug release within the joint space (Shaygani, Shamloo, Akbarnataj, & Maleki, 2024).

The choice of microsphere delivery route largely depends on the therapeutic objective and the characteristics of the targeted inflammatory disease. For instance, the inhalation route is utilized for respiratory inflammation, leveraging optimally sized microsphere particles for alveolar penetration and interaction with alveolar macrophages to improve therapeutic efficacy (Hagbani et al., 2022). Meanwhile, transdermal delivery using microspheres allows for sustained and controlled drug release through the skin, ideal for chronic inflammatory therapy by avoiding plasma concentration fluctuations (Abdallah et al., 2022). Recent studies also demonstrate that combining administration routes with natural polymer-based microspheres can enhance targeting specificity, reduce toxicity, and prolong the duration of anti-inflammatory drug action (M. Elmowafy et al., 2019). With advances in formulation technologies, appropriate selection of microsphere delivery routes increasingly enables more effective and safer personalized inflammatory therapy.

***In vivo* studies**

In vivo anti-inflammatory testing involves evaluating the efficacy of potential anti-inflammatory agents using living animal models to simulate physiological inflammatory responses. The primary aim of these tests is to assess the pharmacological activity, safety, and dosage of compounds under conditions that closely mimic human inflammation. Common methods include the carrageenan-induced paw edema test, which measures acute inflammation through paw swelling in rodents, and the cotton pellet-induced granuloma model, used for chronic inflammation assessment (Marroquín-Segura et al., 2009). Laboratory animals such as rats and mice are frequently employed due to their well-characterized immune systems and ease of handling (Kumar et al., 2010).

***In vitro* studies**

In vitro anti-inflammatory testing evaluates natural polymer-based microsphere formulations at the cellular level before animal studies, providing a controlled, reproducible, and cost-effective platform for screening candidate systems. Commonly used cell models include lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages, which mimic acute inflammatory activation, and chondrocytes exposed to reactive oxygen species or pro-inflammatory cytokines such as IL-1β, which better represent the oxidative and catabolic microenvironment of osteoarthritic joints. Inflammatory status in these models is typically assessed through pro-inflammatory cytokine expression (IL-1β, TNF-α, IL-6), nitric oxide (NO) production, and, in cartilage-focused studies, extracellular matrix markers such as collagen type II and matrix metalloproteinases. These in vitro assays allow direct comparison between free drug and microsphere-encapsulated formulations, demonstrating whether encapsulation enhances anti-inflammatory efficacy through sustained release or improved cellular uptake.

DISCUSSION

Table 1 through Table 6 collectively illustrate that the choice of natural polymer strongly influences microsphere performance, but with markedly different sets of advantages and constraints.

Chitosan-based microspheres benefit from an inherently cationic backbone, which supports mucoadhesion and electrostatic complexation with anionic drugs or polymers such as alginate (Agnihotri et al., 2004; Dash et al., 2011), and from a well-documented anti-inflammatory efficacy across both the *in vitro* (Table 6.) and *in vivo* (Table 5.) datasets summarized here. Its main limitation remains variable solubility across pH ranges and inconsistent molecular weight/deacetylation degree between commercial batches,

which affects the reproducibility of particle size and DL (Rampim et al., 2025; Rinaudo, 2006; Table 1.).

Sodium alginate offers the mildest, solvent-free fabrication route among the four polymers, relying on ionotropic gelation with divalent cations, which makes it particularly suitable for encapsulating sensitive biomolecules and for combination with other polymers such as chitosan (Table 2, Table 5, Table 6.). However, alginate microspheres are prone to burst release (Huang & Brazel, 2001) and can lose structural integrity in the presence of chelating agents or under mechanical loading in a joint space (Bajpai & Sharma, 2004; Lee & Mooney, 2012), limiting their standalone use for sustained intra-articular delivery.

Table 5. Natural polymer-based microspheres for anti-inflammatory drug delivery: *in vivo* studies

No	Polymer	Delivery system	Active agent	Preparation method	Characterization	Animal model	Results	Reference
1	Gelatin	Microspheres	Arbutin	Emulsification	Not reported	Mice	Reduced IL-1β and inhibited NF-κB	Jin et al., 2022
2	Gelatin methacrylate	Microspheres	Tendon-derived stem cells (TDSCs)	Microfluidic emulsification	Particle size: 188.38 μm	Rat	Promotes healing and regeneration of injured tendons by involving the RAS/ERK pathway	Mao et al., 2024
3	Chitosan Alginate	Microspheres	Diclofenac sodium	External gelation	Particle size: 10.744 ± 1.246 μm	Rabbit	Reduce edema	Qi et al., 2016
4	Alginate	Microspheres	*Phyllanthus amarus* and *P. muellerianus* extracts	Ionotropic gelation	Not reported	Rat	Reduce carrageenan-induced paw edema in rats	Adeyemi, Ajayi, & Ajala, 2024
5	Alginate Chitosan	Microspheres	Vascular endothelial growth factor (VEGF)	Ionotropic gelation	Particle size: ~200 μm Release: sustained release	Rat	Reducing IL-6 levels and decreasing inflammation caused by bacteria	Yang et al., 2023
6	Calcium alginate-Silk fibroin peptide-*Bletilla striata* polysaccharide (BSP)	Microspheres	Tannic acid	Reverse emulsion	Particle size: >10 μm Morphology: spherical Release: slow release	Mice	Reduce inflammatory cytokines	Wang, Tian, Cheng, Guang, & Xu, 2022
7	Gelatin	Microspheres	Puerarin	Emulsification cross-linking	Particle size: <5 μm Morphology: uniform in shape, free from clumping, and smooth-edged Release: sustained release	Mice	Reduce inflammation	Xin et al., 2025
8	Gelatin/Silk fibroin	Microspheres	Curcumin	Not reported	Not reported	Rat (MIA-induced OA)	Reduce serum IL-6; delay cartilage/synovial degradation	Ratanavaraporn, Soontornvipart, Shuangshoti, Shuangshoti, & Damrongsakkul, 2017

Table 6. Natural polymer-based microspheres for anti-inflammatory *in vitro* studies

No	Polymer	Active agent	Preparation method	*In vitro* model (cell type, stimulus)	Inflammatory markers (assay)	Results	Reference
1	Chitosan	Resveratrol	Spray-drying	RAW 264.7 macrophages (LPS-induced)	IL-1β, TNF-α (mRNA expression)	Microspheres reduce the mRNA expression of IL-1β and TNF-α.	Li et al., 2021
2	Alginate	Quercetin	Ionotropic gelation	Chondrocytes (H_2O_2-induced oxidative stress)	IL-1β, TNF-α	Microspheres reduce IL-1β and TNF-α levels in H_2O_2-induced chondrocytes, demonstrating superior anti-inflammatory activity compared to free quercetin.	Chen et al., 2025
3	Gelatin Microspheres (GM@HDC@HGF)	Hepatocyte growth factor (HGF), heparin-dopamine conjugate (HDC)	Microfluidics	Tenocytes (inflammatory challenge)	iNOS, IL-1β, TNF-α, IL-6, MMP-3, MMP-13, COL-1, COL-3 ratio (Western blot)	Reduced inflammatory cytokines; restored matrix protein balance; synergistic anti-inflammatory effect	Han et al., 2024
4	Gelatin (genipin-crosslinked)	IL-4, IL-10, IL-13 (anti-inflammatory cytokines)	Water-in-oil emulsification + genipin crosslinking	ATDC-5 chondrocytes (IL-1β/LPS-induced)	Nitric oxide (NO)	IL-4 and IL-13 microspheres reduced NO production by 65–80% by day 3 (comparable/better than bolus dose at 2–5× lower cytokine amount); IL-10 showed marginal effect	Park et al., 2020

Pectin, particularly at a low degree of esterification, provides colon- and site-specific release through susceptibility to microbial/enzymatic degradation (Munarin et al., 2012; Sinha & Kumria, 2001), which is advantageous for gastrointestinal inflammatory conditions but of more limited relevance for systemic or intra-articular anti-inflammatory applications (Table 3.). A recurring limitation observed across the pectin studies summarized here is inconsistent reporting of DL, with several studies providing entrapment efficiency but not DL values.

Gelatin, being protein-based rather than polysaccharide-based, uniquely allows chemical crosslinking (e.g., glutaraldehyde or genipin) to fine-tune degradation rate and mechanical stability, and its degradation by cell-secreted proteases enables a responsive, on-demand release profile that is attractive for intra-articular applications (Park et al., 2020; Young et al., 2005) (Table 4, Table 5, Table 6.). Its principal drawback is batch-to-batch variability arising from differences in collagen source and extraction method, and the need for crosslinking agents that may themselves raise biocompatibility concerns if not adequately controlled (Gómez-Guillén et al., 2011; Mugnaini, Gelli, Mori, & Bonini, 2023).

Across all four polymers, a consistent research gap emerges: in vitro anti-inflammatory efficacy is more frequently and rigorously demonstrated than in vivo efficacy, and among the in vivo studies, disease models are skewed toward general paw-edema or joint-injury models, with only a single study in this review employing the monosodium iodoacetate-induced osteoarthritis model (Ratanavaraporn et al., 2017). Direct head-to-head comparisons between polymers under matched drug, dose, and disease-model conditions are also absent from the current literature, making it

difficult to draw firm conclusions about which natural polymer is optimal for a given anti-inflammatory application. Future studies that standardize the animal model, dosing regimen, and outcome markers across polymer types would substantially strengthen the evidence base for natural polymer-based microspheres in anti-inflammatory drug delivery.

Table 7. Comparison of natural and synthetic polymer-based microspheres for anti-inflammatory drug delivery

Characteristic	Natural polymers (chitosan, alginate, pectin, gelatin)	Synthetic polymers (e.g., PLGA, PLA, PCL, PVA)	References
Biocompatibility	Generally high; derived from biological sources with low immunogenicity	Variable; acidic degradation byproducts (e.g., PLGA) can trigger local inflammation	E. M. Elmowafy, Tiboni, & Soliman, 2019; Fu, Pack, Klibanov, & Langer, 2000; Hu et al., 2023
Biodegradability	Enzymatic/hydrolytic degradation, tunable via crosslinking	Hydrolytic degradation, rate tunable via monomer ratio and molecular weight	Hu et al., 2023; Hua et al., 2021
Fabrication conditions	Mild, aqueous-based methods (ionotropic gelation, emulsification); minimal organic solvent	Often requires organic solvents (e.g., dichloromethane) and higher processing temperatures	Hariyadi & Islam, 2020; Hua et al., 2021; Katou, Wandrey, & Gander, 2008; Lee & Mooney, 2012
Batch-to-batch consistency	Lower; source-dependent (plant/animal origin) variability in molecular weight and purity	Higher; produced under controlled polymerization conditions	Rampim et al., 2025
Mechanical stability	Often requires crosslinking (glutaraldehyde, genipin, Ca^{2+}) for adequate stability	Generally higher intrinsic mechanical and structural stability	Hua et al., 2021; Muzzarelli, 2009
Drug release precision	Moderate; influenced by swelling, ionic strength, and enzymatic activity	High; release kinetics can be precisely engineered via polymer composition/molecular weight	Hu et al., 2023; Hua et al., 2021
Regulatory/clinical familiarity	Fewer approved parenteral products; regulatory pathway less established for some sources	Well established (e.g., PLGA-approved in several long-acting injectables)	Hu et al., 2023; Hua et al., 2021; Kraus et al., 2018
Cost and availability	Generally low-cost, abundant, renewable sources	Higher production cost, but consistent commercial supply	Hariyadi & Islam, 2020; Lee & Mooney, 2012
Typical anti-inflammatory application niche	Mucosal, colon-targeted, and intra-articular delivery leveraging stimuli-responsiveness	Long-acting systemic/parenteral depot formulations requiring precise, extended release	Hariyadi & Islam, 2020; Hu et al., 2023; Kraus et al., 2018

FUTURE PROSPECTS

Natural polymer-based microspheres, such as those composed of gelatin, chitosan, and alginate, offer significant advantages in terms of biocompatibility and biodegradability, making them promising systems for drug delivery and tissue engineering applications. However, several challenges must be addressed to optimize their use. A primary limitation is the variability in the physicochemical properties of natural polymers like gelatin, which can differ depending on their source and extraction methods, thereby affecting the consistency of microsphere formulations (Gómez-Guillén et al., 2011). Additionally, the mechanical stability of natural polymer-based microspheres often remains inadequate without appropriate crosslinking, which may introduce toxicity concerns when using chemical crosslinkers such as glutaraldehyde (Mugnaini et al., 2023). Other challenges include limited precision in controlling active substance release and difficulties in scaling up production for industrial demands (Zhang et al., 2020). Nonetheless, future development of natural polymer-based microspheres remains promising, particularly through chemical and physical modification strategies and the integration of natural polymers with synthetic materials to improve structural stability, processability, and control over drug release. Advances in microsphere fabrication technologies, including microfluidics, membrane emulsification,

spray drying, coacervation, and other precision fabrication approaches, are also enabling better control of particle size, morphology, EE, and cargo distribution. These advances may facilitate the development of more reproducible and functionally tailored microsphere systems for therapeutic and other biomedical applications (Zhai, Wu, Liao, Wu, & Zhao, 2024).

Clinical translation of natural polymer-based microspheres will require substantially more attention to manufacturing consistency and regulatory readiness than most preclinical studies currently address. Natural polymers are inherently subject to batch-to-batch variability in molecular weight, degree of deacetylation or esterification, and source-dependent impurity profiles, all of which can shift particle size, DL, and release kinetics between production lots. Good Manufacturing Practice (GMP)-compliant production will therefore need tighter raw-material specifications and in-process controls than are typically reported in laboratory-scale studies, alongside pharmacokinetic and toxicology data in larger animal models before first-in-human intra-articular or systemic use can be considered.

Terminal sterilization is another translational consideration that warrants greater attention in natural polymer-based microsphere development. Heat-based sterilization, including moist heat, can alter the physicochemical properties of natural polymer matrices. For example, moist-heat sterilization of sodium alginate can induce main-chain scission and changes in glycosidic bonding, while gamma irradiation can also affect the physicochemical properties of alginate (Hu et al., 2014). Gamma irradiation may additionally alter the performance of polysaccharide-based microspheres; for example, gamma-irradiated chitosan microparticles exhibited a slightly higher drug-release rate and lower swelling capacity than non-irradiated particles (Desai & Park, 2006). Therefore, sterilization strategies should be selected according to the physicochemical stability of each polymer–drug system and experimentally validated with respect to polymer integrity and drug-release performance. When terminal sterilization is unsuitable, alternative approaches such as sterilizing filtration or aseptic processing may be considered, although these approaches require additional process controls and validation.

Building on the research gaps identified in the Discussion, future studies should emphasize systematic head-to-head comparisons of natural polymers using matched drug candidates, doses, administration routes, and disease-model conditions. Greater methodological standardization of in vivo osteoarthritis models is also warranted, particularly for monosodium iodoacetate (MIA)-induced osteoarthritis, because differences in MIA dose and timing can influence the severity and trajectory of pain outcomes (Jin et al., 2023). In parallel, stimuli-responsive and hybrid natural–synthetic polymer systems represent promising directions for achieving more controllable drug release and improved formulation performance. PLGA is particularly relevant as a synthetic counterpart because PLGA-based microspheres have been extensively investigated for controlled drug delivery, with polymer composition and physicochemical characteristics influencing degradation and drug-release behavior (Su et al., 2021). Hybridization strategies may therefore be explored to combine the biological properties of natural polymers with the tunable physicochemical properties of synthetic polymers, although the stability, safety, interactions between components, and manufacturing requirements of each hybrid system require dedicated evaluation. Other polysaccharides not covered in this review, such as konjac glucomannan, whose mannose-containing structure may promote macrophage uptake (Guerreiro et al., 2021), also merit evaluation as carriers for macrophage-driven inflammatory conditions. These approaches may contribute to the development of more reproducible and clinically translatable natural polymer-based microspheres for sustained anti-inflammatory therapy.

CONCLUSION

The utilization of natural polymers in microsphere-based formulations offers distinct therapeutic advantages compared to conventional drug delivery systems. Their ability to combine safety, biodegradability, and responsiveness to physiological environments allows for improved drug targeting, extended therapeutic duration, and reduced systemic exposure. Preclinical evaluations, which are predominantly in vitro, indicate that these carriers can modulate inflammatory pathways and often outperform the corresponding free drugs. Nonetheless, technical barriers such as batch variability, limited mechanical robustness, and scale-up constraints remain challenges to be addressed. Moreover, the current evidence base has important gaps: in vivo evidence is less extensive than in vitro evidence, disease-specific models such as monosodium iodoacetate-induced osteoarthritis have rarely been used, release kinetics are often reported only qualitatively, and head-to-head comparisons between polymers under matched drug, dose, and disease-model conditions are lacking. Addressing these gaps through standardized disease models, quantitative release reporting, and systematic polymer comparisons, together with continued research on polymer modification and hybrid systems, is expected to further advance the application of natural polymer microspheres in personalized inflammatory treatments.

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AUTHOR CONTRIBUTION STATEMENT

Determination of the Subject (IW, AM, DMH), Literature Research (IW, DMH, AM), Preparing the Study Text (IW), Reviewing the Text (IW, AM, DMH).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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