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Chitosan, a Natural Polymer, is an Excellent Sustained-Release Carrier for Amide Local Anesthetics

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Abstract: Local anesthetics, particularly amide types, play a crucial role in perioperative anesthesia to alleviate pain and manage chronic, long-term pain, with their brief effect period remaining a universal challenge that needs resolution. There is a high anticipation for creating materials that maintain prolonged effectiveness of local anesthetics through a straightforward administration technique. Chitosan is the most typical natural amino polymer, which is highly reactive and easy to modify. It has been widely and deeply used in the field of medicine. At present, it is mainly used in tissue regeneration and repair, hemostasis and wound healing, antibacterial and anti-infection, disease diagnosis and treatment detection, and drug delivery. In the field of anesthesia, chitosan is regarded as a potential perfect carrier for the sustained release of amide local anesthetics. This document aims to analyze the current application of chitosan as a prolonged-release substance in amide-type local anesthetics, encapsulate the associated research advancements, and subsequently investigate the practicality and prospects of its medical uses.

Keywords: extended-release carrier, chitosan, amide local anesthetics, duration of action

Importance of Local Anesthetic Slow-Release Materials

In clinical settings, amide local anesthetics and lipids are employed, with amide local anesthetics gaining popularity due to their superior safety features and the benefits of quicker initiation and extended action duration. Local anesthetics such as lidocaine, ropivacaine, and bupivacaine exemplify amide, with sodium channel blockade as the primary anaesthetic method (Figure 1).[1–3] Clinically, these medications are user-friendly, cause minimal disruption to the body, and facilitate recuperation post-surgery, yet their effectiveness lasts short time, exemplified by 1–2 hours for lidocaine hydrochloride, 3–6 hours for ropivacaine hydrochloride, 5–8 hours for bupivacaine hydrochloride, and 5–8 hours for bupivacaine hydrochloride[4–6]. Local anesthetics are frequently required in clinical settings, for pain relief during surgery or for managing pain after the operation, to ensure a prolonged inhibitory impact. According to the demand for local anesthetics, they were used to prolong the duration of action of local anesthetics: a one-time large-dose administration, small-dose continuous administration, delayed local anaesthetic absorption and metabolism and the use of sustained-release materials, and so on.

Administering a single high dose sustains the therapeutic concentration for an extended duration, yet, the peak plasma drug concentration often breaks through the therapeutic limit, resulting in harmful side effects.[7]. Frequent administration of small doses can largely avoid the risk of exceeding the therapeutic window. But it is limited by the surgical position, repeated punctures, and the difficulty of patient co-operation. Local anesthetic conduit, on the other hand, is often associated with high technical requirements and increased infection rates.[8] Patients suffering from hypertension, sinus bradycardia, and diabetes mellitus are advised against using vasoconstrictors like epinephrine for decelerating drug

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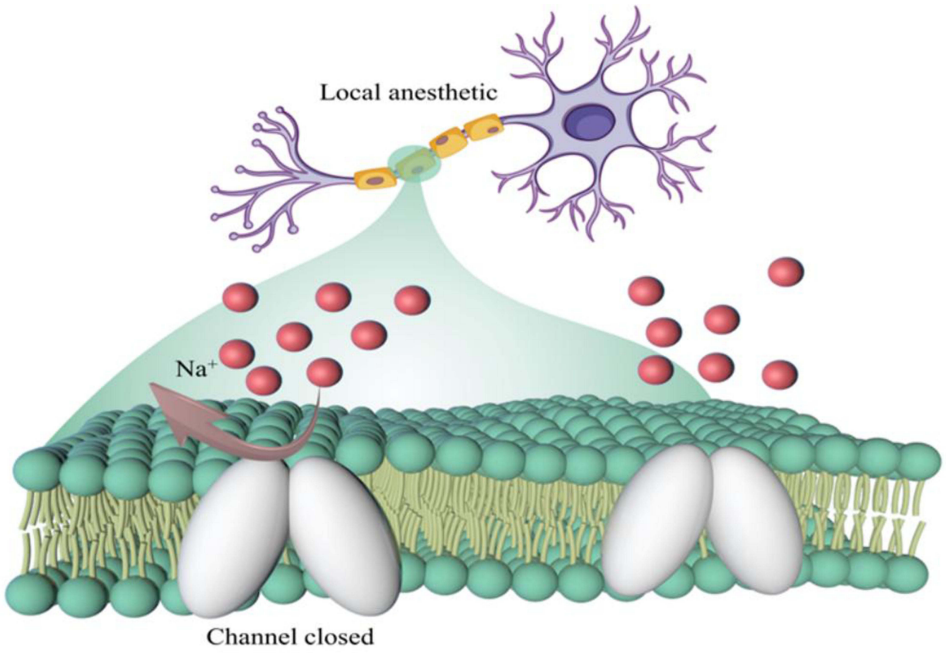

Figure 1 How amide local anesthetics work.

metabolism[9–11]. Administering vasoconstrictors like adrenaline for decelerating drug metabolism is advised against individuals suffering from hypertension, sinus bradycardia, and diabetes.

To sum up, employing long-release local anesthetics can lessen the necessity for patient collaboration, particularly during surgery. And circumvent side effects from drug combination with enduring impacts prevent puncture damage from repeated use, represents the optimal approach for extending the effectiveness period of amide-type local anesthetics. Nonetheless, existing amide local anaesthetic slow-release substances continue to encounter significant hurdles: enhancing their stability, preventing drug explosion, hastening their breakdown, favoring the pricing of formulations, and reducing the time it takes to act, among others. Addressing the demand for durable, consistent, secure, cost-effective, and quick-acting amide local anaesthetic sustained-release carriers will remain a central research topic in local anesthetics for an extended period.

Chitosan as a Gradual-Liberation Carrier for Amide-Based Local Anesthetics

Chitosan identified chemically as poly glucosamine (1-4)-2-amino-b-d-glucose (Figure 2). It represents a cationic polysaccharide originating from chitin. Owing to its remarkable benefits, this has become a gradual-release medium for amide-based local anesthetics, prompting pertinent research.

Benefits of Using Chitosan as a Gradual-Release Medium for Amide-Derived Local Anesthetics

Presently, polymer materials are the predominant choice for local anesthetic sustained-release materials. Within these, chitosan stands out due to its favorable biocompatibility, strong drug affinity, enhanced drug sustained-release efficacy, effective biodegradability, and affordability, making it a suitable candidate for use as an amide-based local anesthetic sustained-release. ①Regarding biocompatibility, chitosan, a naturally occurring polysaccharide, is well-suited for human tissues and cells, and it almost not trigger immune or inflammatory responses.[12] ②Regarding biodegradability, Chitosan, a naturally occurring polysaccharide, is well-suited for human tissues and cells, and it does not trigger immune responses or inflammation[12]. ③Regarding performance in releasing drugs: By modifying its molecular weight, distribution, chemical composition, and various other factors, Chitosan regulates the speed and length of drug release[13].

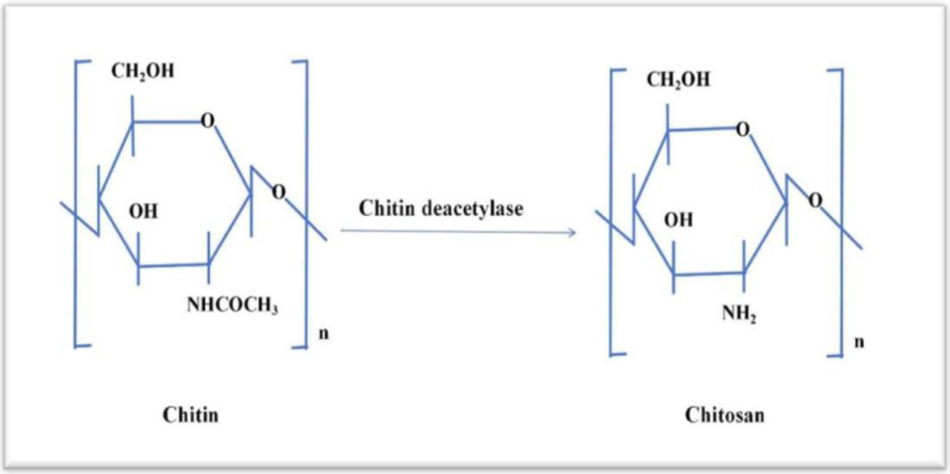

Figure 2 The molecular configuration of chitosan.

④Regarding strong affinity for drugs, chitosan, known for its strong drug affinity, possesses hydroxyl and amino groups capable of forming hydrogen bonds and electrostatic interactions with amide local anesthetics. And they enhance the drug's stability and bioavailability.[14,15] ⑤Regarding simplified creation and alteration, chitosan can be synthesized through traditional methods like chemical reactions and physical mixing, among others. Concurrently, the hydroxyl and amino groups in chitosan offer an adequate base for merging various other alteration molecules or compounds, known for their ease of modification.[16] ⑥Regarding affordable, Chitosan, a naturally occurring polysaccharide, comes from diverse sources and is affordable, making it suitable for extensive production and usage[17].

Studies have focused on Chitosan as an extended-release agent for common amide local anesthetics, revealing its enhanced long-release properties. This substance exhibits superior slow-release characteristics and can be administered through various methods, such as oral, transdermal, injectable, and transmucosal methods.[18–20]

Morphological Classification of Chitosan Slow-Release Materials

Chitosan is highly processable, and it can be processed in forms like nanoparticles, microspheres, films, gels, sponges, tablets, and more. Selecting an appropriate morphology for chitosan carriers can cater to the varied requirements of the gradual release of local amide anesthetics[21] (Figure 3). ①Regarding Chitosan nanoparticles, they typically measure between 10–100nm in size. They are frequently produced using solvothermal, co-precipitation, and sol–gel techniques, and characterized by a substantial surface area and a larger relative surface area.[22,23] Local anesthetics are generated through the dissolution and encapsulation of the anesthetic. Local anesthetics can be found within chitosan particles through dissolution and encapsulation, or on the surface via adsorption and adhesion.[24] Chitosan particles exhibit a significantly large surface area, accompanied by a larger relative surface area. Chitosan nanoparticles, serving as carriers for drug delivery and controlled release, boast benefits such as a high encapsulation rate for local anaesthesia, enhanced stability, and extended release duration.[25] ②Regarding chitosan microspheres, they typically ranging from 1 to 250 micrometers in size. And they are typically produced through processes like emulsion polymerisation, precipitation polymerisation, microfluidic control, and spray drying.[26] ③Regarding chitosan membranes, they are typically, typically, a few millimetres in thickness, and commonly created through solution casting, coating, and evaporation deposition.[27] By dissolving and uniformly distributing the local anesthetic within the chitosan substance, a film is formed that snugly covers the wound area, alleviating pain on the skin's surface.[28] ④Regarding chitosan hydrogel, this 3D networked form dissolves in water, holding onto a significant quantity of water, yet remains undissolved, typically resulting from cross-linking and graft polymerization. Chitosan hydrogels, infused with water, are capable of transporting substantial quantities of amide-based local anesthetics and gradually dispersing these anaesthetics.[29] Sensitive chitosan hydrogels are capable of transforming liquids into hydrogels, aiding in the swift initiation of local anesthesia in the initial phase and extending the action period in the intermediate and advanced stages. ⑤Chitosan sponge, typically created through

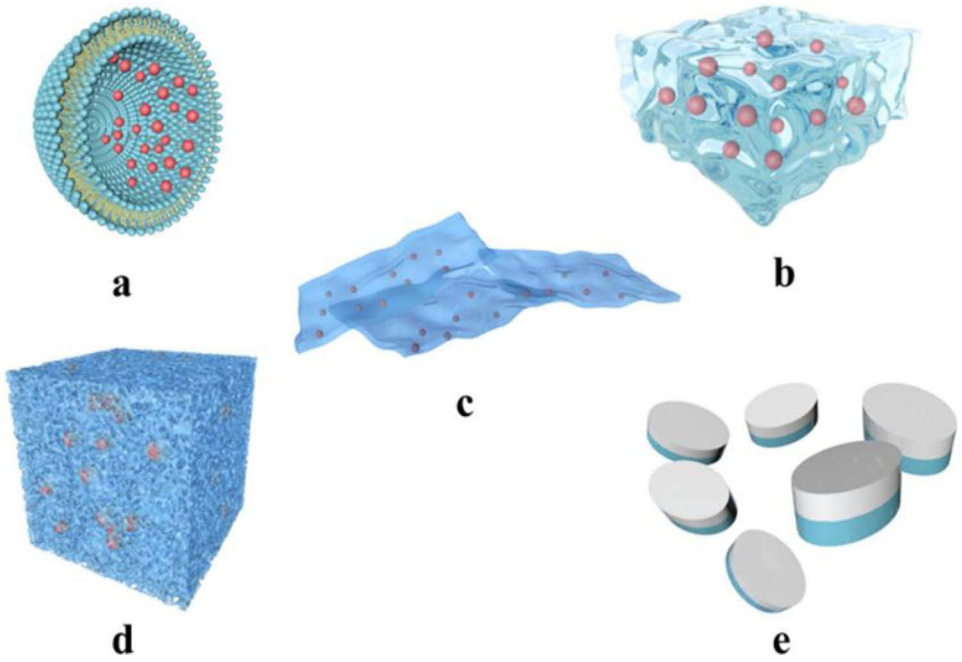

Figure 3 Diagrammatic depiction of the structural categorization of chitosan slow-release substances.
Note: (**a**): Schematic diagram of chitosan nanoparticles or microspheres; (**b**): Schematic diagram of chitosan hydrogel; (**c**): Schematic diagram of chitosan membrane; (**d**): Schematic diagram of chitosan sponge; (**e**): Schematic diagram of chitosan sheet.

freeze-drying, effectively absorbs amide local anaesthetics but suffers from low compressive resistance, weak structural integrity, and is seldom utilized in amide local anaesthetics due to slow release.[30] ⑥Regarding tablets of Chitosan, this medication powder is blended into the chitosan mixture to ensure uniform distribution and micronization, followed by compression into tablets post-drying.[31] It is conducive to preserve local anaesthetic-chitosan sustained-release materials. Still, it is seldom used for the sustained release of amide-type local anesthetics because of the difficulty of direct injection.

Modification of Chitosan Retardation Materials

While Chitosan excels in features, researchers have various alterations to it under diverse circumstances to broaden its use across different local anesthetics. ①Acylated chitosan: By reacting the amino and hydroxyl groups of chitosan with diverse organic acids, anhydrides, chlorides, and others, acylated chitosan can be produced.[32] The added group has the potential to dilute the chitosan. By integrating groups, the intramolecular yet intermolecular hydrogen bonds in chitosan can be weakened, the substance's water solubility and enhancing its ability to be injected.[33] ②Upon carboxylation, the primary reaction process of chitosan involves its amino and carboxyl groups with glyoxylate, resulting in the synthesis of carboxylated chitosan.[19] Chitosan with carboxylation. Enhanced binding of carboxylated chitosan fosters a secure connection of surface anesthetic drugs to tissues, enabling effective medication release.[32] ③Alkylated chitosan: By converting the amino and hydroxyl groups of chitosan into alkyl chitosan, one can synthesize alkyl chitosan. Alkylated chitosan markedly diminishes intramolecular hydrogen bonds, leading to a rise in its solubility in water.[34] Alkyl chitosan's ability to dissolve in water is enhanced. Furthermore, alkyl chitosan enhances the biological compatibility of chitosan.[35] ④Quaternised chitosan: Through direct quaternary ammonium substitution, N-alkylation, or interaction with quaternary epoxides, chitosan undergoes quaternisation.[36] Quaternised chitosan: This chitosan compound results either from the direct substitution of quaternary ammonium or its reaction with quaternary epoxides. Quaternary chitosan's enhanced ability to create films and combat microorganisms proves advantageous for surface anesthesia and anesthetic practices in environments rich with microbes like the mouth.[37,38] ⑤For graft copolymerisation, chitosan, along with other polymers, is used to enhance its mechanical robustness, resilience, and other characteristics, a process that is not typical of chitosan and is utilized frequently. ⑥Thiolation Process: When the amino group of chitosan binds

with thiol-containing coupling chemicals, it enhances the chitosan material's permeability, stickiness, and gel formation in its natural state[26].

Working Basis and Intelligence of Chitosan Sustained-Release Amide Local Anesthetics

The basis of Chitosan extended-release amides in local anesthetics aligns with the distribution principles of drugs like other carriers, typically facilitated through physicochemical and biological processes. The most common reactions observed are solubilization, diffusion, osmosis, swelling, and interactions between matrix and drug molecules[39,40]. In detail, drug dissolution within a carrier represents how drug molecules merge inside the carrier to create a solution. Diffusion involves transporting drug molecules from areas of elevated concentration to zones with diminished concentration within the carrier. The entry of drug molecules into the environment via the carrier's micropores or membrane pores occurs through osmosis. Solubilization refers to a phenomenon where the carrier absorbs fluid and expands upon interaction with the fluid. The dynamics of carrier and drug molecules encompass hydrogen bonds, van der Waals forces, and electrostatic forces, among others. Such interplays can influence the speed and length of the medications. Furthermore, the carrier's surface coat can smartly react to specific triggers, enabling the activation of on-demand drug release. This leads to Chitosan extended-release amide local anesthetics intelligently adjusting to external factors by integrating reactive molecules or groups like heat-sensitive molecules, light-sensitive molecules, and enzyme-sensitive molecules, allowing for the actual initiation of drug release as needed release.[39,40] As an illustration, using temperature-critical chitosan can initiate the immediate release of medication when required. Chitosan, sensitive to temperature changes, can dispense medication slowly at the same body temperature and swiftly when heated locally, thereby facilitating immediate drug release. Molecules that emit light can unleash drugs, thereby facilitating a drug release governed by the light. The drug can be discharged by molecules sensitive to enzymes under enzymatic actions, enabling controlled release by the enzyme. Local anesthetics derived from chitosan long-release amides aid in directing specific drugs by adding certain molecules or clusters, like antibodies, ligands, and antigens, specifically targeting certain cells or tissues.

Factors Influencing the Effect of Chitosan Extended-Release Amide Local Anesthetics

When using different slow-release carriers, the gradual-release impact of chitosan slow-release amide as a local anesthetic varies based on the drug dose, carrier attributes, the drug-carrier interface, slow-release setting, and so on (Figure 4). Such as: ①Regarding the medication's quantity: assuming that amide local anesthetics are not poisoned, a greater concentration of the drug accelerates its release, thereby prolonging the extended effects of its slow-acting effect.[41] ②Regarding the drug quantity: Particle size indicates that a stable ratio of drug to chitosan carrier means as chitosan molecules diminish in size, the surface area becomes more comprehensive, leading to quicker local anaesthetic release and faster drug efficacy. Nevertheless, this results in lower material viscosity, thereby reducing the gradual release duration for the drug.[42] Nonetheless, the substance's viscosity diminishes, resulting in a reduced duration for the drug to be released. ③Regarding the crosslinking agent, with a suitable level of crosslinking, there's an increase in the agent's crosslinking duration, a boost in the intermolecular force, a reduction in the diffusion rate of local anesthetic molecules in the medium, a deceleration in the release rate, and lengthier delay of the release timeline.[43,44] ④Slow-release environment: Given the goal of preserving the body's internal equilibrium, an acidic milieu promotes the material's expansion and dissolution. This arrangement better facilitates drug discharge from chitosan rather than an alkaline one, enabling the practical application of the amide localized anesthetic.[45] ⑤Decoacetylation intensity: Enhancing the deacetylation level can improve the steadiness of chitosan's prolonged-release substances with amide as a local anaesthetic and intensify the effects of such release. The deacetylation level of chitosan entities, along with the binding force of local anaesthetic drugs and chitosan molecules, shows a positive correlation; however, if deacetylation surpasses 90%, there's no more extended variation in the drug's release efficiency[46]. Notably, a pleasing gradual release outcome is likely to represent a mix of these elements instead of an isolated factor.

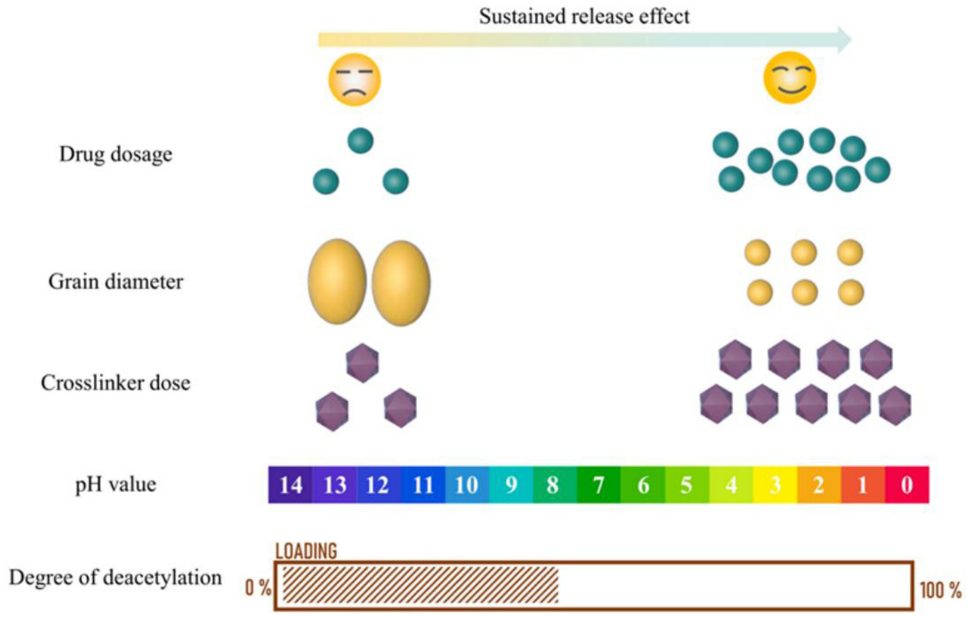

Figure 4 Factors influencing the effect of chitosan extended-release amide local anesthetics and the trend of change.

Local Anesthetics Derived from Amides Offset the Tissue Inflammation Triggered by Chitosan Solvents

Chitosan offers numerous benefits and extensive use, though it's not without its challenges, including solvents that might irritate tissue cells, and by chance, amide local anaesthetics that can neutralize these adverse effects.

Chitosan originates from the deacetylation process of chitin, a protein known for its solid crystalline structure with intermolecular and inner hydrogen bonds. Its limited water solubility, and frequent necessity to be dissolved in acidic environments. Currently, the most frequently utilized weak acid solvents encompass dilute acetic acid and hydrochloric acid, posing a possibly harmful threat to tissue cells.[40,41]

Enhancing chitosan's solubility through intensifying deacetylation and chemical alteration, while reducing solvent utilization, can lessen this harmful irritation[32]. Yet, with the former, excessive deacetylation results in lower viscosity and sluggish drug release, whereas typical chitosan slow-release carriers achieve 70–90% deacetylation, predominantly using weak acids as the solvent[47]. Addressing the chemical alterations intended to enhance solubility, further work is required based on the solubilization of chitosan using mild acids. Ultimately, existing substances of chitosan in a slow-release form persist in undergoing a certain level of solvent annoyance. Current investigations into the local anesthetics of chitosan materials' long-release amides reveal a dearth of research exploring their toxicity to tissues. Furthermore, various research has confirmed the efficacy of chitosan slow-release amide local anesthetics in improving the survival of tissue cells.

The potent anti-inflammatory properties of amide local anesthetics could be responsible, as they lessen the adhesion, movement, and buildup of polymorphonuclear leukocytes at inflammation sites, as well as the secretion of inflammatory substances.[48–50] This anti-inflammatory reaction may neutralize the inflammation triggered by the chitosan solvent, thereby ensuring that chitosan-laden amide local anesthetics are generally free from tissue cell inflammation or tend to exhibit chitosan's beneficial effect in promoting tissue cell proliferation. Local anesthetics made of chitosan and amide are ideally suited.

Targeted Application of Chitosan Extended-Release Amide as a Local Anesthetic

Chitosan Extended-Release Lidocaine

Chitosan demonstrates the ability to gradually emit lidocaine as nanostructures, membranes, and hydrogels. And it is excelling in providing pain relief on surfaces (Table 1).

Table 1 Related Studies on Sustained Release of Lidocaine by Chitosan

Local anesthetics	Type of Study	Time of publication	Clinical application	References
Lidocaine	exploratory	2018.9	Relieve pain in burn, trauma and diabetes patients	[51]
		2015.12	Wound dressing	[52]
		2022.10	Treatment of dry pit and gingivitis	[53]
		2022.10	Reduces pain in burn patients	[54]
		2020.7	Treatment of oral surface pain	[55]
		2019.11	Enhance wound care and reduce dressing change pain	[56]
		2020.2	Promotes wound healing and relieves pain	[57]
		2015.1	Dental pain management	[60]

Chitosan Nanostructures Extended-Release Lidocaine

Li et al aim to alleviate intense pain and severe infections in individuals suffering from burns, trauma, or conditions like diabetic foot ulcers. Utilizing electrostatic spinning techniques, they created versatile, dual-layered nanofiber structures composed of polycaprolactone (PCL)/mupirocin and chitosan/lidocaine hydrochloride. Laboratory tests revealed that around 66% of lidocaine escaped the scaffold in the initial hour, with the total drug release progressively rising to 85% in 6 hours. This indicates a swift initial discharge of lidocaine from the substance for pain relief, followed by a gradual release to extend its effect duration[51]. Shahrzad et al created a dual drug delivery system consisting of polyvinyl alcohol (PVA), chitosan, lidocaine hydrochloride, and erythromycin nanofibre within the core sheath composite[52]. The mechanism of this mechanism emits lidocaine via fick diffusion over a period of 72 hours, resulting in a total release ratio of 84.69%. Nuttawut Supachawaro chose tiny chitosan molecules for dry socket or odontitis treatments and manufactured nanomaterials made from chitosan-pectin-hyaluronic acid-multiplying electrolyte. The compound released lidocaine hydrochloride in a slow fashion, exhibited a swift commencement in 5 minutes, and maintained lidocaine secretion for 24 hours to alleviate dry socket discomfort. Moreover, it was evidenced that the development process did not harm gingival fibroblasts and maintained uniformity after three months in storage[53].

Chitosan Film Extended-Release Lidocaine

Andra et al innovated the creation of porous membranes featuring chitosan-succinic anhydride/1,3-bis (3-glycidylpropyl) tetramethyldisiloxane-lidocaine, aiming to alleviate pain and aid in skin recovery in patients with burns. Laboratory release tests evaluated the effectiveness of two kinds of membrane types varying succinic anhydride and 1,3-bis (3-glycidylpropyl)tetramethyldisiloxane cross-linking agents in lidocaine release: around 77% and 81% of lidocaine escaped within the initial 20 minutes, and the peak of 83.16% and 95.24% release rates was attained after one hour. In addition, confirmation was obtained that elevating the quantity of succinic anhydride and reducing the cross-linker ratio were factors conducive to the carrier discharging lidocaine[54]. Addressing the issue of mouth area moisture, which hinders the surface positioning of local anesthetic prolonged-release substances, Michelle et al developed nanostructured hybrid nanofilms combining chitosan-pectin and 5% lidocaine-procaine eutectic. The modification involved adding catechol to chitosan, enabling the persistently released substance to adhere closely to the mucous lining. Observations in the lab showed that the secretion of lidocaine-prilocaine extended over 8 hours, and this reaction could last over 7 hours in mice's oral mucosa, devoid of any localized or general toxic effects[55].

Chitosan Hydrogel Extended-Release Lidocaine

Aiming to enhance wound care through personalized and better handling, Jinjunjiao Long and team crafted a series of 3D printed materials combining chitosan, pectin, and lidocaine hydrogel. Grouping of the complexes was done based on the mass percentages (w/W) of lidocaine and the material itself, encompassing 0 w/W, 2 w/W, 5 w/W, and 10 w/W, culminating in a quartet of groups. Observation revealed that all groups with drug administration exhibited swift release within one hour, followed by a slower release within four hours. The ultimate drug release rates were high at 88%, 91%, and 94%, respectively. Moreover, as the drug is released, the material breaks down, weakening the adhesion force and thus lessening tissue damage and easing patient pain while changing wound dressings[56]. Given chitosan hydrogel's

effectiveness in promoting tissue healing as an injury bandage, it stands out as an advantageous 3D material for managing wound pain. There were explorers synthesized an unbound, entirely physically soluble chitosan hydrogel, noting its gradual release of lidocaine in a laboratory setting. Initially, the Lidocaine secretion stood around 50% in the first hour, escalated to about 80% in 3 hours and 15 minutes, and ultimately peaked at 88% approximately at 5 hours and 25 minutes[57]. Jinke Xu et al developed a new catecholamine genipin crosslinking chitosan by catecholamidating it and crosslinked it with the safe polymer genipin.[58] This structure predominantly operates within dentistry. This compound predominantly facilitated the expulsion of lidocaine from the mouth mucosa, extending the duration to 3 hours. Moreover, in rabbit bushy mucosa, rabbit serum's peak lidocaine level reached approximately 1 ng/mL, substantially less than lidocaine's plasma poisoning level, and the tissues remained unaffected[48].

From the preceding, it's evident that chitosan extended-release lidocaine is more prevalent in surface pain relief applications. In addition, concerning chitosan's nanostructure, membrane, or hydrogel type, lidocaine's extended release is typically marked by quick secretion in early phases and enduring release in the advanced stages. When paired with lidocaine's rapid activation compared to other amide local anesthetics, and its natural anti-inflammatory and tissue-rerepair abilities, chitosan extended-release lidocaine stands out as especially apt for pain relief in superficial injuries.

Chitosan Extended Release Ropivacaine

Predominantly present as hydrogels and nanoparticles, chitosan gradually emits ropivacaine, commonly utilized in nerve blockages and localized permeation (Table 2).

Chitosan Hydrogel Extended-Release Ropivacaine

Kyle et al devised a diverse delivery mechanism consisting of ropivacaine-dexamethasone-chitosan thermogel to manage acute and chronic pain. Notably, administering ropivacaine 75 and 150 mg/kg with dexamethasone in a hydrogel for 6 hours resulted in a sciatic nerve sensory blockage comparable to the single dosages of 10 and 150 mg/kg ropivacaine in animals. Patients receiving dexamethasone experienced a more extended period of blockage, and their sensory block was sustained for 24–48 hours, yet it's crucial to grasp the contraindications linked to dexamethasone.[59]

Pain affecting the somb muscle after surgery, including bone repairs, complete knee surgery, hip replacements, and rotator cuff mending, can result in significant pain after surgery within 48 hours. Patricia et al, to alleviate these kinds of patient pain, slow-release ropivacaine was injected using a chitosan thermal gel system and encased in dexamethasone. An examination using a rat sciatic nerve block model revealed the system's ability to restrict sensory and motor functions for a duration of up to 48 hours.[56] Unsatisfied with this, Manakamana and team advanced to a more advanced stage in optimization. The innovation of a novel chitosan nanocomposite carrier involved embedding the area-specific anesthetics ropivacaine and dexamethasone inside lipid nanocapsules, which were then integrated into enzymatically linked glycol-chitosan hydrogels. In the research, a rat model for chronic constriction injury pain was employed to evaluate its analgesic effectiveness. Notably, the nanocomposite carrier experienced notably enhanced pain relief over the past 7 days, in contrast to the control group[60].

Chitosan Nanostructures Extended-Release Ropivacaine

Rong-Qin et al invented nanoscale chitosan-encapsulated mesoporous silica nanoparticle-based structures that are glycosylated and can be stimulated through external ultrasound to emit ropivacaine. Analysis of the drug's release pattern indicated that ropivacaine's release rate hit 50% in 2 hours, escalating to 90% at the 12-hour mark. An assessment

Table 2 Related Studies on Sustained Release of Ropivacaine by Chitosan

Local Anesthetics	Type of Study	Time of Publication	Clinical Application	References
Ropivacaine	exploratory	2015.1	Surgical anesthesia and reduction of postoperative pain	[59]
		2019.11	Relieve pain after orthopedic surgery	[56]
		2018.7	Relieve pain after orthopedic surgery	[60]
		2021.12	Surgical anesthesia and relief of postoperative pain	[61]
		2021.7	Reduce skin pain	[64]

of the nerve block impact was conducted with a live model of sciatic nerve constriction, revealing that ropivacaine's gradual release using this agent could notably postpone the pain relief duration. Moreover, cytotoxicity tests demonstrated that this compound could enhance cell longevity and multiplication[61]. Zhang et al created a chitosan-coated polycaprolactone nanoparticle substance designed for simultaneous administration of ropivacaine and the dexamethasone complex. Research revealed that ropivacaine, when coated with the material, penetrated the skin 1.7–5.5 times better, with the skin receiving a considerably greater dose than uncoated Ropivacaine. Concurrently, experiments involving tail dumping on mice revealed that ropivacaine could extensively extend and intensify its sedative impact. Moreover, we noted the absence of harm to tissue cells.[62] The primary application of Chitosan, which aids in sustained-release ropivacaine, is in nerve blockage. It also serves to enhance Ropivacaine's ability to penetrate the skin, thereby assisting in its use as an analgesic for surface infiltration.

Chitosan sustained-release ropivacaine primarily serves the purpose of nerve block. Whereas chitosan enhances ropivacaine's skin-transmitting capabilities, enabling its application for pain relief on surface infiltrates.

Chitosan Extended-Release Bupivacaine

Chitosan can slow-release bupivacaine in the form of hydrogels, nanostructures, and membranes, and has good slow-release properties (Table 3). Liposomal bupivacaine is a sustained release formulation of bupivacaine that claims to prolong the action time to 72 hours. Chitosan bupivacaine and liposome bupivacaine have different characteristics (Table 4).

Chitosan Hydrogel Extended-Release Bupivacaine

In an effort to alleviate both sudden and long-term pain, resulting from minor invasive techniques during and after surgery, Reemal et al created heat-sensitive nanocomposite hydrogels made of graphene oxide/chitosan, to extend the duration of pain relief locally using bupivacaine. Observations indicated that within 6 hours, the bupivacaine entirely discharges unbound ropivacaine, in contrast to the full and continuous release of all bupivacaine embedded in the substance within 24 hours. This extended the local anesthesia impact of bupivacaine markedly, extending the pain-related blockade period by sixfold and showing no clear indications of toxic local or systemic effects within the body[63]. Nagella et al created a nano-hydrogel made of grafted chitosan polymer with 2-hydroxyethyl methacrylate (Chitosan-g-[Poly (MMA-co-HEMA-cl-EGDMA)]) to facilitate gradual release of bupivacaine. The delayed liberation of bupivacaine from the hydrogel showed a notable relationship with its methyl methacrylate chain length, hydrogen bond count, and the Ph value within the release milieu. A combination of different elements revealed that a particular carrier subtype could decelerate bupivacaine release and maintain stability over a 24-hour span.[64] The secretion of bupivacaine remained steady for approximately 24 hours. Deng et al engineered a method to deliver bupivacaine via chitosan and genipin hydrogel to the skin. The pain relief was notably enhanced by the bupivacaine-enriched hydrogel compared to using solely bupivacaine, consistently over a period of at least 7 days. Furthermore, its biodegradability and biocompatibility were notable, with no neurotoxic effects detected at 7, 14, and 21 days during the measurement of tissue cells.[19]

Chitosan Nanostructures Extended-Release Bupivacaine

In line with the current trend in multifactorial de-opioidization for pain relief, Francesca et al synthesized nano-complexes of chitosan-polylactic acid-hydroxyacetic acid, encased in heat-sensitive gels, aimed at extending

Table 3 Related Studies on Sustained Release of Bupivacaine by Chitosan

Local Anesthetics	Type of Study	Time of Publication	Clinical Application	References
Bupivacaine	exploratory	2022.6	Relieve the pain after minimally invasive surgery	[63]
		2023.11	Postoperative pain management	[64]
		2022.12	Relieving postoperative pain	[19]
		2014.11	Relieve acute and chronic postoperative pain	[65]
		2018.4	Surgical anesthesia and postoperative pain management	[66]
		2023.6	Relieves wound pain and promotes healing	[67]

Table 4 Comparison of Liposomal Bupivacaine and Chitosan Bupivacaine

	Liposome Bupivacaine	**Chitosan Bupivacaine**
①Carrier	Liposome	Chitosan
②Mode of drug release	Disruption of liposomal vesicles	Biodegradation of chitosan
③Administration methods	Local injection	Local injection and Surface application
④Special use contraindications	Stop mixing with other local anesthetics	None
⑤Duration of action	Up to 72 hours	Up to 7 days
⑥Direction of clinical application	Local infiltration anesthesia and nerve block anesthesia	Local infiltration anesthesia, nerve block anesthesia and Topical anesthesia
⑦Side effects	Same as bupivacaine	Same as bupivacaine
⑧Listed drug	Yes	No

bupivacaine's effectiveness and alleviating both short and long-term post-surgery pain among patients. The substance proved to facilitate a prolonged discharge of bupivacaine for as long as 7 days, devoid of any cytotoxicity or inflammatory reactions in the tissue[65].

Cintia et al engineered chitosan nanoparticles alongside sodium alginate to maintain the secretion of bupivacaine. They observed that this method required 900 minutes for its total liberation from the substance, significantly exceeding the 350 minutes needed to entirely free bupivacaine when dissolved. Administrated in rabbits for infraorbital nerve block, this substance extended the sensory block period beyond that of pure bupivacaine, with its overall painkiller effect escalating by approximately 1.4 times.[66] SohaHabibi et al created a two-layer mixture of chitosan, buupivacaine, and macirocin pad through the process of electrostatic spinning and subsequent crosslinking with glutaraldehyde. The application of bupivacaine to the injury site proved pain-relief effectiveness for two days[67].

Summary and Prospect

Theoretically, chitosan is capable of securely and consistently discharging local amides anesthetics, thereby extending the duration of pain blockage, anticipated to emerge as an outstanding, widely used for amides local anesthetics carrier. Yet, the majority of our research and developmental progress remains halted in either the in vitro or animal-based validation phase, and we anticipate tangible outcomes for clinical application while genuinely offering patients pain control assurance.

Ethical Approval and Informed Consent

Ethical approval and informed consent are not involved in this article.

Consent for Publication

All the authors gave their consent for the article to be published in the journal.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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