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Review

Konjac glucomannan, a promising polysaccharide for OCDDS

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ABSTRACT

Oral colon targeting drug delivery system (OCDDS) is a highly effective formulation for drugs absorbed by colon, or to treat colonic diseases specifically. To obtain colon targeting, many pharmaceutical approaches have been studied, among which, taking advantage of specific degradation of excipients by colon enzymes is one of the most promising strategies. With properties of specific colon β-mannanase degradation, biocompatibility, gel-forming, low toxicity and high stability, konjac glucomannan (KGM) becomes a promising natural excipient for oral OCDDS. This paper summaries structure and properties of KGM, reviews achievements and prospects on KGM and modified konjac glucomannan about their application as pharmaceutic excipient for the OCDDS recently.

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1. Introduction

Orally administered preparations have brought us conveniences for thousands of years though its first standard classification was brought out after 1995 when biopharmaceutics classification system (BCS) was introduced (Lindenberg, Kopp, & Dressman, 2004). However, oral administration has drawbacks, for instance, low bioavailability resulted from first-pass effect for some drugs like aspirin (a kind of antipyretic analgesics) (Chourasia & Jain, 2003). And low effective utilization of protein and peptide drugs, for they will be destroyed under some relatively hostile in vivo environments such as stomach and small intestine (Patel-Parul, Satwara-Rohan, & Pandya, 2012). In order to improve bioavailability and obtain effective utilization of these drugs, three main approaches are adopted. First, change routes of administration to intravenous injection for some drugs like insulin (Heinemann, 2013). Second, apply proper oral pharmaceutical dosage forms. Thirdly, adopt the method of drug design, modifying the targeting drugs to prodrugs. Out of the three options, applying OCDDS is an effective tactic to obtain both good compliance and high bioavailability. To prepare OCDDS, certain coating technologies and excipients are applied, dosage forms of pH-sensitivity,

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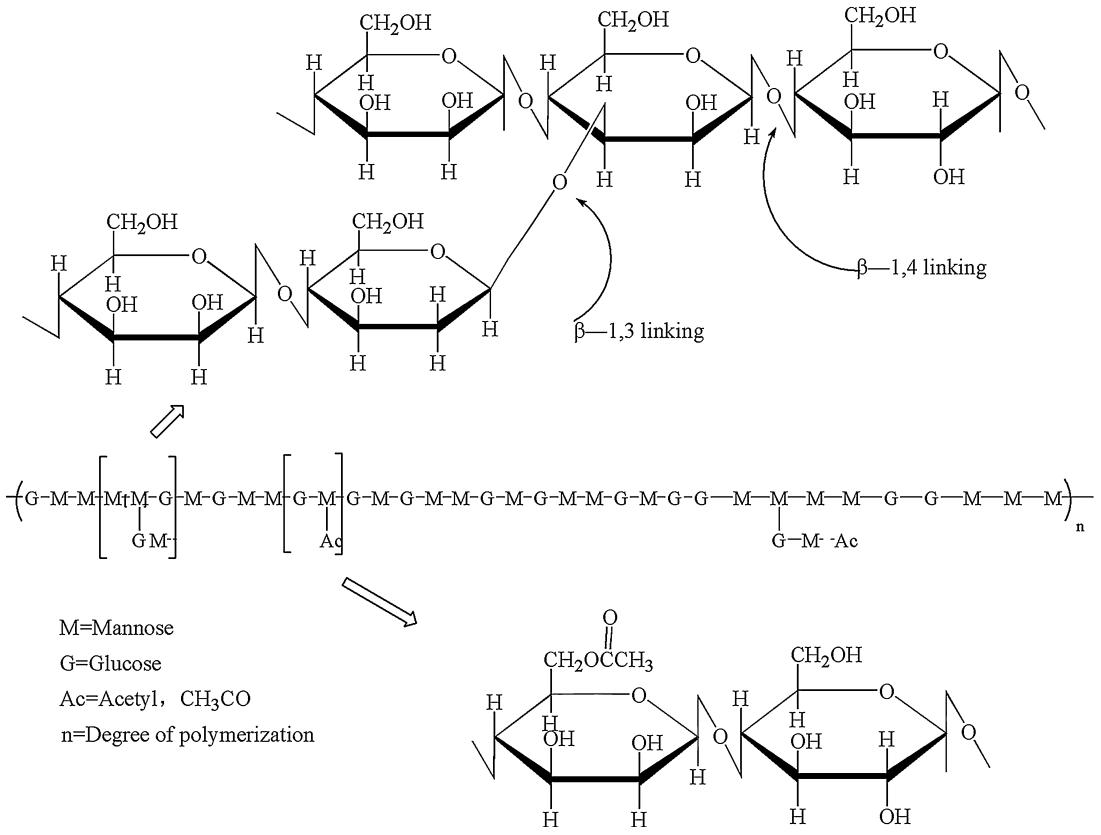

Fig. 1. Chemical structure of KGM.

time-dependency (lag time), microbial degradation, or formulation dependent on osmotic pressure, etc. are developed (Prasad et al., 2011). Thereinto, using excipients that possesses property of microbial degradation is one of the most simple and effective strategy.

Nowadays, cases of colonic diseases are increasing. Researches have found abundant microflora in colon and amounts of drugs which are colon specific absorption. The status and the establishing of theoretical basis all lead OCDDS to be a hot research topic (Singh, Singh, Sharma, & Sharma, 2012). For these excipients degraded by colonic bacterial enzymes specifically, some natural polysaccharides are included, such as chitosan, guar gum, amylase, inulin, konjac glucomannan, locust bean gum are usually used to prepare and study OCDDS (Sinha & Kumria, 2001; Vandemme, Lenourry, Charrueau, & Chaumeil, 2002). They are biodegradable in colon and have good gel-forming ability (Patel-Parul et al., 2012). It was known that KGM gel systems were able to maintain integrity and control the release of theophylline and diltiazem for 8 h (Avachat, Dash, & Shrotriya, 2011). KGM hydrolysate was reported to have prebiotic potential for beneficial gut microbiota (Connolly, Lovegrove, & Tuohy, 2010; Wu, Cheng, & Chen, 2011). So KGM series are safe and making a fine figure in OCDDS. However, KGM derived from commercial konjac has quite high molecule weight, for example, the weight average molecular masses (M_w) determined by studying the KGM originated from Gunma Prefecture, Japan, is in the region of $9.0 \pm 1.0 \times 10^5\,g\,mol^{-1}$ (Ratcliffe, Williams, Viebke, & Meadows, 2005). And there are amounts of hydrogen bonds in its molecule. So it has shortcomings of too high water-swelling ability, together for there is not enough free water in colon, it will finally lead to diarrhea and difficulties in drug release. To improve water-retaining ability and gel intensity of KGM so as to make it a qualified excipient for OCDDS, in recent decades, many researchers have modified it through physical, chemical, biological and irradiation modifications. This review gives an introduction of structure and properties for KGM, focuses on summaries of its modifications and prospects for application in OCDDS.

2. An overview of konjac glucomannan

2.1. Chemical structure and molecule weight

Konjac glucomannan (KGM) is composed of β-1,4 linked D-mannose and D-glucose residues with reported ratio of 1.6:1 (Kato & Matsuda, 1969), or 1.4:1 (Bewley & Reid, 1985), actually, the ratio differs with konjac breeds (Smith & Srivastava, 1959). There are acetyl groups attaching randomly to C-6 position of the saccharide units along the molecule approximately 1 per 19 sugar residues, and some side chains linking to mannoses by joint C-3 (Katsuraya et al., 2003). Differences of acetyl group quantity in KGM chain segments may be caused by different productive technologies applied. The speculative structure of KGM is shown in Fig. 1 (Dave, Sheth, McCarthy, Ratto, & Kaplan, 1998; Katsuraya et al., 2003; Lin et al., 2010). The average molecular weight generally ranges from 500,000 to 2,000,000, changing with different species, producing areas, processing technologies and storage time (European Commission, 2001). The molecule weight (M_W) of KGM was measured by GPC spectrum and its molecule weight distribution was found approximately a normal distribution with polydispersity (M_W/M_n) of 1.21, indicating KGM is relatively a homogeneous polysaccharide (Wang, Xu, Lv et al., 2012; Wang, Xu, Zhu et al., 2012). Therefore, KGMs from different species and produced by different grafts have different M_W. However, there are no standard regulations concerned with different characteristics of the KGMs to give guidance in their application in OCDDS.

2.2. Water solubility and water adsorption

KGM is a water soluble polysaccharide for the plentiful hydroxyl and carbonyl groups on its molecule chain (Kohyama, Iida, & Nishinari, 1993; Shen, Li, Zhang, Wan, & Gao, 2012). Hydrogen bonding has close relationship with its water solubility, the stronger the hydrogen bonding between their molecules, the harder for it to dissolve in water. Chen, Li, and Li (2011) found the presence of acetyl groups in KGM molecule restrained the formation of both intramolecular hydrogen bonds and intermolecular hydrogen bonds between KGM molecules, so the water solubility of KGM decreased with the increase of deacetylation (DD). And the highly hydrophilic KGM macromolecules have poor water solubility in relatively short time without heating.

Meanwhile, KGM can combine lots of water through hydrogen bonding, molecular dipole, induced dipole, instantaneous dipole, finally macromolecules which are hard to move formed, and this phenomenon also contributes to its poor water solubility. It was reported that KGM had high water absorbency near 105.4 g/g (water/KGM), while fully acetylated KGM was 1.0 g/g. The data suggested that acetyl groups contribute to its binding with water (Koroskenyi & McCarthy, 2001). However, 100% purified KGM has not been obtained yet (Fang & Wu, 2004), thus the precise water-retaining capacity of specific KGM is uncertain but with no reason be low according to its structure.

When applied as pharmaceutical excipients or drugs, the high water adsorption rate may lead to diarrhea, for there is not enough free water in gastrointestinal tract. But when prepared as styptic sponge, which used to stop bleeding, the higher the water adsorption rate of it, the better the hemostasis effect may be. Water adsorption rate of KGM can be altered through proper modifications. For example, Li, Ji, Xia and Li (2012) invented superabsorbent KGM–acrylic acid–kaolin polymers with water absorption rate of 1941 g/g in distilled water through frontal polymerization method. It can also be lowered by deacetylation.

2.3. Flow patterns, gelling formation and gel reversibility

Wang, Xu, Lv et al. (2012) and Wang, Xu, Zhu et al. (2012) found when the concentration of KGM is below 0.55%, the hydrosol behaved near-Newtonian fluid. While at higher concentration, but below 7% or 8% (the data varies with konjac species), KGM solution will become sol (Dave et al., 1998; Nishinari & Williams, 1992) and presented characteristics of pseudoplastic fluid. When the concentration of KGM continues to rise, to more than 7% or 8% (differ with konjac species), it will form gel, exhibiting the characteristics of Bingham fluid.

Intrinsic viscosity of KGM solution was found among the highest of polysaccharides (Jacon, Rao, Cooley, & Walter, 1993). KGM can absorb water and swell to form gel. Add into diluents, and through heating and vigorous stirring, the swelling process to form gel can be accelerated. Also, it can form synergistic gels with other polysaccharides, such as xanthan, κ-carrageenan, acetan and deacetylated acetan. The synergistic effect is brought by intermolecular interaction between them (Gao & Nishinari, 2004). Gels formed by physical agglomeration of KGM itself or physical entanglement with other polysaccharides are thermal-reversible.

However, in alkaline environment, KGM itself will experience a chemical process to form gel. Some researchers have proved that in the process, gel forming is resulted from losing of acetyls in KGM molecules (Williams et al., 2000). The gels formed after chemical process usually have good stability and generally are thermo-irreversible. KGM gels formed through heating with ambient pH value ranging from 11.3 to 12.6 (Kohyama & Nishinari, 1990) (the pH variation and difference may vary according to the variation of KGM molecule weight) are accelerated for the irreversible removing of acetyl groups. Both ambient temperature and pH value have great effect on their thermo-reversibility (Nishinari & Zhang, 2004). NaOH, KOH, $Ca(OH)_2$, $NaCO_3$, K_2CO_3 are the alkalis that usually used to trigger gelatinization. KOH has the strongest deacetylation effect among these alkalis (Pan, Meng, & Wang, 2011; Yoshimura & Nishinari, 1999). It is already known that with increasing DD, water solubility of KGM decreased. The reason was that in the process of deacetylation, reunion capacity of KGM molecules strengthened and hydrophilic interaction weakened (Du, Li, Chen, & Lia, 2012).

For composite KGM gel systems, solution concentration, pH value, ambient temperature, crosslinkers (such as heavy metal ions) all are the factors that affect the formation and properties of the gel. The effect of heavy metals in the process has not been investigated systemically yet. With gel forming ability, KGM can be a potential material as carrier for controlled or sustained drug release system.

2.4. Film-forming property

KGM has good film-forming property. When dehydrated by heating in alkali environment, hard film with enhanced crystallinity, lower water-sorptive capacity (WSC) and water vapour permeability (WVP) will form. After deacetylation occurred by adding alkali, these properties will be brought by greater intermolecular forces (Cheng, Abd Karim, Norziah, & Seow, 2002). Adding humectants in the preparation process can improve the mechanical properties of the film. And WVP will change according to the additives added to it. When the additives are hydrotropic substances, WVP will increase; while hydrophobic substances, it will decrease (Cheng, Abd Karim, & Seow, 2007).

A kind of edible film made from acid-hydrolyzed KGM was proved to have higher WSC, WVP and lower melting enthalpy than that made from untreated KGM for the increase of short chains in KGM molecules. Mixtures of KGM with gelatin or some other polysaccharides, such as curdlan, chitosan, starch and cassava starch were featured with good film-forming ability for the strong intermolecular hydrogen bonding (Chen, Liu, Chen, Chen, & Chang, 2008; Li, Kennedy, Jianga, & Xie, 2006; Lin, Li, & Zhu, 2012; Nair, Jyothi, Sajeev, & Misra, 2011; Wu et al., 2012).

These films mentioned above are edible and have good stability in cold water, hot water and even acid solutions. They can be used as packing materials in food industry, meanwhile, the preparation of microcapsules such as powder flavor and powder oil. It has been proved that KGM can form antibacterial film when uniformly blended with poly diallyldimethylammonium chloride (PDADMAC), a strong cationic polyelectrolyte. In the film, strong intermolecular hydrogen bonds and electrostatic interactions were observed by ATR-IR (Lu, Wang, & Xiao, 2008). The film may be prepared for external application. After proper modification, it may have great potential as coating material in OCDDS.

2.5. Other properties

In addition, KGM has many other properties such as thickening, emulsification, suspension, stabilization (Zhang, Xie, & Gan, 2005). These properties still have close relationship with ambient pH value. When the ambient pH value is lower than 10, KGM will mainly show the properties of water retaining, suspension, stabilization. While for about 10–12 and under certain temperature, the treated KGM will present the property of fresh-retaining (Supapvanich, Prathaan, & Tepsorn, 2012). Therefore, it can be applied in more comprehensive areas, such as food industry, pharmaceutical industry.

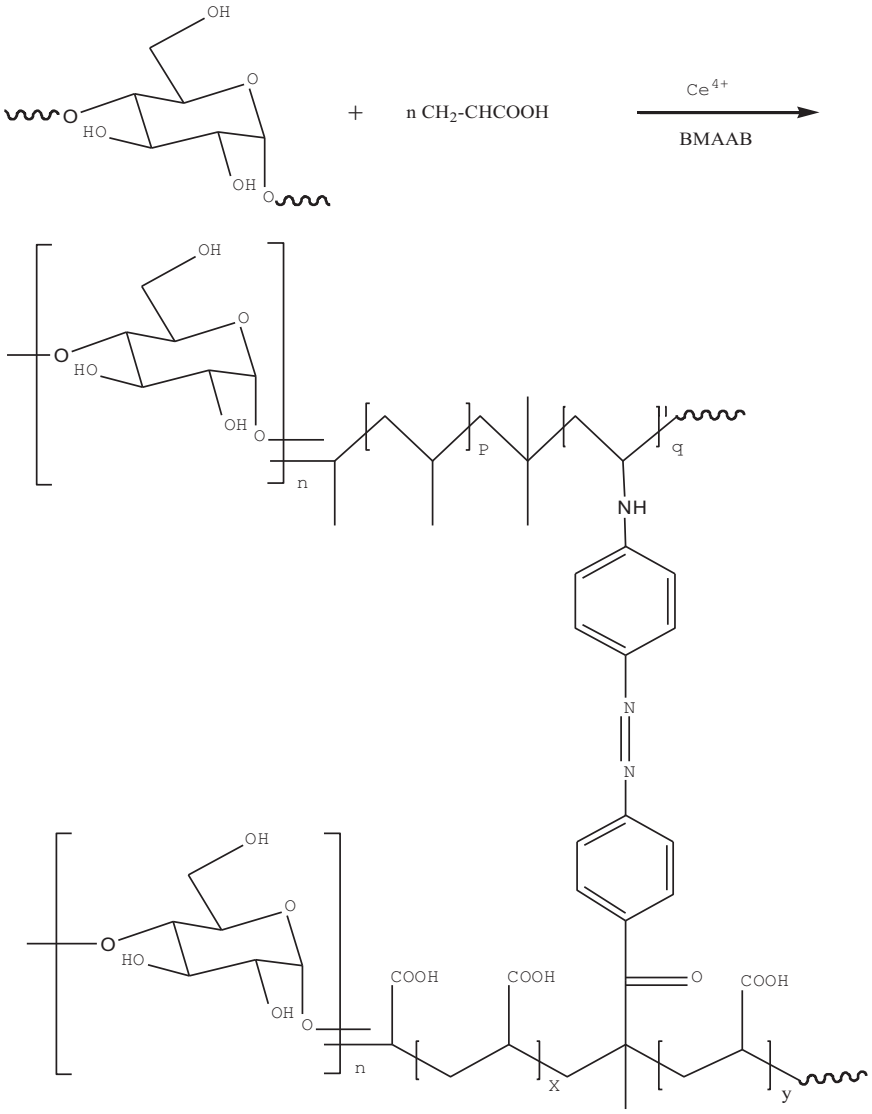

Fig. 2. Preparation of KGM-graft-AA hydrogels containing azo cross-linker.

3. Modified KGM for colon-targeting drug delivery system

Being studied early in late 19th century (Smith & Srivastava, 1959), KGM, a natural neutral polysaccharide produced from tubers of *Amorphophallus konjac* (Fang & Wu, 2004), has been found a promising excipient for colon targeting drugs in recent decades for it can specifically degraded by colon β-mannanase (Li, Qi, Li, Ding, & Zong, 2004), a kind of enzyme generated by human colon bacteria (Patel-Parul et al., 2012). Ma, Wang, Du and Guo (2009) studied extraction, purification, physical and chemical properties of KGM, content and toxicity tests indicated that KGM was a stable and safety material for medicinal purpose.

To get stable KGM products with good film and gel forming abilities, a series of chemical modification methods contribute a lot, including graft copolymerization, crosslinking, and crosslinking-blending methods. Usually, these chemical modifications can change the response of KGM to ambient pH, degradation degree by β-mannanase, mechanical properties, etc. However, for physical blending, it is mostly the superposition of two materials' properties. And it is a handy and important way to obtain polymeric materials with better performances in OCDDS.

3.1. KGM-grafting–acrylic acid and KGM–poly (acrylic acid) IPN hydrogels

Liu, Hu, and Zhuo (2004) invented a novel hydrogel systems designed for colon-targeting drug delivery, it was composed of KGM, copolymerized with acrylic acid, and crosslinked by the aromatic azo agent bis(methacryloylamino)-azobenzene. The schematic is showed in Fig. 2. After copolymerizing, the density of KGM increased, the gel remained specific degradation by β-mannanase as well as KGM, and the degradation of the copolymerized KGM by cereflo® lasted more than 30 days in 0.1 mol/L pH 7.4 phosphate buffer under 37 °C. In vitro release of bovine serum albumin (BSA) showed that the release process can be controlled by biodegradation of the hydrogel, and the release rate was faster in pH 7.4 medium than in pH 2.2 medium, indicating the material may be pH sensitive. The release pattern is zero-order kinetics and can continually release for more than 10 days. All results suggested that the co-polymer can be exploited as protein and peptide drug carriers for colon-targeting drug delivery.

Chen, Liu, and Zhuo (2005) copolymerized KGM and acrylic acid (AA) with N, N-methylene-bis-(acrylamide) (MBAAm) to form a novel hydrogel system. The crosslinking mechanism is similar

with Fig. 2. The swelling ratio of the hydrogel was inversely proportional to the content of MBAAm, indicating that the release rate of drugs can be adjusted by controlling of MBAAm quantity. Studies on swelling behaviors and degradation showed that the gel was pH-sensitive and could be degraded by Cellulase E0240 which containing enzyme of β-mannanase. Release of the model drug 5-ASA was proved to be controlled by swelling and degradation processes. The accumulative release percent of 5-ASA reached 95.19% after 36 h. So the hydrogel would be a kind of potential colon targeting drug carrier. Further researches demonstrated that the IPN hydrogel composed of KGM and poly(acrylic acid) (PAA) and cross-linked by N,N-methylene-bis-(acrylamide) (MBAAm) was still pH-sensitive and a potential carrier for colon-targeting drug delivery. SEM of the hydrogel showed that pore size becomes smaller than KGM hydrogel for the entering of acrylic acids into the pores of KGM hydrogel, indicating a decrease for water adsorption (Wen, Cao, Yin, Wang, & Zhao, 2009). They are potential carriers for OCDDS.

3.2. OKG and CTS–OKG hydrogels

Xu, Li, Liao, and He (2009) oxidized KGM with sodium periodate and finally prepared OKG (oxidized konjac glucomannan). Aldehyde groups in OKG could combine with adipic dihydrazides to form stable Schiff base. Then with the cross-linker glutaraldehyde, 5-aminosalicylic acid (5-ASA) was loaded on it by weak intermolecular interaction. The swelling ratios increased with the increase of pH value, so the drug delivery system was pH-sensitive. The cumulative release curve showed that in vitro release of 5-ASA reached the maximum after 24 h when the environment pH value was 6.8–7.4, indicating the novel pH-sensitive complex could be used for OCDDS without the destruction of drugs in gastric acid.

Korkiatithaweechai, Umsarika, Praphairaksit, and Muangsin (2011) prepared controlled release of diclofenac sodium (DFNa) film from CTS (chitosan)–OKG. After reacting with sodium periodate, the carbon–carbon bonds of the cis-diol group in KGM are simultaneously cleaved and generating reactive aldehyde functions, then, the reactive functions crosslinked with CTS via imino bonds. The highest % encapsulation efficiency (EE) is 95.6 ± 0.6, release profiles of DF-Na from the CTS–OKG polymer matrices operated in simulated intestinal fluid showed that it may have controlled release effect for more than 24 h. It was suggested that the proportion of OKG in the formulation may affect the release profile and the formulation may be used for further study as a long term intestine controlled release drug model (at least 3 days), including as colon targeting drug carrier.

3.3. KGM–PAsp hydrogel

Liu, Chen, and Chen (2010) crosslinked KGM and poly (aspartic acid) (PAsp) with trisodium trimetaphosphate (STMP), yield a novel pH-sensitive hydrogel which had semi-interpenetrating polymer network (semi-IPN). Studies on the swelling ratios found that with increasing amount of PAsp and STMP (before maximum content), the swelling ratios of the semi-IPN hydrogels were found to increase and decrease respectively. In vitro cumulative release of model drug 5-fluorouracil showed that the maximum release reached 95% in simulated intestinal fluid (pH 7.4) within 7 h while in gastric fluid (pH 2.2) was 23% within 3 h. However, its enzymatic degradation performance by colon enzymes is unknown. According to previous study, mostly, without destruction of KGM main chains, the property of specific biodegradation in colon still reserved, the semi-IPN hydrogel may be a suitable polymeric carrier for colon-targeting drug delivery.

3.4. KGM–XG mixture

Xanthan (XG) is the gum thus far being proved to have the strongest and true synergistic gelling effect with KGM. Mao, Klinthong, Zeng, and Chen (2012) proposed that the acting sites with XG were on the consecutive glucose residues of KGM with six or more units. Alvarez-Manceñido, Landin, and Martínez-Pacheco (2008) have successfully invented KGM/XG/sucrose tablets by wet granulation with model drug bore diltiazem. Degradation result by β-mannanase showed that XG had no effect on degradation of KGM. Assays of the tensile strength and drug release profiles of the tablets showed that for both Japanese and American KGMs, there were significant regions of (KGM, XG, S) space in which the tablets were both satisfactorily strong and exhibit slow, nearly zero-order release of this highly soluble drug. The release rate would be accelerated in the presence of *A. niger* β-mannanase at concentrations equivalent to human colonic conditions. It also found that the varieties of KGM should be considered for different degree of acetylation and particle size led to significant differences in swelling rate and drug release. It was suggested that tablet based on the combination of KGM/XG was a simple and inexpensive dosage form to achieve sustained release effect in colon for water-soluble drugs.

Wang, Fan, Liu, and He (2010) prepared compression coated tablets for oral colon specific delivery systems with KGM and xanthan gum (XG) mixture as compression coat. It is proved that a KGM70 tablet with a 0.4 g coat is of good design for a less than 5% drug loss in the mimic upper gastrointestinal solution and about 50% cumulative release in the mimic colon solution by degradation after 24 h. According to Nair et al. (2011), ST (Cassava starch)-KGM films with good properties can be invented for controlled drug release studies. It is suggested that the film can be used for coating of OCDDS, too. Further more, konjac micro-balls (KMBs) composed of KGM and XG prepared by drying and wetting method respectively all achieved sustained-release effect for more than 24 h (Wang, Xu, Lv et al., 2012; Wang, Xu, Zhu et al., 2012). These researches suggest that KGM/XG mixture can be used in OCDDS with good controlled release effect.

3.5. KGM–SA hydrogel

Wang, Liu, Shuai, Cui, and Nie (2014) prepared KGM/sodium alginate (SA-3)/graphene oxide (GO) hydrogels at 90 °C using a $Ca(OH)_2$ suspension. Their aim was to find new composite materials for the controlled release dosage form. The adding of graphene oxide had effectively controlled the release rate of 5-FU from the functionalized KGM/SA. SEM of three hydrogels showed that the surface of the neat KGM hydrogel showed many pores, the surface of KGM/SA-3 hydrogel showed a multi-plated structure with larger gaps among the leaf-like plates compared to the pores of the neat KGM hydrogel for the mutual repulsion between the dissociative COO-groups of SA. However, while the surface of KGM/SA/GO-3 exhibited the most compact structure among these hydrogels. The KGM/sodium alginate (SA-3)/graphene oxide hydrogels were proved having controlled release effect for more than 12 h at pH 6.8, so it is also a promising carrier for OCDDS.

3.6. KGM–HPMC mixture and CKGM–CS nanoparticles

Liu et al. (2009) invented an oral administrated capsule, a 5-aminosalicylic acid rapid-disintegrating tablet was sealed inside an impermeable capsule body with a KGM–hydroxypropyl methylcellulose (HPMC)–lactose plug. It had 5 h lag time for in vivo release after administration, indicating the pulsatile capsule can avoid its destruction in stomach and had therapeutic potential as colon targeting drug delivery (Liu et al., 2012).

Apart from the hydrogel systems mentioned above, Du et al. (2004) made carboxymethyl konjac glucomannan–chitosan (CKGM–CS) nanoparticles via polyelectrolyte complexation. The process is spontaneously. CKGM was the core and CS served as the coating layer. The in vitro release behavior of BSA from the nanoparticles showed that the release rate can be controlled by adjusting the thickness of CS shell. The CKGM–CS matrices exhibited pH-responsive properties, suggesting it may have colon targeting effect.

4. Summary and perspective

From the aforementioned content, KGM have broad application prospects in many fields. Nowadays, it is well known that konjac powder is mostly used as healthy food. However, KGM is still a promising polysaccharide as excipients for OCDDS with relatively low cost and desired properties. It is a good choice for OCDDS. Nevertheless, there are three limitations for its application in OCDDS. Firstly, in view of the characteristics of the colon, low content of free water in colon will limit the disintegration and drug release from preparations. Secondly, high molecule weight, poor water solubility and high water adsorption rate are not conducive to its using as excipients in OCDDS. Thirdly, a faster degradation rate by colon β-mannanase for KGM, Therefore, many modifications are aiming at changing its water adsorption and swelling rate without destroying of its main chain and special enzyme degradation property in colon. And usually, the modified KGM is expected to have slower degradation rate.

As a natural abundant polymer and possesses the property of colon specific biodegradability, KGM is increasingly attracting much more attention as pharmaceutical excipients, such as disintegrating agent, coating material, skeleton material for OCDDS. However, the species of KGM are vast, for application as pharmaceutical excipients, their characteristic parameters have not been assured roundly to give a guidance for their further study and application. These will be challenge and heavy works for their future standard use. With deepening of researches, a general conclusion is that KGM will be a promising and versatile choice for the preparation of OCDDS. More modifications on KGM will be done and more advanced formulations will be developed to prepare OCDDS.

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