Preparation of Grain β-glucan Gel and Characteristics of Its Slow-release

Ting Xu¹, Jia Wu², Lan Zhao¹*,

¹College of Life Sciences, Fujian Normal University, Fuzhou, 350117, China
²College of Biological Science and Engineering, Fuzhou University, Fuzhou, Fujian 350116, China

*Corresponding author: zhaolan@fjnu.edu.cn

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Abstract The β-glucan freeze-thaw gel has been used as a carrier to release curcumin. The freeze-dried gel has the ideal sustained release following 5% β-glucan solution by adding 1% β-glucan quality curcumin, repeated freezing and thawing 8 times. The Peppas equation can significantly describe the release mechanism of curcumin in the β-glucan gel. This study further shows that the release of curcumin in the oat β-glucan gel is the Fick diffusion mechanism and coated barley β-glucan is a non-Fick release. Trying to use β-glucan as a completely natural drug delivery carrier opens up new ideas for the use of β-glucan.

Keywords: cryogelation, curcumin, sustained-release, non-Fick

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1. Introduction

Oat, also known as oat, is a kind of nutritious food in cereals [1]. It enjoys cold and warm climate conditions and is one of the important food crops in China [2]. Oats have high nutritional value and are rich in health-friendly ingredients [3]. They are hailed as the best full-price foods in cereals. With the increase in public awareness of the balanced mix of various nutrients and health awareness, China's oat products have excellent development prospects and trends. Barnyard referred to as “naked” barley, which belongs to cold and warm climate conditions [4,5]. In addition, the barnyard grass has strong adaptability to the environment, strong stress resistance [6], and short growth cycles, which make it one of the precious crops with abundant resources, extensive use, and high value [7]. In addition to brewing oats, oats can also be processed into a variety of delicious foods.

2. β-glucan

β-glucan is a linear polysaccharide located in the endosperm and aleurone layer of cereal grains [8,9]. Oat β-glucan is a linear polysaccharide formed by β-(1→3) and β-(1→4) glycosidic linkages connected to glucopyranose units [10,11], with more than 85% of β-glucan chains. There is a β-(1→3) glycosidic bond between 2 to 3 β-(1→4) glycosidic bonds in the segment, and about 15% of the segments are composed of β-(1→4) glycosidic bonds, and β-(1→3) glycosidic bonds are alternately connected. The structure of barley β-glucan is similar to that of oat β-glucan [12]. A large number of studies have confirmed that β-glucan has important physiological functions. It can promote the proliferation of probiotics, prevent colon cancer [13], reduce blood lipids and cholesterol [14], regulate blood sugar [15,16], improve immunity, anti-aging and moisturizes the skin [17,18].

2.1. Extraction and Purification of β-glucan

Wood et al. in the study of oat β-glucan extraction found that endogenous β-glucanase has an important effect on the extraction of glucan [19,20], so inactivation of the enzyme by refluxing ethanol is the first step, and the different extraction conditions will have a greater effect on the extraction rate, solubility, and viscosity of β-glucan [21,22]. The commonly used β-glucan extraction process can be summarized into the following steps [23]. First step: refluxing with ethanol to inactivate the enzyme, inactivating the activity of endogenous β-glucanase and removing some small molecular substances such as free sugars, proteins, and some other substances; second step: using high-temperature resistant amylase and protease to remove starch and protein from cereals; third step: precipitation of relatively pure glucan by ethanol [24]. For further purification of β-glucan, high-temperature resistant amylase can be used to remove starch for 1 h at 95°C [25]. The common methods for further protein removal are the Sevag method, trifluoroacetic acid method, and trichloroacetic acid method. Similarly, research on the use of activated carbon and polymer amide column chromatography has been employed to remove residual protein, and ammonium sulfate precipitation has been used to remove residual protein and pentosan [26,27].
2.2. Determination of β-glucan Contents

The contents of β-glucan are addressed by the variety, place of production, and environment. In addition, the contents generally range from 3 to 16%. The commonly used methods for determining the contents of β-glucan include viscosity method, precipitation method, enzyme method and fluorescence, respectively [28,29,30]. The measurement method results in large differences in measurement results. The results of different laboratories using the same method are not the same. Whether the β-glucan is completely extracted is the root cause. For example, the ammonium sulfate precipitation method makes it difficult to completely precipitate β-glucan [31], so the measurement results are lower than normal levels. It can be seen that the most critical factor determining the accuracy of β-glucan content determination is the complete extraction of β-glucan. In response to this problem, Forrest and others proposed to use hydrazine to treat samples to extract β-glucan [32]. This method has been used for the determination of total β-glucan in cereals. Nevertheless, because of the long analysis period and easy cause the degradation of β-glucan which lowers the measurement outcomes. When we continued to explore the method for determining β-glucan content, it was found that the enzyme method is not only easy to...
operate and does not require extraction of conventional measurement methods, but also uses specific enzymes for measurement, which has high accuracy and high specificity. Similarly, results obtained are accurate and reliable, so it is widely used. For example, Martin [33] and others have measured the β-glucan content with cellulase.

2.3. Structural Studies on the β-glucan

In the analysis of β-glucan linkages in cereals, β-glucans are obtained by methylation, acid hydrolysis, and acetylation to obtain partially methylated sugar alcohol acetates. Finally, gas chromatography-mass spectrometry is used for the GC-MS analysis of the glycosidic bond structure. In addition, nuclear magnetic resonance spectroscopy has been widely used for the structural analysis of β-glucan, including liquid nuclear magnetic resonance and solid-state nuclear magnetic resonance technology [34]. Morgan [35] et al. studied the gel structure of barley β-glucan by 13C CP/MAS nuclear magnetic resonance (NMR), and found that β-glucan interacts in some regions to form a gel, while β-glucan in other regions The sugar chains form amorphous regions. NMR analysis also shows that there are continuous β-(1→4) bonds in β-glucan. Wang et al. used x-ray diffraction to analyze oat β-glucans with different molecular weights. The X-ray diffraction pattern of oat β-glucans showed typical characteristics of high molecular polymers, and the peak width was substantial, indicating that there are several similar crystal morphologies and lattice types. In addition, Fourier transform infrared spectroscopy (FT-IR) has been widely used to analyze the structure of polysaccharides, such as Sekkal et al. used FTIR to study the structure of agar polysaccharides [36,37].

3. β-glucan Gel

Macromolecular viscous polysaccharides can form gels under certain conditions. β-glucan is one of them, so it also has the conditions to form a gel [38]. The frozen gel is a series of physical changes that occur in various synthetic and natural polymers through the process of freezing, frozen storage and thawing, thereby forming a non-covalent bond cross-linked network structure. This phenomenon is also known as freeze gelation [39,40,41]. Usually, there are two main stages in this process. One is the rapid precipitation or the formation of a weak gel during the freezing process, and the other is the slow process of increasing frozen structures during the thawing process. After research, β-glucan solutions (3 to 5%, w/v) with different mass fractions and different molecular weights can form frozen gels after repeated freeze-thaw cycles, mainly due to the effective inter-molecular chain in the freeze-thaw process. Collisions result in the rearrangement of β-glucan molecules to form a cross-linked structure and then a gel [42]. In a high-quality fraction of the β-glucan solution system, the probability of β-glucan molecules colliding with each other will increase, there are many cross-linked regions, and β-glucan molecules are easy to aggregate so that it will readily form a gel. Low-molecular-weight β-glucan solutions are more likely to form gels, mainly because of low molecular weight, fast diffusion speed, high mobility, and weak intramolecular interactions, which increases the probability of effective collisions between chains, so gel forms in a relatively short time. Lrakli [43] and others found that the formation of β-glucan gel is related to substances such as polyhydroxy compounds. When a certain mass fraction of glucose, fructose, maltose, xylose, etc. are added to the β-glucan solution, they can extend the time of gel formation and have a certain effect on the strength of the gel.

The main factors affecting the gel performance are the mass fraction of dextran, the relative molecular mass, the number of freeze-thaw cycles, polyhydroxy compounds, and temperature. In the existing literature, more attention is focused on the effects of initial polymer mass fraction, a number of freeze-thaw cycles, freezing temperature and thawing rate on the gel yield and the mechanical and thermal properties of the formed gel [44,45,46,47].

3.1. Studies on the Gel Properties

3.1.1. Characteristics of Water Relaxation

Field NMR equipment is mainly used to detect H protons in water. The H protons resonate with the emitted radio frequency to absorb the pulse energy. When the RF pulse ends, the H protons will release the pulse energy absorbed in the previous period. In order to detect the energy released by H protons, a special coil is used for the induction, and the resulting signal is a NMR signal. The so-called relaxation time is the characteristic time of the process. In order to describe the process of the magnetization returning to the equilibrium state, the longitudinal relaxation time $T_1$ and the transverse relaxation time $T_2$ are used to represent. Low-field NMR (LF-NMR) technology [48,49] is used to determine the relaxation time of hydrogen protons in the system. The water content, water distribution, and other related properties of the system can be studied, especially the distribution of lateral relaxation time [50]. According to the existing experimental research and theoretical simulation results, in the $T_2$ time distribution of hydrogen nuclei in food and biological systems, the $T_2$ of hydrogen nuclei of water molecules is smaller than that of pure water, and multiple distributions of $T_2$ will be produced. The reason may be that chemical exchange occurs between the hydrogen of the water molecules in the system and the active hydrogen of the macromolecules in the aqueous solution, and the water molecules in different environments also undergo diffusion exchange [51]. The free water existing between the particles or in the pores of the material can flow and have the effect of dissolving solutes. Therefore, under the action of the nuclear magnetic moment, it can still rotate at high speed, with a short correlation time and a long $T_2$. The properties of the gel are directly related to the water distribution state and relevant content in the gel. At this stage, low-field nuclear magnetic resonance technology is mostly applied to the water phase, distribution, and migration in the gel. The H nucleus is the research object reflects the changes in the internal composition of the gel, and is used to characterize the change in the gel quality. Compared with other detection methods, NMR detection technology has
the advantages of less sampling and maintaining the integrity of the sample. It can non-destructively study the mobility and distribution of water in the sample. It is a non-destructive detection method which can be used to detect gels, mobility and distribution of water in food. Yang Wenge et al. studied the effect of salt solution rinsing on gel quality of minced fish with low-field NMR.

3.1.3. Scanning Electron Microscope Observation

The gel strength was found to be related to the mass fraction and conditions of β-glucan to form a gel. In the field, SEM has been widely used in gels formed from tofu, the development of various related disciplines. In the food field, SEM has been widely used in the fields of biology, medicine, and metallurgy, and has promoted the development of various related disciplines. In the food field, SEM has been widely used in the fields of biology, medicine, and metallurgy, and has promoted the development of various related disciplines. In the food field, SEM has been widely used in the fields of biology, medicine, and metallurgy, and has promoted the development of various related disciplines.

The research by Wang et al. found that as the shear rate increased, the viscosity of oat β-glucan solution showed a tendency to decrease, which showed the characteristics of typical shear thinning non-Newtonian fluid. Studies by Wood [53] and others point out that oat gum has potential value in the application of food thickeners. Because in the aqueous solution, when the mass fraction of oat gum is greater than 0.2%, the shear-thinning behavior of non-Newtonian fluids appears. Jestin compared the difference between unhydrolyzed and partially hydrolyzed β-glucan [54] and found that the hydrolyzed β-glucan is more likely to form a network structure in three dimensions, i.e. a gel. However, the molecular structure of the two is not significantly different, so the reason why the hydrolyzed β-glucan is more likely to form a gel can only be explained by the partial hydrolysis that makes the β-glucan molecules smaller, and the molecules move more easily in the aqueous solution. Burkus [55], Lazarido [56], and Temelli [57] also discussed the mass fraction and conditions of β-glucan to form a gel. The gel strength was found to be related to the β-glucan mass fraction and molecular weight. When the mass fraction is higher, and the molecular weight is lower, the strength of β-glucan to form a gel is greater. At the same time, the higher the ratio of cellobiose to cellotriose, the shorter the gelation time of β-glucan, and the higher the gelation rate.

3.1.3. Scanning Electron Microscope Observation

Scanning Electron Microscope (SEM) is a new type of electronic, optical instrument. It has the characteristics of simple sample preparation, adjustable magnification, wide range, high resolution of the image, and large depth of field. For decades, SEM has been widely used in the fields of biology, medicine, and metallurgy, and has promoted the development of various related disciplines. In the food field, SEM has been widely used in gels formed from tofu, konjac, and surimi, and the structure and characteristics of β-glucan gel have been studied accordingly [58,59].

3.2. Study on Gel Sustained Release

3.2.1. Curcumin Introduction

Curcumin is a plant polyphenolic substance and a relatively small pigment with a diketone structure. It was originally extracted from ancient Chinese medicine in China and had antioxidant, liver-protective, anti-inflammatory; it has anti-cancer, lowering blood lipids, inhibiting thrombus formation, and eliminating peroxides, and has no side effects on the body. It is considered to be one of the ideal natural anti-cancer compounds [60,61,62,63]. But its poor water solubility, less absorption in the body, too fast metabolism, and low bioavailability limit its applications. Sustained-release dosage forms have the characteristics of prolonging the action time of drugs, increasing the therapeutic index, reducing the dosage, reducing toxicity, facilitating the administration of drugs, and increasing patient adaptability [64], so they have broad application prospects and development trends.

3.2.2. Common Sustained-release Models

With the in-depth study of drug release systems, a large number of drug release models have appeared. In recent years, there have been more than ten drug release models. The following are common:

(1) Zero-order kinetic model of drug release [65]

\[ Q = Q_0 + K_0 t \]  

Among them, \( K_0 \) is the zero-order release constant, \( Q_0 \) is the initial drug mass fraction in the solvent, which is 0 in most cases, \( t \) is the release time, and \( Q \) is the cumulative percentage of the drug in the solvent at time \( t \). The calculation formula is as follows:

\[ Q = \left[ C_n V_0 + V_i (C_1 + C_2 + \cdots + C_{n-1}) \right] / m \times \% \]  

(2) First-order kinetic model of drug release [65]

\[ Q = Q_w (1 - M \times e^{-K_1 t}) / Q_w \]  

Among them, \( Q_1 \) is the first-order release constant, \( Q_w \) is the maximum cumulative release degree, and \( M \) is a constant.

(3) Weibull model [66]

The Weibull equation distribution function for reliability studies. Its distribution model is:

\[ \frac{dQ}{dt} = \alpha (t) (\alpha - 1) e^{-t / \beta} \]  

For the integration of this formula, the Weibull distribution equation of the cumulative release rate at time \( t \) is given by:

\[ Q_t = 1 - e^{-\alpha t / \beta} \]  

Where \( dQ / dt \) represents the growth rate of the cumulative sustained release rate at \( t \), and \( Q_t \) is the cumulative
sustained release rate at time $t$. $t > 0$, $\alpha > 0$, $\beta > 0$; $\alpha$ is a scale parameter; $\beta$ is a shape parameter.

(4) Higuchi model [67]

The Higuchi model is often used to describe the mathematical model of sustained release of water-soluble active substances and similar formulations from the semi-solid or solid matrix:

$$Q_t = Q_0 + KH^{1/2}. \quad (6)$$

Among them, $KH$ is the sustained release rate constant of the corresponding substance in Higuchi's equation. $Q_t$ and $Q_0$ are cumulative sustained release rates at time $t$ and initial time, respectively.

(5) Hixson-Crowell model [68]

The Hixson-Crowell model is proposed based on the Higuchi model. According to the cubic root of the surface area of the spherical particles, which is proportional to the volume, it is used to describe the sustained release model from the spherical matrix. The expression is:

$$W_0^{1/3} - W_t^{1/3} = kt. \quad (7)$$

Among them, $W_t$ and $W_0$ are the sustained release rates of the corresponding substances in the system at time $t$ and the initial time, respectively. According to the calculation formula of cumulative release rate (1-7), the above formula is rewritten as:

$$\left(1 - Q_t\right)^{1/3} = Q_0 + kt \quad (8)$$

Among them, $K$ is the kinetic constant of the Hixson-Crowell model. $Q_t$ and $Q_0$ are cumulative sustained release rates at time $t$ and initial time, respectively.

(6) Peppas equation [69]

$$Q = Kt^n. \quad (9)$$

Among them, $Q$ is the cumulative release fraction (in%) at time $t$, $t$ is the release time, $K$ is a constant, the $K$ value is different for different drugs or different prescriptions and different release conditions, $n$ is the release parameter, and this parameter is Peppas Characteristic parameters in the equation characterizing the release mechanism.

4. Conclusions and Future Prospects

With the gradual improvement of people's living standards, people pay more and more attention to a reasonable diet and balanced nutrition. WHO and FAO experts agree that the diet structure is unreasonable, and the proportion of meat foods is relatively high, which will correspondingly absorb more cholesterol, fats, sugars, and additives, which will cause physical discomfort and, if severe, cause diseases. Modern people are pursuing a "four high and four low" healthy life with high protein, high fiber, high vitamins, high minerals and low fat, low cholesterol, low sugar, and low salt. Because $\beta$-glucan has a good effect in reducing blood lipids, cholesterol, regulating blood sugar, and improving immunity, some oats, barley, and their products containing $\beta$-glucan and other healthy ingredients are particularly popular with consumers. Therefore, strengthening the research of $\beta$-glucan has important practical significance for the human health [70,71,72]. $\beta$-glucan can form a gel under certain conditions, but the effects of the microstructure and advanced structure of $\beta$-glucan molecules on the mechanism of gel formation and gel characteristics and their applications need further research provide theoretical basis for the practical use of $\beta$-glucan in the food industry [73], provide theoretical basis for the finishing of oats and barley, and contribute to the development of cereal science.

With the application of polymer materials in medicine and further research on the mechanism of drug action, slow-release pharmaceutical preparations have become widely used in clinical practice. The use of gel sustained-release agents has many advantages over conventional pharmaceutical preparations. The treatment time for humans is relatively long, the frequency of drug administration is relatively small, the gastrointestinal tract is less irritating, non-toxic side effects, and drug valley. The peak fluctuation is low, which can avoid the release of oral drugs in the stomach and the small intestine and the repeated stimulation of the gastrointestinal mucosa and reduce systemic side effects, etc., and the effectiveness and safety of the drugs have been greatly improved. The emergence of controlled-release and slow-release drugs has met the needs of patients with chronic-onset diseases to a certain extent. Not only can side effects be avoided, but also it is easy to take, especially for patients who are difficult to take medicine, such as children and the aged people. Moreover, details to use $\beta$-glucan to encapsulate curcumin, to study the slow-release process of curcumin in $\beta$-glucan gel, and to try to use $\beta$-glucan as a completely natural drug delivery vehicle. Hence, the use of glycans opened up new ideas for improved human health.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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