# CHAPTER 2

# Innovations in the development of water-soluble polymer systems for drug delivery

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**Abstract**

This study focuses on developing and investigating innovative water-soluble polymer systems based on sodium alginate for drug delivery, specifically for controlled lidocaine release. A novel hydrogel was formulated with a unique composition, including sodium alginate, azithromycin, lidocaine, and levomenthol, among other auxiliary components. These hydrogels exhibit a significant capacity for water absorption, directly proportional to the sodium alginate concentration. Enhanced moisture retention was observed, attributed to the proposed hydrogel composition and its excipients. The hydrogels demonstrate non-Newtonian, pseudoplastic behavior, with viscosity dependent on both sodium alginate concentration and temperature; an increase in temperature notably reduces hydrogel viscosity. Furthermore, the research confirms the feasibility of controlled and prolonged drug release, particularly for lidocaine, with approximately 60% of lidocaine released within 60 minutes and over 80% within 90 minutes. Ultimately, optimizing sodium alginate concentration and controlling temperature allow for the targeted regulation of key hydrogel properties, including water absorption, viscosity, and release kinetics. These findings highlight the broad potential for applying sodium alginate-based hydrogels in the pharmaceutical industry to create advanced controlled-release systems, especially for lidocaine delivery.

**Keywords**

Water-soluble polymers, sodium alginate, hydrogels, rheological properties, drug delivery, dentistry, innovations, pharmaceutical ingredients.

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## 2.1 Introduction

Alginate is a natural polymer frequently used in drug delivery systems. The use of alginate offers several advantages, including ease of preparation, biocompatibility, biodegradability, and non-toxicity. It can be applied for various routes of drug administration, including targeted or localized drug delivery systems. The development of alginate-based formulations as the chosen polymer in different delivery systems can be adjusted depending on the challenges that need to be overcome by the drugs or the system itself. Therefore, researchers need to update their knowledge on advancements in alginate-based drug delivery systems and develop an effective and comprehensive approach to treating diseases that are often accompanied by pain, inflammation, and bacterial infections, particularly in dentistry.

Modern dentistry aims to develop local agents that allow for: reducing the systemic burden on the body; more effectively treating chronic processes due to the sustained release of active components at the site of action; promoting better adherence to the treatment regimen through the use of gel form; and ensuring an effect on various pathogenetic links of the disease (pain, inflammation, infection).

Alginates are capable of forming bioadhesive films that adhere to the mucous membrane, fixing active components in the application area. This allows active pharmaceutical ingredients to act for a prolonged period, increasing the therapeutic effect and reducing the frequency of administration. Alginate can also have a mild anti-inflammatory effect and promote tissue regeneration.

Therefore, it is relevant to develop a hydrogel based on sodium alginate that will include pharmaceutically active components. The novelty of the research will lie in the complementary combination of components, where each performs its role (structure formation, antibacterial, analgesic, prolonged action), ensuring a comprehensive therapeutic effect. This can become the basis for developing an effective local agent that will improve the quality of treatment and life for patients with dental problems.

## 2.2 Current status of alginate in drug delivery

Alginates are natural polymers widely used in the food industry because of their biocompatible, biodegradable character, nontoxicity and easy availability (**Fig. 2.1**). The bioadhesive character of alginates makes them useful in the pharmaceutical industry as well. The application areas of sodium alginate-based drug delivery systems are many and these systems can be formulated as gels, matrices, membranes, nanospheres, microspheres, etc. [1–4].

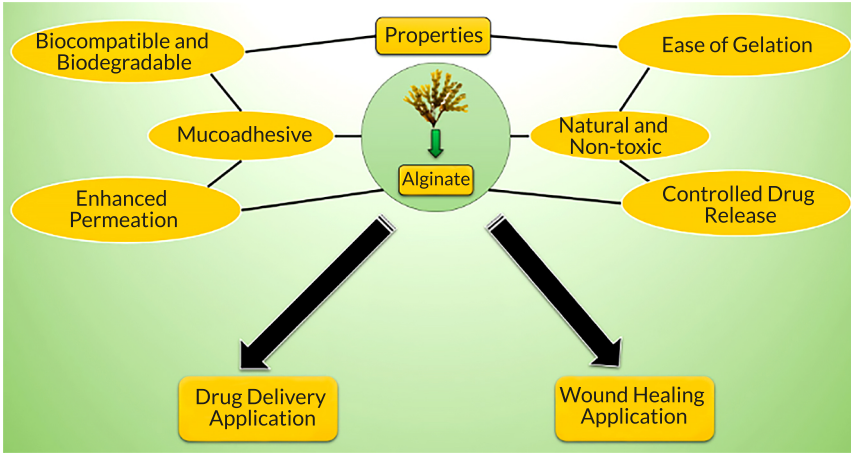


**Fig. 2.1** Alginate-based systems
*Source: [4]*

Alginate is a polysaccharide extracted from brown seaweeds, including *Laminaria hyperborea*, *Laminaria digitata*, *Laminaria japonica*, *Ascophyllum nodosum*, and *Macrocystis pyrifera*. Alginate with molecular weight between 32,000 to 400,000 g/mol is mainly comprised of a sequence of liner polymers of $\beta$-(1-4)-D-mannuronic (M-blocks), $\alpha$-L-guluronic acid (G-blocks), and inserted MG sequences (MG-blocks), with varying proportions and linear arrangements [5]. That organized in homogenous patterns with repeated G residues, repeated M residues, and heterogenous patterns with alternating G and M residues [6]. Alginate derived from different sources displays different M/G ratios and contents in M and G [7], leading to the change of molecule weight and physicochemical properties. These parameters are related to the characteristics and applications of alginate. Generally, alginate with high M units shows good biocompatibility and more immunogenic [8]. Alginate with high M units has soft and elastic properties, G-rich alginate exhibits hard and brittle characteristics [9, 10]. The rigidity of the chains increases in a sequence, MG < MM < GG, due to the electrostatic repulsion between charged groups. G-rich alginate gels have better mechanical stability (**Fig. 2.2**) [6].

For example, alginate extracted from *Laminaria digitata* and *Ascophyllum nodosum* has been shown to have M/G ratios of 1.16 and 1.82, respectively. Alginate is a biocompatible polymer with very low toxicity [11]. These are the main advantages that make alginate one of the biopolymers with the widest biomedical applicability. One of the most common applications of alginate is their use as an excipient

in drug-delivery systems, namely, acting as a stabilizer agent in various pharmaceutical formulations [12].

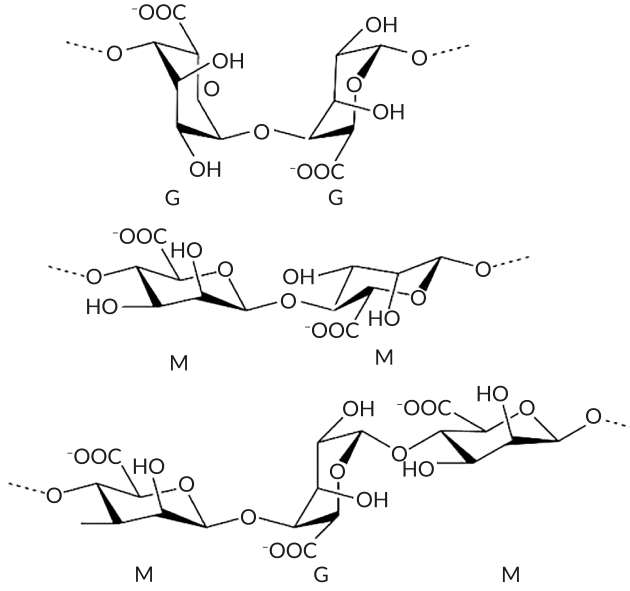


**Fig. 2.2** Chemical structure of alginate
*Source: [6]*

Alginate has received much attention due to its biocompatibility. However, the properties of pure alginate are limited, such as weak mechanical strength, which limits its application. Alginate-based composite effectively overcomes the defect of pure alginate. The molecular weight and microstructure can be designed. More importantly, the essential properties for clinical application are improved, including mechanical properties, biocompatibility, gelation ability, chondrogenic differentiation and cell proliferation. This chapter will describe development of alginate-based composite in biomedical application. In the fields of wound dressing, drug delivery, and tissue engineering, the impact of structural changes on performance has been stated [13].

Alginate has excellent biocompatibility, that has been widely assessed. However, some gaps of biocompatibility between alginate and alginate complex still exist. For purified alginate gels, the relative amounts and distribution of M and G have an effect on biocompatibility [14]. S. K. Tam et al. found that gel beads prepared with alginate contenting intermediate guluronate (IntG, 44% G) exhibited better biocompatible

than high guluronate content (HiG, 71% G). There are no inflammatory reactions around alginate implants. For the alginate complex, the impurities from alginate-based materials, such as heavy metals, proteins, and polyphenolic compounds, have the potential to cause an immunogenic response. A multi-step extraction procedure reduces the concentration of impurities and will not cause foreign body reactions. Meanwhile, the biocompatibility properties of alginate are attributed to hydrophilicity, chain migration, and water-absorbing [15]. Swelling properties contribute to enhance biocompatibility, that limiting the adsorption of proteins and cells of immune response. Alginate is a natural and versatile polymer that has gained significant attention in the biomedical and pharmaceutical industries due to its diverse biological activities and physicochemical properties. Alginate possesses several advantages, such as biocompatibility and ease of gelation, making it suitable for various biomedical applications. Its structural similarity with extracellular matrices of tissues and ability to undergo several critical processes have also contributed to its popularity. The alginate hydrogel's ability to retain a large amount of water provides it with a soft nature, making it effective in wound healing, drug delivery of bioactive molecules, tissue engineering, and other biomedical research and engineering fields. Modern technological advancements in alginate research have led to its potential applicability in the form of a matrix for three-dimensional cell lines, antibiotic adjuvants in cell transplantation, and the management of several ailments, including diabetes or neurodegenerative disorders. This chapter aims to provide an overview of the characteristics of alginates and their existing and potential uses and suggest new avenues for future research. The biological and pharmacological mechanisms of alginates are explained, along with their current use and future promise as a drug delivery approach. In conclusion, alginates' multifunctional nature and biocompatibility make them an attractive option for biomedical and pharmaceutical applications. The review [16] highlights the importance of understanding alginate's unique properties and its potential to address current and future biomedical challenges.

Alginate, as a potential biomaterial, has been successfully explored in different applications such as wound dressing, drug delivery, bone, cartilage. It could afford a moist microenvironment for wound dressing, serve as the carrier for drug delivery, and act as a scaffold for tissue engineering. The outstanding characteristic of alginate for its applications contains biocompatibility, degradable properties, gelatinization capacity, and effective modification to obtain new performances. In the future, more novel alginate composites with controlled properties should be constructed by chemical or physical modification. That will play a vital role in intricating drug or cell-loading. Novel alginate composites also could provide mild and targeted degradation properties.

### 2.3 Novel alginate composites

Alginate capacity to form gel is the major reason for its uses mostly in soft tissue engineering and wound healing. Nowadays, alginate is mixed with other distinct materials to form alginate composites that suit the need of biomedical applications.

The review article [17] describes the preparation process of alginate and alginate composites and discusses their biomedical applications. Future prospects for the preparation and biomedical applications of alginate and alginate composites are also included.

To enhance alginate physical characteristics, other substances had been mixed with alginate to form alginate composite. Alginate composites are formed by adding natural polymer such as collagen, chitosan and gelatin, synthetic polymer such as polylactide and polypyrrole, and inorganic compounds such as tetraethylorthosilicate (TEOS) and hydroxyapatite (HA) [18].

Alginate-based hydrogel for biomedical purpose can be either non-injectable or injectable. Non-injectable alginate hydrogel is pre-formed prior its *in vivo* implantation. On the other hand, injectable hydrogel has wider gelation working windows before its final shape is assumed. This enables defect with irregular shape and size to be filled with minimally invasive procedure [19]. Both kind of hydrogel often incorporated with foreign material whether in particle or fibrous form to produce alginate composite hydrogel with improved overall structural integrity and desirable properties.

For both alginate and alginate composite to be used for various biomedical applications, they had to be made into different forms such as fiber, bead, hydrogel, or 3D printed material depending on the specific demand of each biomedical applications.

In the composites, the alginate is mainly made into hydrogels by cross-linking mechanism using counter ions such as calcium or other multivalent ions (e.g., calcium and sodium ions). Although there are several reported making the alginate into fiber mat by electrospinning process [20], sponge and foam sheet [21], the alginate dressings subsequently became hydrogel form when in-contact with water and the moist exudate. In an alginate composite, other materials such as polyvinyl alcohol, chitosan [22], and gelatin [23] are also added during the formation of the hydrogel. The presence of polyvinyl alcohol affected the physicochemical properties of the hydrogel dressing such as its swelling ratio, tensile strength and elongation [21]. In many cases, the higher content of sodium alginate decreases the gel fraction, maximum strength and break elongation, but increases swelling ability, protein adsorption, hydrolytic degradation and thermal stability. In study [21], crosslinked PVA-alginate (PVA-SA) hydrogel films, loaded with sodium ampicillin as an antibiotic model, were prepared by the freeze-thawing cycle method to avoid the harms which are

arising from the traditional chemical crosslinking. PVA-SA hydrogels formed a matrix of physically crosslinked polymeric chains containing uncrosslinked polymers, water, and sodium ampicillin. Properties of hydrogel films such as gel fraction, swelling behavior, mechanical, morphology, and roughness, in addition, release studies of ampicillin from the prepared films were investigated. Finally, bio-evaluation studies of essential wound dressing characters like protein adsorption, hemocompatibility, hydrolytic degradation and antibacterial activity behavior were investigated under *in vitro* conditions.

Ensuring the therapeutic molecules reaching the intended target organ or tissue for maximum effectiveness of the drug has been the main goal of drug delivery [24]. Various materials have been studied and tested for drug delivery. among all, alginate hydrogel has been attractive because the gentle gelation process of making them can be used for cell encapsulation and sustained drug release [25]. The drug delivery system of alginate is commonly associated with wound dressing applications. The alginate microcapsules were used for a sustained release of antimicrobial agents or drugs of the wound dressing [26]. Recently, a double membrane hydrogel composed of alginate and cellulose nanocrystals had shown a promising potential for a targeted released of antibiotic drugs via controlled swelling mechanisms [27].

The clinical study of alginate and alginate composite-based drug delivery system have been reported as well. However, as compared to wound dressing application the clinical study of the alginate and alginate composite-based drug delivery system is still low and rare.

Thus, the creation of alginate composites is extremely feasible for a wide range of biomedical applications due to the unique combination of alginate properties and the possibility of integrating other materials. Alginate, a polysaccharide derived from brown algae, is a bioinert material that does not cause an immune response or toxic reactions in the body. This is critically important for implants, drug delivery systems, and other biomedical devices in contact with living tissues. Alginate readily forms hydrogels in the presence of divalent cations (e.g., $Ca^{2+}$) under mild conditions (room temperature, neutral pH). This allows for the encapsulation of cells, biomolecules, and other sensitive components without damage. Due to the ability to encapsulate biomolecules, composites can serve as systems for controlled and prolonged drug delivery directly to the site of action, minimizing side effects. In summary, alginate composites are a powerful tool in biomedicine due to their exceptional biocompatibility, the possibility of precise control over mechanical and biological properties, and their versatility in application. Their ability to be adapted to the specific needs of the body makes them indispensable in the development of a new generation of therapeutic solutions.

It should be noted that the prospects for the use of alginate hydrogels in dentistry are very broad. Research is actively underway to develop new composites with improved properties: greater accuracy, better mechanical strength, the ability to more targeted delivery of bioactive molecules and cells to accelerate the regeneration of oral tissues. It is of interest to conduct research on the development of the composition of composite hydrogels based on alginate and lidocaine for controlled drug delivery systems, in particular for local anesthesia. Attention should be paid to the selection of additional components that can be included to improve the properties of the hydrogel for dental purposes.

### 2.4 Research materials and methods

In order to develop a water-soluble polymer composition, the following main and additional components were selected: sodium alginate (NaAlg) (Sigma-Aldrich, Germany) as the main polymer; antimicrobial agent Azithromycin; active pharmaceutical ingredient (API) lidocaine; soothing ingredient Levomenthol; preservatives Nipagin, Nipazole; crosslinking agent Calcium chloride. Calcium gluconate was used as a cross-linking agent at a concentration equivalent to 1.0 mole of $Ca^{2+}$ ions per 2.0 moles of alginate carboxyl groups. This specific proportion was chosen to form a stable yet elastic hydrogel structure suitable for dental applications. Therefore, calculations showed that for a 100 g sample of a 5% alginate solution, 56–57 ml of a 10% calcium gluconate solution was added, and for a 100 g sample of a 7% sodium alginate solution, 79–80 ml of a 10% calcium gluconate solution was added to achieve the desired cross-linking ratio.

To create a dental gel, it is necessary to prepare a base that includes sodium alginate and water. After preparing the base, medicinal components are added, namely azithromycin, lidocaine, levomenthol, along with other auxiliary components. The mixture is then thoroughly blended until a homogeneous mass is obtained.

Purified water (PW) (CAS No. 7732-18-5) and sodium alginate are used to prepare the mixture. The formula of sodium alginate is presented in **Fig. 2.3**.

Lidocaine – 2-(Diethylamino)-N-(2,6-dimethylphenyl)acetamide (CAS No. 137-58-6) was also used to prepare the gel. The structural formula is shown in **Fig. 2.4**.

Nipagin is used in cosmetic and pharmaceutical products to preserve their shelf life and prevent the growth of microorganisms such as bacteria and fungi (**Fig. 2.5**).

Nipazol (Propylparaben) – propyl 4-hydroxybenzoate (CAS No. 94-13-3) (**Fig. 2.6**) is active against yeast and mold fungi, and is also known for its effectiveness against gram-positive and gram-negative microorganisms, exhibiting the greatest antimicrobial activity at pH 4.0–8.0.

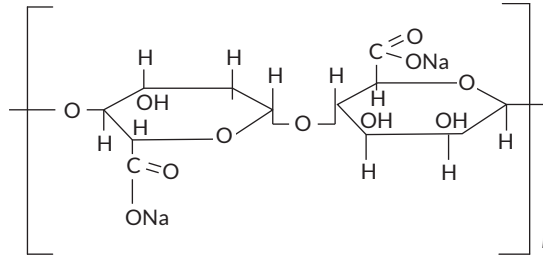


**Fig. 2.3** Structural formula of sodium alginate

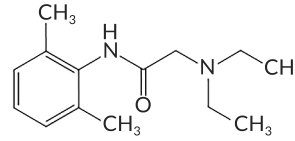


**Fig. 2.4** Structural formula of Lidocaine – 2-(Diethylamino)-N-(2,6-dimethylphenyl)acetamide (CAS No. 137-58-6)

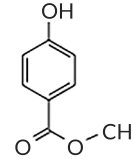


**Fig. 2.5** Structural formula of nipagin

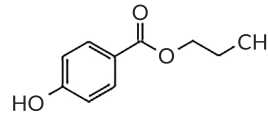


**Fig. 2.6** Nipazol (Propylparaben) – propyl 4-hydroxybenzoate (CAS No. 94-13-3)

Azithromycin (Azithromycin) – 2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-11{[3,4,6-trideoxy-3-(dimethylamino)-$\beta$-D-xylo-]oxy}-1-oxa-6-azacyclopentadec-13-yl 2,6-dideoxy-3-C-methyl-3-O-methyl-$\alpha$-L-ribo-hexopyranoside (CAS No. 83905-01-5).

Azithromycin has a broad spectrum of activity and is used to treat many infections, including respiratory and skin infections. It is a derivative of erythromycin and is known for its high efficacy and convenience due to its short course of treatment (**Fig. 2.7**).

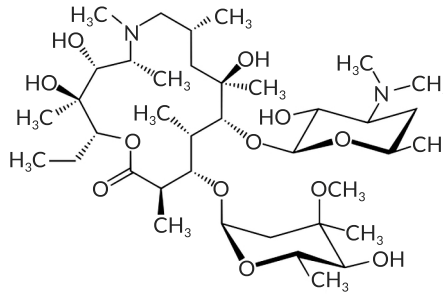

**Fig. 2.7** Structural formula of Azithromycin

Levomenthol – (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol (CAS No. 2216-51-5) (**Fig. 2.8**) – is a volatile crystalline substance known for its characteristic fresh aroma and cool taste. It occurs as white or crystalline colorless needles or plates. The melting point of levomenthol is approximately 42–45°C. It has a characteristic minty aroma, which is used in many perfumery and pharmaceutical products. This substance is known to have a cooling effect when in contact with the skin or mucous membranes.

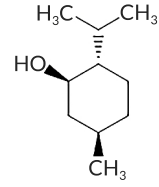

**Fig. 2.8** Levomenthol structural formula

Tween-80 (CAS No. 9005-65-6) – Polysorbate-80 or polyoxyethylene sorbitan monooleate, is a synthetic nonionic surfactant and emulsifier widely used in the food, pharmaceutical, cosmetic and other industries. Its main function is to mix ingredients that do not normally mix, such as oil and water (**Fig. 2.9**).

Sodium alginate (NA) was used to prepare the polymer-based gel.

First, preservatives were mixed in distilled water at the specified concentrations using a paddle mixer (**Fig. 2.10**) at a speed of 400–1400 rpm: nipazol – 0.01%, nipagin – 0.02%, and lidocaine 2%. When all the crystals dissolved, 5% NA was added and mixing continued.

The mixture was prepared by grinding in a mortar a mixture of ingredients: Tween-80 – 0.25%, Levomenthol – 0.5% and Azithromycin – 1%.

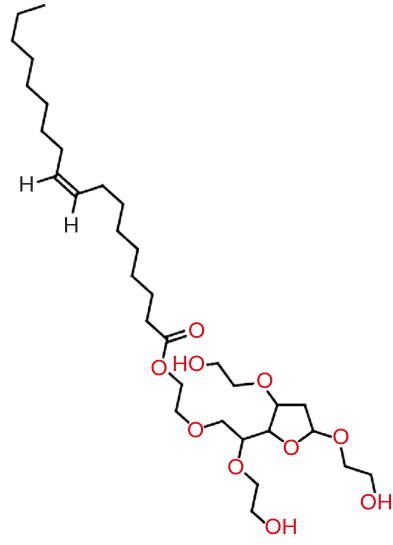


**Fig. 2.9** Structural formula of Tween-80

**Fig. 2.10** Mixer for preparing a homogeneous hydrogel solution

The finished mixture was added to the solution with AN and mixed until homogeneous.

The prepared solution was poured onto plates 1.5 mm thick and cross-linked with $Ca^{2+}$ ions.

In a similar way, several hydrogels with different ratios of AN were prepared, namely 5%, 7% and 10%.

**Methodology for studying rheological properties.** The study of viscoelastic properties of hydrogels using rheological tests is the main experimental method. Measuring the viscosity of the gel is important in the quality control of hydrogels and determining their properties. Rheological characteristics directly affect the structural and mechanical properties of these gels.

In order to determine the rheological properties of a polymer composition, including a gel based on sodium alginate, a rotor is used: a device that allows to measure the deformation of the material when a force is applied to it and determine its viscosity and elastic properties.

The viscosity of the gel was measured using a rheometer at different temperatures: 25°C, 32°C, 37°C. During the measurements, the shear rate was changed, and the values of shear stress and deformation were recorded. The chapter presents the results of studies at a temperature of 32°C, which corresponds to the average temperature of the oral mucosa. This approach ensures that the conditions closely model the real environment, allowing for an accurate assessment of the hydrogel's rheological properties and stability during clinical use.

The method of measuring rheological properties consists of the following stages:

1. Sample preparation: the measurement is carried out on a gel that was prepared according to the technology described above and is in a liquid state. For measurement, the sample is placed on a rheometer platform.

2. Setting the initial pressure and temperature: a certain initial pressure and temperature are applied to the sample, which allows to establish the initial state of the gel.

3. Deformation measurement: forces begin to act on the sample, changing its shape. The rheometer measures the deformation of the sample when a given force is applied.

4. Registration of rheological properties: based on the data obtained, construct flow curves at different concentrations and temperatures.

To determine the rheological properties of the studied samples, a Brookfield DV-III rheometer (**Fig. 2.11**) with a thermal platform and a block providing temperatures of 25, 32 and 37°C was used.

The experiment was carried out by immersing the spindle at an angle of 45° to the surface of the liquid in a chemical beaker filled with the solution. The spindle was fixed on the axis in a vertical position and rotated by a motor at a constant speed.

**Fig. 2.11** Brookfield DV-III viscometer

Viscosity measurements were carried out using a Brookfield DV-III rheometer, which is used to determine the average dynamic viscosity. This device is an effective tool for analyzing the rheological characteristics of a liquid and allows to obtain reliable research results.

The measurement of the fluid resistance to spindle rotation, which depends on the viscosity of the solution, was determined by the torque recorded by the corresponding sensor on the viscometer display. During stabilization of the meter, which showed a constant value, the viscosity values were recorded.

An important practical indicator is the viscosity of the solution of a polymer composite material.

Viscosity is defined as the proportionality coefficient between the shear stress $\tau$ and the shear rate gradient $\gamma$ (2.1)

$$\eta = \tau \cdot \gamma. \tag{2.1}$$

Viscosity for most low-molecular liquids is a constant and does not depend on deformation. These systems are called Newtonian. Changes that occur under the action of external forces are quickly restored due to thermal motion.

To determine the flow of water-soluble polymeric materials, the Ostwald-de Villa equation is used. At $n < 1$, the equation of behavior of pseudoplastic liquids.

In logarithmic coordinates, the dependence of $\tau$ for many non-Newtonian materials often becomes linear in a fairly wide range of shear rates, which explains the widespread use of the equation. At $n = 1$, the law of Newtonian flow.

The Ostwald-de Villa equation is the only empirical model used to describe non-Newtonian fluid behavior, in particular polymer solutions. This equation allows for accounting for changes in fluid viscosity depending on the shear rate or shear stress. The equation is as follows (2.2)

$$\eta = K \cdot \gamma^{n-1}, \tag{2.2}$$

where $h$ – shear stress; $K$ – constant; $\gamma$ – shear rate; $n$ – exponential constant, which determines the technical index.

If in the Ostwald-de Villa equation the value of the exponent $n < 1$, this is a conflict about the pseudoplastic behavior of the liquid. In this case, with an increase in the shear rate or shear stress, the viscosity of the liquid decreases.

If the Ostwald-de Villa level has an exponent $n < 1$, this is a conflict about the pseudoplastic behavior of the fluid. In this case, with increasing shear rate or shear stress, the viscosity of the fluid decreases. This means that at rest the parts in the medium are arranged in a chaotic order. However, with increasing shear rate, they begin to orient themselves in the direction of flow. As the speed increases, the interaction between the parts decreases. These changes in the material occur so quickly that they are difficult to detect in conventional measuring instruments.

**Methodology for studying hydrogels for water absorption.** The hydrogel sample was dried in a drying oven at a constant temperature (40–50°C) until a constant mass was reached. After drying, the samples were cooled to room temperature in a desiccator.

The dried hydrogel sample was weighed on an analytical balance. This mass is the initial mass of the dry sample.

The weighed dry sample was placed in a beaker with distilled water so that the liquid completely covered the sample. The beaker was left at room temperature, and the samples were weighed every 10 min.

Water absorption ($W$, %) was calculated by the formula (2.3)

$$W = \frac{m_1 - m_2}{m_1} \cdot 100\ \%, \tag{2.3}$$

where $m_2$ – initial weight, g; $m_1$ – weight after immersion, g.

The amount of lidocaine ($\lambda$ = 262 nm) released from hydrogel samples was determined by spectrophotometric method using the OPTIZEN POP UV VIS device ("Mecasys", South Korea).

When developing the technology of polymer-based hydrogels, it is important to investigate the possible interaction of API with excipients.

### 2.5 Research on hydrogels water absorption

In this study, the task was to develop a hydrogel composition for use in cases where a comprehensive approach to treatment is required, including the fight against infection, reducing pain and inflammation, and promoting tissue repair, in particular, in diseases of the oral cavity. Therefore, components were added to create a product with a multifactorial effect. This includes an anti-inflammatory action achieved by reducing the bacterial load (Azithromycin); an antibacterial effect through the direct action of Azithromycin on pathogenic microorganisms; an analgesic effect provided by the local action of Lidocaine and Levomenthol, resulting in rapid pain relief; and protective and regenerative effects due to the ability of sodium alginate to adhere to mucous membranes. This adhesion allows the formulation to remain at the application site (in the oral cavity) for a longer period, thereby enhancing the effectiveness of the other components. Additionally, sodium alginate forms a protective film and promotes healing, contributing to a prolonged therapeutic effect, as the gel form ensures sustained contact of active substances with the affected surface.

In this work, the ratios of components in the composition were calculated to achieve the desired consistency and maximum efficiency. The percentage ratios (per 100 grams of product) were determined as follows:

– sodium alginate: 7%;
– Azithromycin: 1%;
– Lidocaine: 2%;
– Levomenthol: 0.5%;
– other auxiliary components: 0.28%;
– water: 86.22%.

The pH of the composition is 6.5–6.8. This is attributed to sodium alginate forming a slightly alkaline environment (pH 6.5–7.2), azithromycin slightly shifting it toward alkalinity, while lidocaine in its hydrochloride form can slightly acidify the system, bringing it closer to neutral values. Thus, the resulting pH range of 6.5–7.0 is optimal for alginate stability: this range ensures adequate swelling of the polymer network and stability of the cross-linked structure. The pH is close to the

physiological range (≈ 6.8–7.2), which prevents mucosal irritation. Azithromycin is a weak base (pKa ≈ 8.5–9.5). In the gel, it may slightly shift the pH toward alkalinity (up to 6.8–7.2). This was taken into account during formulation optimization to maintain the stability of the alginate matrix.

The moisture retention index for sodium alginate-based hydrogels is critically important, since it directly affects the functional properties of the material and its effectiveness. Therefore, it was advisable to determine how the components of the composition affect its properties in terms of moisture retention. The results at concentrations of 5, 7 and 10% of the base – sodium alginate – are shown in **Fig. 2.12**.

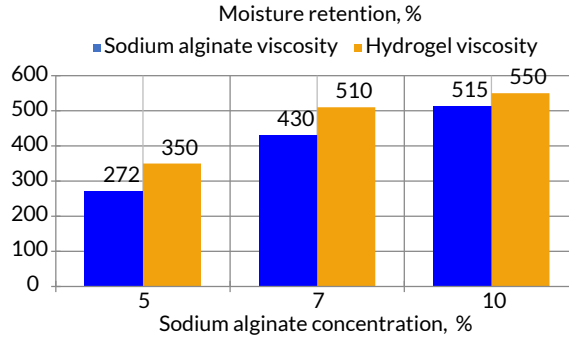


**Fig. 2.12** Moisture retention

Sodium alginate is the main gelling agent and, of course, the main component responsible for water absorption. It is able to retain a significant amount of water by forming a network of polymer chains. The higher the concentration of sodium alginate (up to a certain limit), the more water it can absorb and retain.

The data shown in **Fig. 2.12** indicate that the proposed hydrogel composition provides increased water retention. At a sodium alginate concentration of 5% – excipients provide increased moisture retention by 22.5%, at 7% – by 18.6%, at 10% – by 6.8%. The data obtained indicate that the synergistic interaction of the components is the primary factor influencing the properties of the sodium alginate hydrogel in this phenomenon.

One of the main components of the composition is lidocaine. It is a base and can affect the pH of the gel. If the pH of the composition is more optimal for swelling and formation of stability of alginate (for example, slightly shifted to the side, which contributes to greater hydration or the formation of a denser, but hydrated structure), this can lead to better water retention.

Interaction of azithromycin (1%) and lidocaine (2%) with the polymer is possible. Although their main function is pharmacological, they can weakly interact with the polymer chains of alginate (for example, through hydrogen bonds, ionic interactions, or hydrophobic interactions). These interactions can either strengthen the polymer network, making it less prone to "squeezing out" water, or, conversely, creating conditions for better hydration of polymer chains, which leads to increased water retention.

The combination of components can create a special microenvironment in the gel that more effectively retains water compared to pure alginate. This may be due to ionic strength, polarity of the medium or specific molecular interactions.

The reason for increasing the water retention of the composition is the addition of auxiliary components that act as humectants, even in small quantities (0.28% of "other components"). These components actively bind water molecules, enhancing the natural ability of sodium alginate to retain water.

Thus, increasing the moisture retention of an alginate-based hydrogel is achievable in the proposed composition.

The main property of hydrogels is the ability to swell under the influence of water. They can absorb water in large quantities, which provides them with a high-water content. At the same time, hydrogels are able to retain water in their structure, without losing it under the influence of gravity. The results of the research are presented in **Fig. 2.13**.

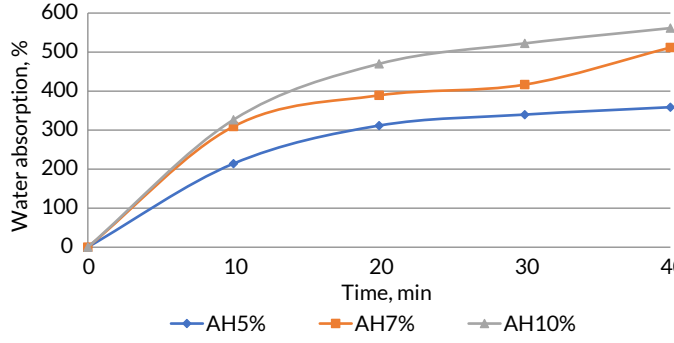


**Fig. 2.13** Water absorption kinetics of sodium alginate-based composition gel

The degree of water absorption of hydrogel samples directly depends on the concentration of AN in their composition. With an increase in the concentration of sodium alginate from 5% to 10%, a significant increase in maximum water absorption is observed. In 40 minutes of study, the sample with the highest concentration

of AN10% showed the best result, reaching a water absorption of over 550%. The sample with AN7% absorbed about 510% of water, while the sample with the lowest concentration of AN5% absorbed only 360%. Similar dynamics are characteristic of all samples: the highest absorption rate is observed in the first 10–20 minutes, after which the process slows down and gradually approaches the equilibrium state. Thus, increasing the concentration of sodium alginate effectively increases the ability of the hydrogel to absorb and retain water.

**Research on rheological characteristics.** During the experiment, the viscosity of polymer compositions was studied at different concentrations of AN and at different temperatures in the studied mixtures.

Based on the results obtained, graphs of the flow dependence at different concentrations and temperatures were constructed (**Fig. 2.14**, **2.15**).

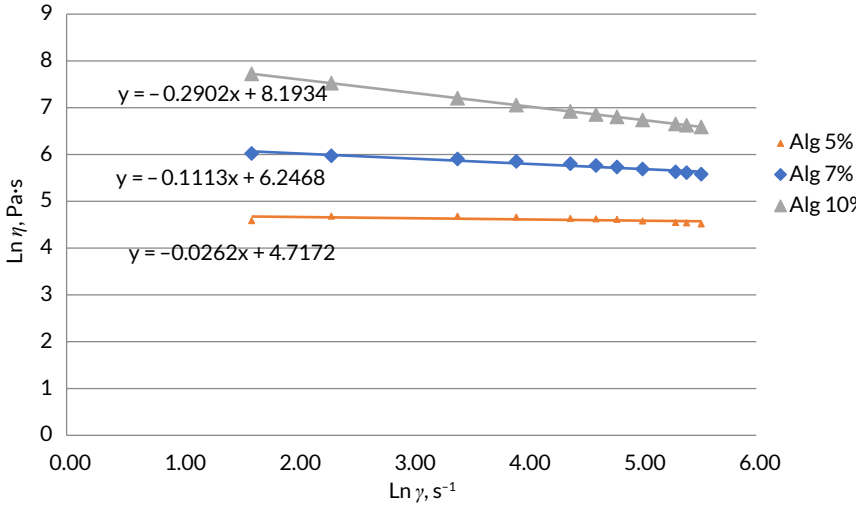


**Fig. 2.14** Dependence of the viscosity of the solution of the sodium alginate-based composition on the shear rate gradient at a temperature of 32°C

From the processed research results presented in **Fig. 2.14**, it was found that the viscosity of solutions directly depends on the concentration of sodium alginate. The highest viscosity indicators were recorded in the 10% solution, while the 5% solution is the least viscous. This indicates that with an increase in the polymer content in the solution, intermolecular interactions increase, which leads to an increase in flow resistance.

All the studied solutions are non-Newtonian fluids. They are characterized by pseudoplastic behavior, the viscosity decreases with increasing shear rate. This is confirmed by the negative slope of all three trend lines on the graph. The solution with the highest concentration (AN10%) demonstrates the largest slope of the curve, indicating the most pronounced pseudoplastic properties. This means that its viscosity depends most strongly on the applied shear rate.

Therefore, increasing the concentration of sodium alginate leads not only to an increase in the overall viscosity of the system, but also to an increase in its pseudoplastic character.

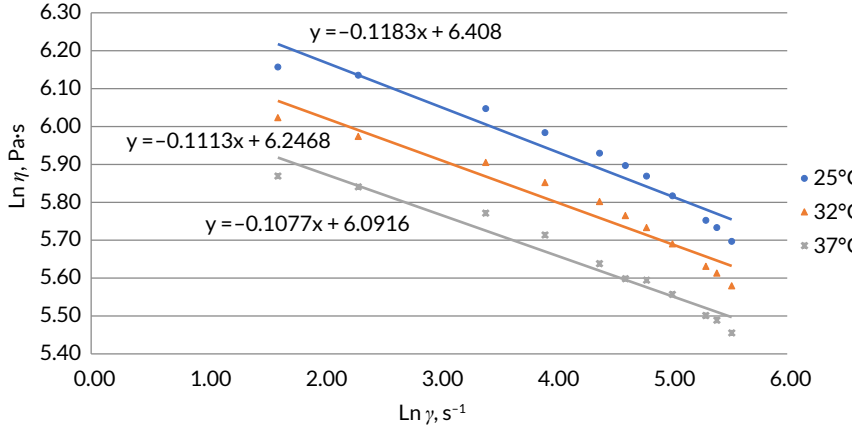


**Fig. 2.15** Dependence of viscosity of 7% solution of composition on temperature from shear rate gradient

With increasing temperature from 25°C to 37°C, viscosity of 7% sodium alginate solutions decreases significantly. Increasing temperature increases kinetic energy of molecules, reduces intermolecular interactions and leads to decrease in viscosity of polymer solutions. For all temperatures, a linear dependence of Ln $\eta$ on Ln $\gamma$ with negative slope is observed. This indicates non-Newtonian, namely pseudoplastic behavior of sodium alginate solutions. That is, with increasing shear rate (increasing Ln $\gamma$), the viscosity of the solution decreases. The absolute value of the slope of linear regressions decreases with increasing temperature (0.1183 at 25°C, 0.1113 at 32°C, 0.1077 at 37°C). This may indicate that the shear thinning rate decreases slightly with increasing temperature. In other words, at higher temperatures, the solution becomes less "sensitive" to changes in shear rate than at lower

temperatures. The value of the free term ($b$) in the regression equations ($y = mx + b$) is the logarithm of the viscosity at Ln $\gamma = 0$ – extrapolated to zero shear rate. This value also decreases with increasing temperature: 6.408 at 25°C, 6.2468 at 32°C, 6.0916 at 37°C. This confirms the general decrease in viscosity of sodium alginate solutions with increasing temperature.

**Study of lidocaine release kinetics.** A spectrophotometric method was used to determine the content of lidocaine in buffer solutions. The processed research results are presented in **Fig. 2.16**.

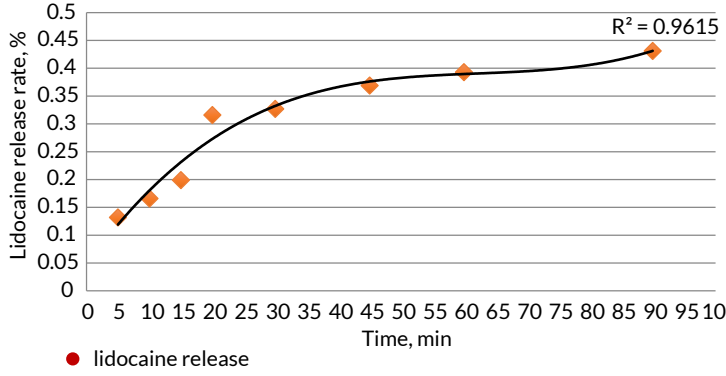


**Fig. 2.16** Kinetic curve of lidocaine release from a polymer carrier into a phosphate buffer medium (pH 6.8)

With increasing time, the percentage of released lidocaine increases. In the initial stages (first 10–20 minutes), a relatively rapid increase in lidocaine release is observed. Over time, the rate of lidocaine release gradually slows down. This is evident from the fact that the slope of the curve becomes less steep as time increases. During the observed period (up to 60 minutes), the release of lidocaine reaches approximately 60%, and after 90 minutes the degree of its release from the hydrogel exceeds 80%.

## 2.6 Conclusion

Sodium alginate-based hydrogels demonstrate significant potential as controlled drug release systems, as evidenced by their unique physicochemical properties. An innovative hydrogel with the following composition has been developed:

Sodium alginate – 7%; Azithromycin – 1%; Lidocaine – 2%; Levomenthol – 0.5%; other auxiliary components – 0.28%; water – 86.22%.

Hydrogels are capable of absorbing and retaining large amounts of water, with the degree of water absorption being directly proportional to the sodium alginate concentration. Increasing the AN concentration from 5% to 10% significantly increases the maximum water absorption (from 360% to over 550% in 40 minutes), indicating the possibility of tuning this important property. The kinetics of water absorption is characterized by a rapid initial phase (first 10–20 minutes) followed by a slowdown. It was found that the proposed hydrogel composition provides increased moisture retention. At a sodium alginate concentration of 5%, the excipients provide an increase in moisture retention by 22.5%, at 7% – by 18.6%, and at 10% – by 6.8%.

Sodium alginate solutions are non-Newtonian fluids with pronounced pseudoplastic behavior, i.e. their viscosity decreases with increasing shear rate. It was found that the viscosity of solutions directly depends on the AN concentration: higher concentrations (10%) provide higher viscosity and more pronounced pseudoplastic properties.

The viscosity of solutions is inversely dependent on temperature, with increasing temperature (from 25°C to 37°C) the viscosity decreases significantly. At the same time, the degree of shear thinning decreases somewhat with increasing temperature, making the solution less sensitive to changes in shear rate.

According to the results of the study of the kinetics of lidocaine release from hydrogels, a release in time was established. The release process is characterized by a relatively fast initial phase (the first 10–20 minutes) with a subsequent gradual slowdown. About 60% of lidocaine is released within 60 minutes, and after 90 minutes this figure exceeds 80%, which indicates the possibility of controlled and prolonged release of the drug.

Thus, by optimizing the concentration of sodium alginate and controlling the temperature conditions, it is possible to purposefully regulate key physicochemical and functional properties of hydrogels, such as water absorption, viscosity and release kinetics of active pharmaceutical ingredients. This opens up wide opportunities for the development and application of sodium alginate-based hydrogels in the pharmaceutical industry to create controlled-release systems, in particular, lidocaine.

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