Modification of Glucomannan as an Excipient

Subjects: Polymer Science

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Glucomannan (GM) is a polysaccharide generally extracted from the tuber of *Amorphophallus konjac*. It consists of mannose and glucose residues linked by β-(1-4) and exhibits hydrocolloid characteristics which can be applied as thickening and gelling agents. However, it has poor water resistance and low mechanical strength when used as an excipient in solid form. Several physical and chemical modifications have been carried out to improve these drawbacks. Chemical modification involves the substitution of functional groups in GM's structure including esterification and etherification. It causes a decrease in its high hydrophilic film behavior and produce water-resistant films. Physical modification involves mixing native GM with other excipients through processes involving milling, moisture, temperature, pressure, radiation, etc. It causes variations to particle size, shape, surface properties, porosity, density, and to functional properties such as swelling capacity and gelation ability

glucomannan chemical modification physical modification excipient

1. Introduction

Solid dosage of drugs is most preferable because it provides accurate dosage and is more stable than other forms [1]. Common uses include uncoated and film-coated tablets and film. Production requires polymers to enable pharmaceutical products to optimally control drug release [2][3] and to improve physicochemical properties [4][5]. Natural polymers such as glucomannan (GM) have attracted extensive attention due to their biodegradability, nontoxicity, harmlessness, and biocompatibility.

Glucomannan (GM) is a polysaccharide typically extracted from *Amorphophallus oncophyllus* [6] and *Amorphophallus muerelli* Blume [7]. It has the ability to thicken and form a gel; hence, this compound is widely used in various industries, including the pharmaceutical industry as a binder [8], thickener [9], gelling agent [10], film former [11], coating material for tablets [12][13], emulsifier [14], and stabilizer [15].

As a natural polymer, GM has properties that are superior to other polysaccharides when used as excipients for solid preparations, especially in tablet production. GM could be the excipient of choice for direct compression—the most efficient tablet manufacturing method—because it has desirable free-flowing and compressibility behavior [16][17][18]. GM is also reported as a widely used coating material and stabilizer in the pharmaceutical industry due to its gelling properties and particular rheological properties [11][13][19].

Native GM has several disadvantages for pharmaceutical applications, such as extremely high viscosity and low mechanical strength [20][21]. In addition, GM's high-water absorption index causes poor water resistance and limits

some potential applications [14][22]. However, these shortcomings of native GM could be overcome through chemical or physical modification to enhance its structural and functional quality.

Chemical modification involves the substitution of functional groups in GM's structure including esterification and etherification and elongation of the molecular chain through the formation of crosslinks and encapsulation. Depending on the degree of substitution (DS), these modifications alter several characteristic of GM, such as homogeneous film formation [11], increased tensile strength [15], improved thermal stability [15], and sustained release [23].

GM can be physically modified to improve functionality without undergoing chemical changes. Physical modifications involve mixing native GM with other excipients through processes involving milling [24], moisture [25], temperature [26], pressure [27], radiation [28][29], etc. Physical modifications cause variations to particle size, shape, surface properties, porosity, density, and to functional properties such as swelling capacity and gelation ability. These modifications directly influence disintegration and mechanical properties when used as an excipient in solid form.

2. Structure and Physicochemical Properties of GM

GM is a natural heteropolysaccharide with a linear chain consisting of D-glucose and/or D-mannose in various proportions linked by β-1,4 glycosidic bonds. It also has multiple branching at β-1,3 glycosidic bonds to mannose units as shown in **Figure 1** [30].

The molecular weight varies from 200,000 to 2,000,000 Daltons, giving it incredibly higher viscosity than any known dietary fiber such as guar or locust bean gum [31][32]. When GM sol concentration is below 0.55%, it is only slightly affected by shear rate, indicating Newtonian fluid flow characteristics. However, at higher concentrations, shear rate can affect viscosity, leading to shear thinning and indicating non-Newtonian pseudoplasticity [33]. Based on previous reports, the viscosity of konjac glucomannan solution (1.0 g/100 g) can reach ~30,000 cps [34].

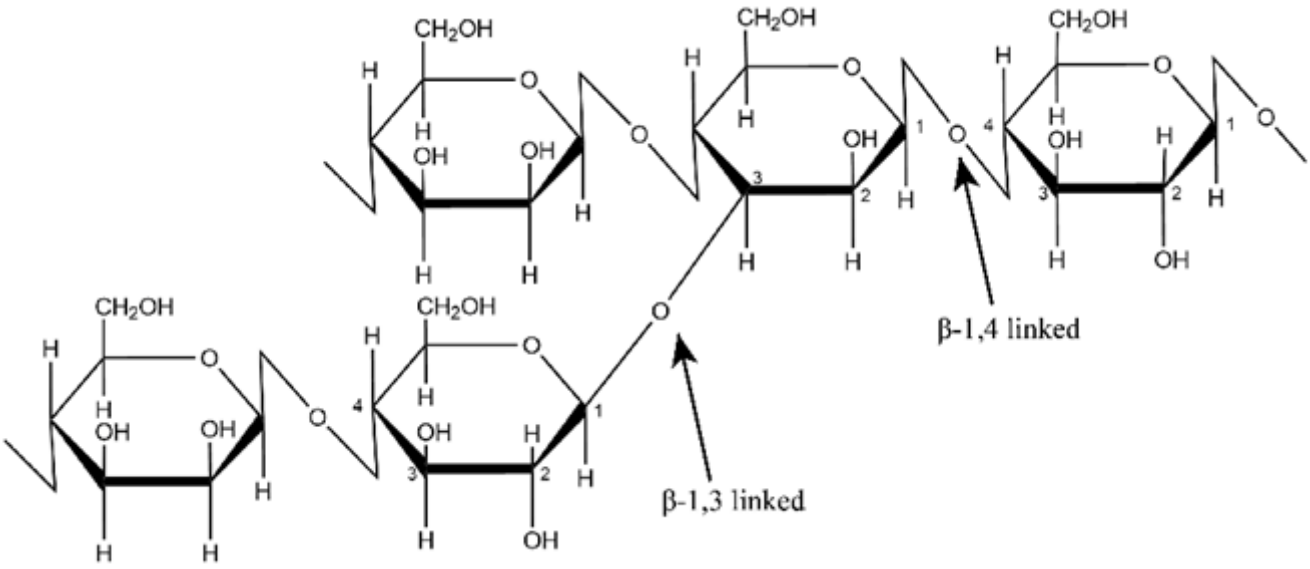

Figure 1. Structure of glucomannan.

GM is a hydrophilic polymer due to the abundance of hydroxyl and carbonyl groups in its molecular chain. The hydrogen bonds between each molecule affect its solubility; hence, the stronger the bonds, the lower the solubility in water. In contrast, low acetyl group branching (5–10% at the C-6 position, i.e., one branch per approximately 19 sugar residues) reduces hydrogen bonding, thereby increasing solubility; this causes high water absorption of 105.4 g/g (water/GM) [35]. Water absorption is also affected by granule size and surface morphology—a reduction in particle size will increase surface wrinkle density, which culminates in higher hydration rates [36].

The formation of gel is by hydration of water; this can be accelerated by heating and vigorous stirring. GM also forms synergistic gels in a thermally reversible reaction with other polysaccharides, such as xanthan gum [37], κ-carrageenan [38], and gum tragacanth [39], which increase the mechanical strength and decrease syneresis. This is presumably due to agglomeration or physical entanglement and dynamic hydrogen bonds with other polysaccharides [37][38][39].

In recent years, GM has attracted special attention from researchers and the food industry due to its bioactive, biodegradable, and hydrophilicity properties. This high-molecular-weight polymer is known as a hydrocolloid and interacts strongly with water [40]. Hydrocolloids are used in the food industry because of their thickening, gelling, stabilizing, texture-modifying, and film-forming properties.

3. Chemical Modification

Native GM forms very high viscosity solutions, where the intrinsic viscosity of 1% can reach 30,000 cps, and so it has potential as a good film-forming agent [41]. However, a very viscous external gel layer on the surface of particles immediately after dispersion prevents water penetration and drug dissolution, and thus its application is limited as a carrier for immediate drug release [42]. As a film, it has poor water resistance due to the large number of free hydroxyl and carboxyl groups distributed along the backbone, and it exhibits high moisture absorption. As a result, native GM has the weaknesses of poor water resistance and low mechanical strength [20][21].

Several structural modifications of GM have been performed to enhance its structural and functional qualities, including oxidation [43][44][45] and etherification by addition of acetyl [30][38][46][47] and carboxymethyl [2][5][13][15][48][49][50][51][52][53] moieties on hydroxyl groups of GM. Chemical modification with different degrees of substitution (DS) give different physical and mechanical properties. DS is largely affected by the amount of sodium hydroxide and by different dispersion media. Higher degrees of substitution contribute to lower viscosity and particle size, denser network structure, and better tablet strength [54].

GM is an ideal candidate for appropriate modification by chemical functionalization. Each of the glucose–mannose units have reactive hydroxyl groups, which are the major sites for chemical modification. In addition, several studies discovered that chemically modified GMs can be used for the sustained release of drugs [2][23][32]. Among various modification methods such as acetylation [46][47][55], carboxymethylation and oxidation [43][44][56][57],

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carboxymethylation, hydroxypropylation, and hydroxyethylation [3][5][13][48]. The effects of carboxymethylation of GM (CMGM) are described in more

3.1. Increased Solubility

Chemical modification of CMGM affects solubility; carboxymethylation with NaOH catalyst substitutes chloroacetic acid with a hydroxyl group, which partially replaces hydroxyl and acetyl groups with carboxymethyl [2][48][49][58]. Incorporation of a carboxymethyl group appears as an extending chain structure that reduces hydrogen bonding between the polymer chains and increases the water-binding capacity, as shown in **Figure 2** below.

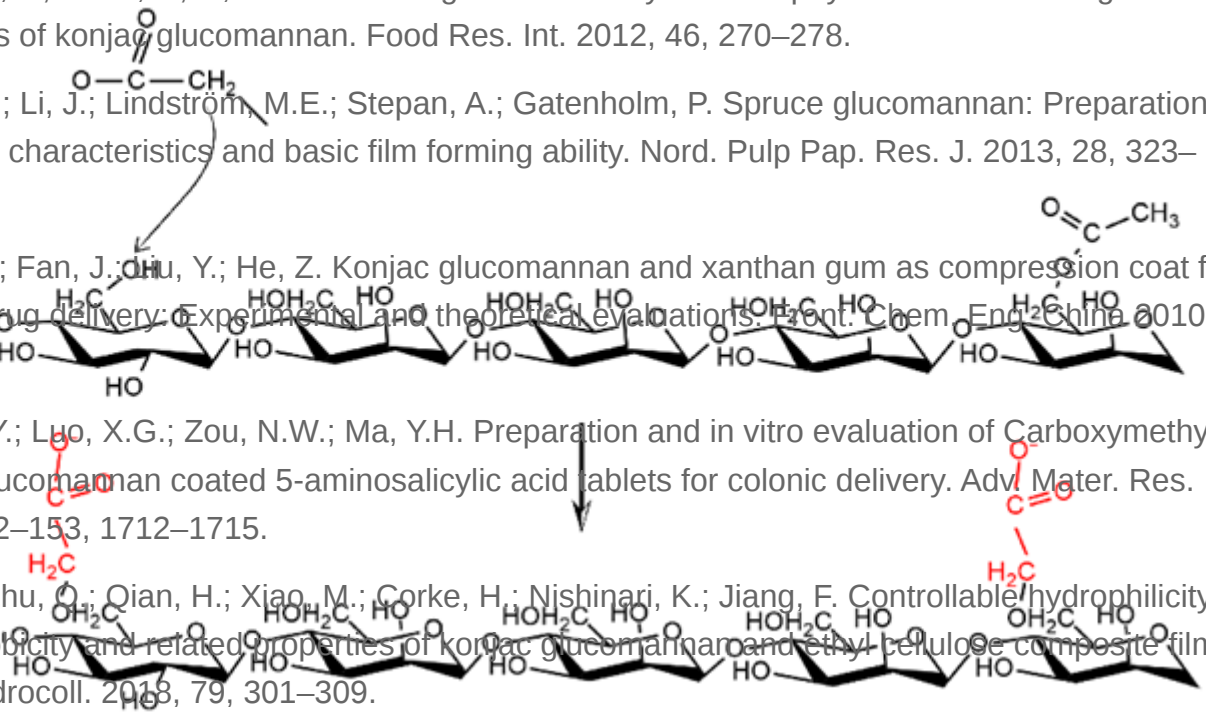

Figure 2 CMGM synthesis pathway.

Modification to CMGM improves solubility because excess substitution by carboxymethyl groups breaks extensive hydrogen bonds, leading to a drastic decrease in crystallinity and an increase in solubility [59]. Modification also changes the amount of acetyl located randomly at the C-6 position of the sugar unit. The increase in solubility is due to the incorporation of water-soluble carboxylate groups during acetylation (**Figure 1**). Additionally, changes in water-binding properties are caused by reduction and/or loss of crystal structure in the granules, making them mostly amorphous and more hygroscopic [50].

However, based on several studies, the smaller the degree of substitution, the lower the hydrophilicity due to the increase in the contact angle from θ_c = 48.4° [14] to θ_c = 97.3 ± 4.2° [54]. Water solubility is also lower in CMGM than in GM. This is because the particles in both are all amorphous; hence, carboxymethylation does not reduce and/or eliminate the crystalline structure inside GM granules, but, rather, alters its granular surface structure, which might affect moisture adsorption [50].

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Ohya et al. reported a carboxymethyl-glucomannan derivative, capable of increasing the solubility of GM in water and interacting with other positively-charged polymers [60].

3.2. Reduced Viscosity

The concentration and type of polymer in coating solutions affects viscosity [61][62]. High viscosity sols produce nonuniform films due to low diffusivity, giving a "solid skin" that retards solvent evaporation and causes hydrodynamic instability. The solid skin is under mechanical tension and might break, thereby causing variations in film thickness [63]. Consequently, moderate viscosity is desirable for film formation. For utilization as a coating material, several studies suggest viscosity lower than 700 cps [64]. The viscosity of the coating solution can be increased by using polymers with high molecular weight (Mw), such as GM, which averages 200,000 to 2,000,000 Daltons [65][66], giving it the highest intrinsic viscosity compared to other polysaccharides at approximately 30,000 cps at a concentration of 1% [6].

Several methods have obtained GM with low Mw, for example, depolymerization, such as deacetylation, and carboxymethylation with strong bases to break the glycosidic bonds [67]. The viscosity of GM at 25 °C decreased significantly from 4660 cps to <500 cps after modification [2][50].

Deacetylation through carboxymethylation changes the structure from semi-flexible straight chains to elastic microspheres that decrease inherent viscosity (**Figure 3**) [54]. As a comparison, substitution of carboxymethylation groups in cellulose also affects viscosity. At a concentration of 1%, cellulose and carboxymethyl cellulose (CMC) have viscosities of 240 cps and <100 cps, respectively.

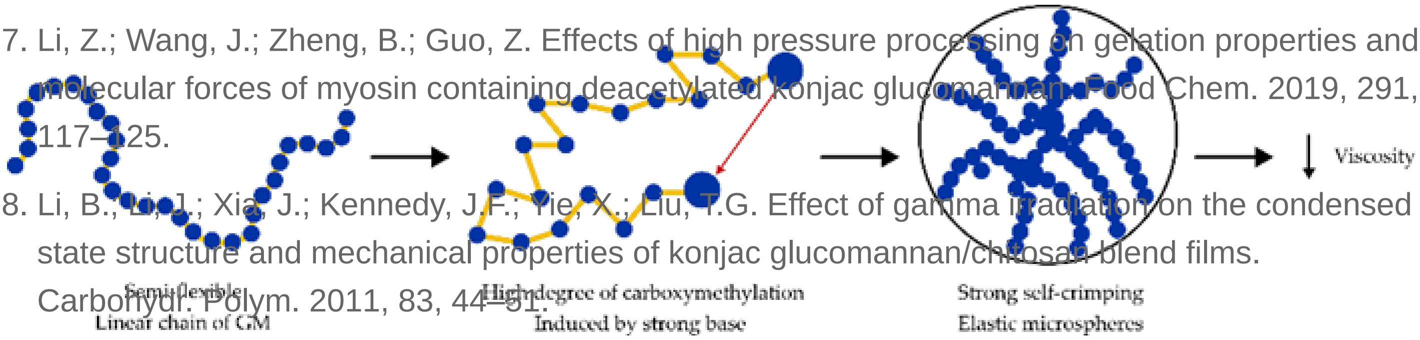

Figure 3. Effect of carboxymethylation on the structure of GM.

3.3. Increased Tensile Strength

Generally, the presence of more -COO- groups due to carboxymethylation of the CMGM backbone improves gel strength by forming more crosslinks, while a high DS also increases mechanical strength [15]. The introduced COO− group can efficiently bind more water, which can act as a plasticizer to improve elongation of the film [68]. As the DS of CMGM increases, formed pore size decreases and the tissue structure becomes denser, indicating stronger interaction at higher DS [55]. This high density also increases tablet strength [3][24], but an excessive amount of CMGM causes charge repulsion, thereby weakening its mechanical properties [48].

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3.4. Improved Thermal Stability

CMGM maintains the gel network through hydrogen bonding upon heating to 95 °C for 2 h, implying excellent thermal stability [15]. Carboxymethylation increases the thermal stability of GM in a DS-dependent manner. Based on thermogravimetric analysis (TGA), GM is degraded in three stages. TGA recorded a change in mass due to moisture removal from 60–200 °C. Meanwhile, from 200–300 °C, great weight loss was recorded in GM, CMGM (DS 0.28), and (DS 0.7), with values of 64.16%, 49.73%, and 43.17%, respectively. In the final stage of decomposition at a temperature of 300–500 °C, there was a greater decrease in mass change in GM than in CMGM due to thermal degradation [2].

4. Physical Modification

Co-processing is a technique for mixing two or more excipients at the sub-particle level to synergistically enhance functionality and mask undesired properties without undergoing chemical changes [69]. This method can change fundamental characteristics such as particle size and shape, morphology, porosity, density, and surface area, which affects flowability, compressibility, compactibility, and ultimately influences the disintegration and mechanical properties of tablets [70]. Some examples of GM processed together with other excipients are shown in **Table 2** for various applications, especially controlling drug release through crosslinking and/or formation of dense hydrogen bonds.

Table 1. Co-processed GM with other excipients.

Combination of Excipients	Co-Processed	Application	Mechanism	Ref.
GM and HPMC K 100 LV	Microwave on level 5 (350 W) for 30 min	Matrix for gastro-retentive tablets forming a porous channel that allows the polymer mixture to absorb more water and expand, followed by prolonged drug release	Hydrogen bonds in single polymers have low energy, but the simultaneous formation of interlinked hydrogen bonds between polymer components provides significant interaction strength, resulting in a matrix that floats quickly and maintains the integrity of the polymer mixture under acidic conditions.	[71]
GM and lactose	Wet granulation	Filler–binder for direct compression of effervescent tablets	GM has a high viscosity and strong adhesive properties, thus providing good tablet binding effectiveness. GM has poor solubility in water, so it is combined with lactose as a water-soluble ingredient and to improve the poor flowability of lactose.	[72]

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Combination of Excipients	Co-Processed	Application	Mechanism	Ref.
GM, sodium alginate (SA), and graphene oxide (GO)	Freeze dried	Microsphere-making polymers that enhance targeted delivery of drugs or nutrients to the colon	GM interacts with SA via hydrogen bonding and physical entanglement, and GO enhances these interactions in the microspheres. In addition, GO can greatly improve the loading efficiency of ciprofloxacin (CPFX) of microspheres, and achieve the sustained release effect of CPFX.	[26]
Oxidized GM, cassava starch, and sucrose esters	Dry heated	The OGM–CS combination exhibits low solubility and swellability, which makes it a possible excipient for the formulation of sustained-release drugs. However, the addition of SE significantly decreased porosity and swelling of the tablets, which inhibited immediate drug release.	Heating OGM and CS to high temperatures causes structural damage that limits the solubility and swelling ability of the polymer. The addition of SE with HLB 5 decreased porosity and slowed drug release because the more closed structure inhibited free movement of the drug out of the matrix. In addition, more hydroxyl groups in SE form hydrogen bonds, increasing intergranular bonding.	[58]
CMGM and 2-hydroxypropyl trimethyl ammonium chloride chitosan (HACC)	Complex coacervation and freeze dried	The coaservation complex formed can encapsulate and control the release of the molecular model for the vaccine, namely ovalbumin (OVA).	The anionic carboxyl group of CMGM and the cationic quaternary amine group of HACC cause intramolecular electrostatic attraction that causes the HACC and CMGM macromolecular chains to aggress and coil, forming the CMGM/HACC composite nanosphere.	[23]

5. Future Recommendations

GM is a polysaccharide that has promise as an excipient for solid dosage forms, especially for direct compression due to its free-flowing nature and compressibility. Some applications of chemically or physically modified GM have been reported. Chemical modification is suggested to modify the solubility, viscosity, and mechanical properties of GM, while physical modification of GM is suggested to modify swelling ability and drug release from the matrix. Although chemical and physical modifications of GM have been studied, compared to other polysaccharides such as chitosan or alginate, the studies are not wide or deep enough. The mechanisms behind the effects of modifications on pharmaceutical characteristics such as the relationship between structure and

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functionality/application of modified GM are not clearly understood. Thus, the study of mechanisms of modified GM is necessary for its development as a potential pharmaceutical excipient.

In recent years, a wide variety of innovative approaches to modify GM have been developed through non-contaminating physical modification methods (green methods) such as microwave heating, ultrasound-assisted and hydrothermal processes, and ball milling. In addition, exploration of other plants as sources of GM may also be conducted, to create a wider range of functionalities, which also may expand applicability.

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