

Review Article

Review of Konjac glucomannan for the development of microspheres for inhalation delivery system

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Abstract

This review examines the use of microparticles or microspheres for targeted lung therapy, utilizing natural polymers as inhalable microsphere polymers. Polysaccharides are safe, biodegradable, biocompatible, bioadhesive, and capable of forming hydrogel systems, making them strong candidates for use in drug delivery systems. The use of microparticles is expected to enhance the efficiency of lung-targeted therapy, as it can reduce drug dosage, provide a faster onset, decrease systemic side effects, bypass the gastrointestinal tract, and improve direct drug delivery to the infected organ area in the lung. This article discusses the physical characteristics of microspheres from polysaccharide polymers derived from different materials. Optimal inhalation microspheres are spherical particles, with sizes ranging from 1 – 5 μm , moisture content <10 %, good flowability, high yield, high encapsulation efficiency, high loading capacity, sustained release, large lung deposition, high potential for macrophage uptake and biological activity. Konjac glucomannan contains a mannan group that stimulates the interaction of mannan receptors, which are commonly found on the surface of macrophages, making it a suitable polymer for targeted inhalation microspheres aimed at alveolar macrophages. However, konjac glucomannan has a relatively high molecular weight and viscosity, even at low concentrations. Therefore, it must be depolymerized first to reduce both molecular weight and viscosity, so that they can produce particle sizes appropriate for inhalation microspheres. The hydrolytic method of konjac glucomannan can be carried out through physicochemical degradation methods, such as irradiation, sonication, acid treatment, or combination of two or more methods. Enzymatic hydrolysis can also be performed using β -mannase enzymes from *Aspergillus niger* or *Penicillium funiculosum*.

Keywords: Inhalation microspheres, Konjac glucomannan, Spray drying, Polysaccharides

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INTRODUCTION

Konjac glucomannan, a fiber biomaterial, is a polymer produced from an extraction process from the tuber of *Amorphophallus konjac* plant from the Araceae family [1]. It has the potential to

be used as a therapy for diabetes, obesity, constipation, and cancer and possesses anti-inflammatory and antioxidant properties. This polysaccharide polymer is also biodegradable, biocompatible, and bioadhesive [2] and has the

ability to form a heat-resistant gel and a film layer, which is safe and easy to renew [3].

Polysaccharides are macromolecular polymers of natural materials, generally composed of 10 or more monosaccharides. They have long and branched glycoside bonds with similar and compound molecular arrangements, and their molecular weight is generally from 10^3 to 10^6 Daltons [4]. Currently, polysaccharides isolated from natural materials such as plants, animals, fungi, and seaweed are in great demand due to their proven pharmacological activities, including antitumor and anticancer [5,6], antioxidant and immunostimulant [4,7], and anti-inflammatory effects [8].

Polysaccharides such as sodium alginate, chitosan, carrageenan, xanthan gum and konjac glucomannan are biocompatible, biodegradable and bioadhesive, such that they can be used as drug delivery systems [9]. Konjac glucomannan is also able to reduce azoxymethane (AOM)-induced genotoxicity by decreasing the damage to deoxyribonucleic acid (DNA) caused by accumulation of reactive oxygen species (ROS) [10]. In addition, konjac glucomannan has very low toxicity profile, can be modified, is non-immunogenic, safe and good for pharmaceutical applications [11,12]. Polysaccharide polymers such as konjac glucomannan also have numerous hydroxyl groups, enabling them to absorb and bind large amounts of water or biological fluids, a characteristic known as hydrogel property [13].

Hydrogel-based polysaccharides have the ability to better encapsulate the active ingredients of drugs so that they can be used as microsphere drug delivery systems [14]. Encapsulation process in the microsphere system has been proven to be effective in loading drugs without changing the structure and activity of the drug, but it may have an impact on particle size [15]. Microsphere systems can be designed for local or systemic purposes. They can also be designed for targeted delivery systems such as pulmonary delivery systems, often called pulmospheres or inhalation microspheres. Inhalation microspheres have distinctive characteristics with aerodynamic particle size requirements so that they can be deposited into their target sites in the lungs, particularly the alveoli. The lung is an organ with a very large absorption surface area and a thin epithelial barrier, making it an effective route for drug delivery [16].

Potential of polysaccharides as polymers in inhalation microspheres

Polysaccharides are natural polymers that are biodegradable, non-toxic, safe, and mucoadhesive. Polysaccharides as polymers of targeted drug treatment systems in the lungs must be purified and have physical characteristics that do not damage the lungs because the lungs are sensitive organs where the accumulation of foreign objects will cause the organs to malfunction, such that airflow becomes ineffective [17]. The drug delivery system in the lung can be designed using a microsphere system, often referred to as inhalation microspheres. Inhalation microspheres are drug delivery systems in the form of encapsulated microparticles containing a certain amount of drugs, with an aerodynamic particle size of 1 – 5 μm [18]. Such microspheres with an aerodynamic diameter (D_{aer}) of 1 – 5 μm have a high probability of reaching the small airways in the alveoli [19]. Aerodynamic diameter depends on the characteristics of the geometric diameter, density, shape and morphology of the particle surface [20]. Several studies have discussed lung-targeted microspheres with polysaccharide polymers, including chitosan, sodium alginate, carrageenan and konjac glucomannan [21-23]. Polysaccharide polymers such as chitosan and sodium alginate are mucoadhesive and interact with mucin, allowing them to function as penetration enhancers. In addition, in the presence of divalent cations such as Ca^{2+} , Ba^{2+} , and Zn^{2+} , alginate has the ability to form a three-dimensional cross-linking network with water as a dispersion medium, enabling it to expand and serve as a controlled-release drug delivery system [24,25]. Kappa carrageenan and konjac glucomannan have recently been shown to be effective as inhalation microsphere polymers, triggering interactions with macrophages [26,27].

Physicochemical characteristics of inhalation microspheres, such as particle shape, particle size, mucoadhesive properties, specific gravity, flow properties, lung deposition ability, entrapment efficiency, drug loading and release profile, are factors that determine therapeutic success through the inhalational route. Inhalation microspheres with an aerodynamic diameter (D_{aer}) of 1 – 5 μm have a high likelihood of depositing their contents in the small airways and are targeted to reach the alveoli [19]. The table below illustrates the influential relationship between the type of polysaccharide polymer, active ingredient used, manufacturing method, and the results of the physicochemical characteristics of inhalation microspheres (Table 1 and Table 2).

Table 1: Physicochemical characteristics of inhalation microspheres with polysaccharide polymers

Polymers and Characteristics	Active ingredients	Method	Characteristics of inhalation microspheres	References
Sodium alginate (Negative charge; mucoadhesive; Hydrogel;)	Isoniazid	Ionic gelation and spray drying	Spherical particles; particle size with aerodynamic diameter ($1.23 \pm 0.07 \mu\text{m}$); yield (26.45%); and trapping efficiency (53.34%)	[28]
	Ciprofloxacin	Ionic gelation with the aerosolization technique	Particle size ($1.23\text{--}1.43 \mu\text{m}$); yield (70.63–82.94%); particles exhibited a spherical morphology; trapping efficiency (27.39–80.74%); drug loading (2.82%–4.13%); drug released reached (80–100%) after 24 hours in Phosphate Buffered Saline (PBS) medium	[29]
	Quercetin	Ionic gelation with the aerosolization technique	Spherical particles; particle size ($1.2\text{--}1.7 \mu\text{m}$); yield (40.8–58.8%); trapping efficiency (4.15–93.8%); drug loading amounted to (4.11–5.49%); drug release after 600 minutes ranges from (25.6–30.64%)	[22]
	Paclitaxel	Emulsification and ionic gelation	Particle size ($<5 \mu\text{m}$); particle volume (2–10 μm); trapping efficiency (35–61%); drug loading (7.8–19.5%).	[30]
	Rifampicin	Spray drying	Particle size ($6.2\text{--}6.6 \mu\text{m}$); yield (60%); drug loading (62.1–71.2%);	[31]
	Ciprofloxacin	Ionic gelation with aerosolization technique	Particle size ($<3 \mu\text{m}$); yield ($>71\%$); trapping efficiency (14–95%); drug loading (15–79%)	[32]

Potential of konjac glucomannan as polymers in inhalation microspheres

Konjac glucomannan is one of the polysaccharides that has great potential as a polymer for targeted drug delivery system in the lungs. Recently, studies of lung-targeted microspheres with konjac glucomannan polymers have been shown to be very effective because they have mannan groups (mannose units) that can increase the interaction of polymers with macrophages through mannose receptors present in alveolar macrophages [26]. Konjac glucomannan are non-ionic polysaccharide bound to acetyl groups through β -1,4 and β -1,6 glycoside bonds at D-glucose and D-mannose, respectively [41,42].

Although konjac glucomannan is hydrophilic, it has low solubility, which limits its use in pharmaceutical applications. This is due to its high molecular weight arising from the presence of acetyl groups and branching in its structure. Depolymerization is a strategy used to reduce the molecular weight and viscosity of glucomannan, and this can be achieved through physicochemical or enzymatic degradation. Physicochemical degradation is carried out by irradiating with γ -rays, which are generally at a dose of 10 kGy [43], and can also be increased

in dose up to 100 kGy [44]. In order to increase the degradation effectiveness of γ -rays, it can be combined with the dissolution of hydrogen peroxide, which functions as a free radical that breaks the glycosidic bond [45]. Physicochemical degradation can also be done by ultrasonication, thermal, or acid hydrolysis. Acid hydrolysis with hydrochloric acid (HCL) will be more effective if combined with sonication hydrolysis [46]. Previous reports show enzymatic degradation of konjac glucomannan using β -mannase from *Bacillus spp.*, *Aspergillus niger*, or *Penicillium funiculosum* [47,48]. The chemical structures of konjac glucomannan before and after hydrolysis are depicted in Figures 1 and 2.

The degradation method of konjac glucomannan (KGM) and the results of konjac glucomannan hydrolysis are shown in Table 3 and Table 4. Based on studies by Wattanaprasert [48], the preparation of microencapsulated microspheres using konjac glucomannan polymer requires hydrolysis, as even low concentrations of konjac glucomannan result in high viscosity, which inhibits the spray drying process. Andrographolide was used as the active ingredient in the study and spray drying, done at inlet and outlet temperatures of 170°C and 85°C , respectively, resulted in an encapsulation percentage of 46.63%.

Table 2: Physicochemical characteristics of inhalation microspheres with polysaccharide polymers

Polymers and Characteristics	Active ingredients	Method	Characteristics of inhalation microspheres	References
Chitosan (Positive charge; mucoadhesive; Permeation enhancer)	Ofloxacin	Emulsification	Spherical particle; particle size (1-6 μ m); drug loading (27%).	[33]
	Levofloxacin	Ionic gelation and Spray drying	Spherical particle; MMAD (5 μ m); drug loading (>90%).	[34]
	Quercetin and Paclitaxel	Spray drying	Trapping efficiency (92.6-90.3%); drug loading amounted to (5.36-14.79%).	[35]
	Rifampicin and Rifabutin	Ionic gelation and spray drying	Particle size (<5 μ m); drug loading with the active ingredient rifabutin (70-89%); drug loading with the active ingredient rifampicin (45-60%).	[36]
Kappa Carrageenan (Negative charge; mucoadhesive: hydrogel; Macrophage targeting)	Isoniazid and Rifabutin	Spray drying	Volume diameter (7.0 μ m); Isoniazid entrapment efficiency (96.3%); rifabutin entrapment efficiency (74.4%); drug loading isoniazid (8.4%); rifabutin entrapment efficiency (3.2%).	[27]
	Ciprofloxacin	Ionic gelation with aerosolization technique	Spherical particle; particle size (1.4-1.6 μ m); yield (36.42-89.33%); drug loading (13-18%).	[29]
	Ciprofloxacin	Spray drying	Particle size (2.61-2.79 μ m); trapping efficiency (94.6–100%); drug loading (1-4.73%).	[37]
Gelatin (Positive charge; mucoadhesive)	Rifabutin and Isoniazid	Spray drying	Spherical particle; particle size (4.89 μ m); yield (48.8%); rifabutin entrapment efficiency (51%); isoniazid entrapment efficiency (22%).	[38]
Guar seeds (Neutral; Macrophage targeting)	Isoniazid	Spray drying	Spherical particle; particle size (3.53 μ m); yield (30.3%); trapping efficiency (51.3%).	[39]
Galactomannan/ locust bean gum (Neutral; hydrogel; Macrophage targeting)	Rifabutin and Isoniazid	Spray drying	MMAD isoniazid (6.2 $\pm$ 0.6); MMAD rifabutin (5.8 $\pm$ 0.3); Drug loading of isoniazid (8.2 $\pm$ 0.3%); drug loading of rifabutin (4.4 $\pm$ 0.1%); association efficiency isoniazid (94 $\pm$ 3%); association efficiency rifabutin (102 $\pm$ 1%).	[40]
Konjac Glucomannan (Neutral; hydrogel; Macrophage targeting)	Isoniazid and Rifabutin	Spray drying	Aerodynamic diameter (1.71 μ m), acceptable for inhalation; encapsulation percentage of isoniazid (88.1%) and encapsulation percentage of rifabutin (92.4%); drug loading of isoniazid (7.7%); drug loading of rifabutin (4%).	[21]

MMAD: mass median aerodynamic diameter

Also, inhalation microspheres were prepared using konjac glucomannan polymers that had been previously degraded by the acid hydrolysis method in a study conducted by Guerreiro [56]. The active ingredients used as model drugs in this study were a combination of isoniazid and rifabutin, and the method of producing microspheres was by spray drying with an inlet temperature condition of 180°C $\pm$ 1°C, air flow rate set at 473 L/h, 90% aspirator, and spraying with a flow rate of 0.8 mL/min. Microspheric

results with spherical morphology in a size range of 1.87 $\pm$ 2.11 to 2.24 $\pm$ 2.18 μ m were obtained. Based on aerodynamic characteristics with cascade impactor, it shows that microspheres could be well dispersed in the lungs, where the emitted dose was above 90 %, Mass of Median Aerodynamic Diameter (MMAD) was approximately 3 μ m with entrapment efficiency ranging from 65.9 $\pm$ 2.6 % – 90.5 $\pm$ 3.4 % while drug loading ranged from 2.6 $\pm$ 0.1 % – 13.0 $\pm$ 0.6 %. Also, particle size < 5 μ m has a great

chance of reaching the alveolar zone [57]. In addition, particle sizes ranging from 1 – 3 μm are very beneficial in inhalation preparations because they enhance phagocytosis by macrophages in the alveolar [58]. Alveolar macrophages are pivotal to phagocytosis of self or foreign bodies in the lungs, and this process is strongly influenced by particle size, particle

shape, and deformability. The physiology of particle size (1 - 3 μm) and interaction of receptors with polymers are very important in phagocytosis [59]. A knowledge of the physiology and biology of phagocytosis in alveolar macrophages can be used as a model of drug delivery systems targeted to macrophages.

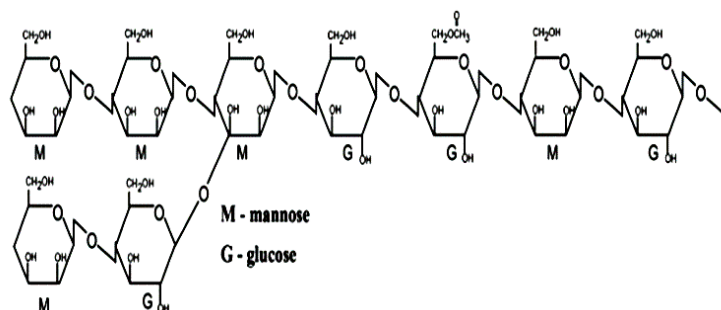


Figure 1: Chemical structure of konjac glucomannan

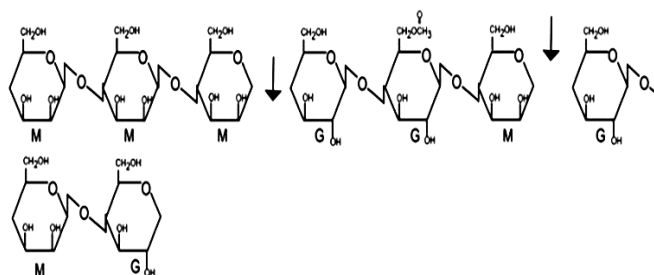


Figure 2: Chemical structure resulting from hydrolysis of konjac glucomannan, separated by arrows

Table 3: Konjac glucomannan hydrolysis methods

Hydrolytic method	Hydrolysis procedure	KGM hydrolysis results	References
Enzymatic (β -mannase)	β -Mannase from <i>Bacillus</i> sp. with an activity of 30 000 IU/g. Then using 1500 units of mananase dissolved in solution 90.95% (w/w), 87.95% (w/w), 84.95% (w/w) and 81.95% (w/w)	Concentration of KGM affects the viscosity of KGMH: KGM 18% produces a viscosity of 285.08 ± 9.20 mPa.s; KGM 15% produces a viscosity of 167.60 ± 0.03 mPa.s; KGM 12% produces a viscosity of 49.48 ± 6.83 mPa.s; KGM 9% produces a viscosity of 11.82 ± 0.76 mPa.s	[48]
Enzymatic (β -mannase)	β -Mannase 150 and 250 U/g were dispersed in 0.1 M sodium acetate buffer solution (pH 5) with KGM concentrations of 20% and 40% at 70°C, 1000 rpm for 5, 15 and 25 minutes	Most optimal result: KGM 40%, enzyme mannanse 250 U/g, 15 minutes yield viscosity of 852.50 mPa.s.; KGM 20%, enzyme mannanse 150U/g, 5 minutes yield viscosity of 124.35 mPa.s	[49]
Physicochemical	γ -rays: 10, 20 and 100 kGy, with H ₂ O ₂ solution	Most effectively, 10 kGy produces a molar ratio of Mannose: Glucose: 2.2:1, Acetyl content $2.07 \pm 0.41\%$, Sugar content $93.2 \pm 3.06\%$, and Moisture content: $7.01 \pm 0.38\%$	[44]
Physicochemical interaction with hydrogen peroxide	Laser irradiation assisted with hydrogen peroxide at power of 10 W, with hydrogen peroxide being added to KGM solutions.	Viscosity of KGM decreased from 8.38 to 2.26 Pa.s. Molecular weight (Mw) of KGM also decreased from molecular weight (Mw) 7.6×10^5 to 5.7×10^5 Da	[50]

Table 4: Konjac glucomannan hydrolysis methods

Hydrolytic Method	Hydrolysis procedure	KGM hydrolysis results	References
Physicochemical	Ultrasonication for 60 min	The molecular weight of KGM was decreased	[51]
Physicochemical	Acid hydrolysis with Hydrochloric acid	The molecular weight of KGM decreased from $1,234 \times 10^3$ Da to 8,029-1,130 Da, with viscosity decreasing to 200-300 mPa.s.	[52]
Physicochemical (Subcritical Water Treatment)	KGM is dispersed in water and stirred for 1 hour. Then it is introduced into a stainless steel vessel and heated at several temperatures, namely 160°C, 180°C, 200°C, 220°C, or 240°C for 10 minutes.	Before the white KGM solution color treatment, viscosity of KGM was 150 mPa.s with a molecular weight of 500-2,000 kDa. After the hydrolysis process, the color changes. At 160-200°C yellowish, at 220-240°C dark brown. Viscosity decreased from 150 to 10 mPa.s. Decrease in sugar (from 5.0 to 2.3 g/L). The treatment at 220°C can be considered the optimal condition for obtaining konjac glucomannan-derived oligosaccharides with several degrees of polymerization and yield. Viscosity dropped from 50 Pa.s to 10 Pa.s after 10-20 minutes of sonication. Molecular weight of 4.096×10^{-5} after 10 minutes of sonication and 1.646×10^{-5} after 40 minutes of sonication with US Power amplitude 50 W/cm ² (80%)	[53]
Physicochemical (Ultrasonic degradation)	KGM 10 g/L in water. Ultrasonic conditions with 40% or 80% amplitude for (2, 5, 10, 20, 40 and 60 min).	Konjac glucomannan microcrystals of 15µm with amorphous structure were obtained	[54]
Physicochemical (Acid hydrolysis)	KGM (2%) was dispersed in sulfuric acid (2.8 M). The suspension was kept at 40°C while shaken at 150 rpm. Sodium azide was added to the suspension before storage at 4°C	Degradation of KGM using acid hydrolysis and sonication methods was more effective, resulting in a molecular weight of 5.60×10 Da with a viscosity of 37.61 Pa.s. Degradation of KGM by acid hydrolysis alone, without sonication, resulted in a molecular weight of 6.11×10 Da with a viscosity of 732.55 Pa.s. Meanwhile, if only by sonication without acid hydrolysis, it produces a molecular weight of 6.26×10 Da with a viscosity of 1323.5 Pa.s	[55]
Physicochemical (Ultrasound-mediated acid hydrolysis)	Thirty-five grams (35g) of KGM was suspended in absolute ethanol as much as 250 mL and 36.7% HCL was added (20 mL) and sonicated for 60 minutes at 45 kHz. The mixture was filtered and washed with 70% ethanol until a neutral pH was obtained. The mixture was stored overnight in the oven for 48 hours at 50°C.		[46]

KGM: konjac glucomannan; KGMH: konjac glucomannan hydrolysate

Konjac glucomannan polymer has also been shown to interact with human receptors on the surface of macrophages and successfully demonstrated access of antituberculosis drugs to macrophages to inhibit or kill *Mycobacterium tuberculosis* effectively. In this study, it was also explained that konjac glucomannan is able to swell with simulated pulmonary fluid after 20 minutes. Lung fluid simulation can be made with a mixture of substances, including cholesterol, Immunoglobulin G, ascorbate, transferrin,

gentamicin, albumin, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-phospho-rac (1-glycerol) ammonium salt, urate, glutathione and Hanks' Balanced Salt Solution [60]. Moreover, it was also mentioned that the release test showed that the drug was released more slowly from the pulmonary fluid simulation medium than from the water or methanol medium. The drug started to detach from the pulmonary fluid simulation media after 45 minutes, reaching 82 – 84 % after 12 hours, and

94 – 99 % after 24 hours. Based on this study, it is necessary to develop konjac glucomannan polymer as a carrier for the inhalational route delivery system, especially for diseases involving alveolar macrophages, such as tuberculosis treatments or vaccines.

CONCLUSION

Konjac glucomannan falls into the category of polysaccharides suitable for application as polymers in inhalation microsphere drug delivery systems. The polymers are safe, biodegradable, biocompatible, non-toxic, bioadhesive, hydrogel-forming and capable of forming a film layer. Notably, it possesses a mannose unit that potentially increases its interaction with macrophages through mannose receptors. However, konjac glucomannan polymers need to be depolymerized or degraded by hydrolysis before application. The hydrolytic degradation method can be carried out through physicochemical degradation methods, such as irradiation, sonication, acid treatment, or combinations thereof. Enzymatic hydrolysis can also be performed using β -mannase enzymes from *Aspergillus niger* or *Penicillium funiculosum*. Based on the results of the above study, acid hydrolysis method is more effective and low cost for reducing molecular weight and viscosity for the subsequent spray drying process.

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Ethical approval

None provided.

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors made significant contributions to the writing of this article, participated in reviewing/editing and approved the final draft for publication.

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