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GUAR GUM HYDROGEL ASDRUG DELIVERY CONTROLLED RELEASE SYSTEM : REVIEW

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A B S T R A C T

Guar gum is one of the largest non-ionic polysaccharides present in nature and has many uses especially in drug delivery applications. Guar gum has high swelling characteristics in water, this limits the use of guar gum as a carrier for drug delivery. Therefore, in order to overcome this, modification can be done by grafting, derivatization, and tissue formation to improve the characteristics so that it can be used as an excipient with good potential release. Along with the development, guar gum and its derivatives are now available in the form of hydrogel, coating, tablet matrix, and nano/microparticles that can be utilized as potential carriers of targeted drug delivery. Several studies have shown that the use of modified guar gum hydrogels for controlled drug release drug functionality gives positive results. Example of application of guar gum hydrogel as a controlled release drug carrier such as a carrier for delivery of a drug targeted to the colon (colon specific controlled drug delivery carrier)

INTRODUCTION

Polysaccharides are monosaccharide polymers that can be found in many sources because they are found in nature. Polysaccharides of algae (alginate) from plants (pectin and guar gum), from microbes (dextran and xanthan gum), and from animals (chitosan and chondroitin) (L. Hovgaard, H. Brondsted, Crit Rev, 1996). Polysaccharides have many reactive groups, varying molecular weights, and varying chemical compositions, which in turn contribute to the diversity of structures and properties of polysaccharides. Given the various groups that can be derived in molecular chains, polysaccharides can be readily chemically modified and biochemically produced various types of polysaccharide derivatives (Prabaharan, Jayakumar, Biomater, 2008, 2009). As a natural biomaterial, polysaccharides are highly stable, safe, non-toxic, hydrophilic, biodegradable and low cost in the process (Prabaharan, 2011).

Most of the natural polysaccharides consist of hydrophilic groups such as hydroxyl, carboxyl and amino groups, which can form non-covalent bonds with biological tissues (especially epithelial and mucous membranes), forming bioadhesi (J.W. Lee, J.H. Park, J.R. Robinson, 2000). Currently a large number of studies on polysaccharides and their derivatives for their applications in drug delivery systems.

Among the hydrophilic polysaccharides, guar gum (GG) is one that is generally regarded as a potential polysaride for delivery of drugs to the colon because it is susceptible to microbial degradation in the colon (Prabaharan, 2011). Guar gum is also a prospective hydrophilic matrix carrier for oral drug delivery with a controlled release system with varying solubility and therefore guar gum has been widely reported to be formulated as a carrier for oral drug delivery (Prabaharan, 2011)

Guar gum (GG), obtained from thelegume seeds Cyamopsis tetragonalobus (Coviello *et al*., 2013), is a functional polysaccharide formed from the linear chain of d-mannose residues (Man) connected with (1 → 4) -β- glycosidic. and d-galactose backlineare (Gal) connected of (1 → 6) -α- glycosidic units (Kono, Otaka, & Ozaki, 2014).

Among the water-soluble polysaccharides, Guar gum is one of the polysaccharides known to have the highest molecular weight of about ~ 2.8 x 107g mol-1 (Barth & Smith, 1981; Vijayendran & Bone, 1984). Due to the presence of these galactose units, water-soluble polymers (Coviello *et al*., 2013). Guar gum is a non-toxic polysaccharide (Panariello *et al*., 2008), biodegradable,

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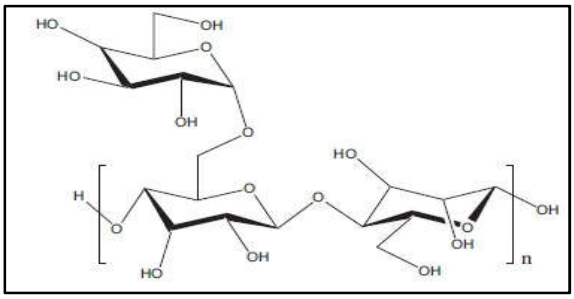
biocompatible, has high viscosity, and high water solubility, Guar gum is now used in many industries (Kono *et al*., 2014): As a binder, stabilizer , and thickeners in the cosmetics and food industry (Wang, Ellis, & Ross-Murphy, 2000). In the pharmaceutical field, the functional nature of guar gum is essential for controlling the release of medications in the gastrointestinal tract, such as target drug carriers of the colon (Das, Wadhwa, & Srivastava, 2006).

Guar gum is also used as a binder and disintegration in solid dosage forms, and has also been used as a hydrophilic matrix, to design the release of oral dosage forms (V, D Prajapati *et al*, 2013). The nature of guar gum that forms gel and enzymatic degradation inthe colon has been reported as an important factor for its potency as a drug carrier (Sharma *et al*., 2013). In addition, the natural biocompatible nature makes guar gum a good protective medicine from peptides and proteins (Sharma *et al*., 2013).

Guar Gum



(Prabaharan, 2011)

In recent years, guar gum and its derivatives are considered potential materials for biomedical, pharmaceutical and environmental applications due to bioavailability, biocompatibility, biodegradability, hydrophilicity and non-toxicology (Mishra, Yadav, Mishra, & Behari, 2011; Prabaharan , 2011; Subhraseema & Usharani, 2015; Yadav, Sand, Mishra, & Behari, 2010; Yadav, Srivastav, Verma, & Behari, 2013).

Hydrogel

Hydrogel particles are one type of delivery system in the form of emulsions that functionally have a wide scope. The hydrogel particles contain biopolymer tissue with a three-dimensional structure capable of absorbing large amounts of water (Hoare *et al*, 2008). Hydrogel particles typically contain oil droplets that are absorbed in biopolymer tissue (McClements, 2010). Lipophilic substances are dissolved in the oil phase, and then the water-in-water emulsion is homogeneous, wherein this oil phase and water phase contain an appropriate emulsifier (Zhang *et al*., 2015).

Currently, there have been numerous discoveries on the design and fabrication of hydrogel particles reported in relation to the form and design of foodgrades of hydrogel particles that can encapsulate lipophilic agents suitable for use in the food industry, such as oil-soluble vitamins and nutraceuticals and specifically focusing on the application of hydrogel particles to a controlled release system or target release of the active substance in the gastrointestinal (Zhang *et al*., 2015).

Composition

Food grade hydrogel particles are typically manufactured from natural polymers known as Generally Recognized as Safe (GRAS) (like proteins and polysaccharides) because they are safe, commercially available, cheap and functional. The properties of biopolymers used to form hydrogel particles determine many functional such as stability, retention, and release properties.

It is therefore important to know about the molecular, physicochemical and physiological properties of the biopolymer molecules used to make hydrogel particles (Zhang *et al*., 2015) but not infrequently also these hydrogels are formed with synthetic polymers and / or combinations of biopolymers and synthetic polymers.

Cross-linking

The higher cross-linking density, have stronger hydrogel and the release of the components carried by the hydrogel are slower (Zhang *et al*., 2015). The nature of cross-links determines the response of hydrogel particles to changes in environmental conditions, such as pH, ionic strength, temperature, and enzyme activity, for specific applications (Zhang *et al*., 2015). The hydrogel cross rate can determine the mechanical strength as well as the encapsulation properties. The level of cross-linking can be controlled by increasing the concentration of biopolymers and crosslinking agents used to make hydrogel particles (Li Y*et al*, 2011).

Specific Interaction

In hydrogel particles there is a bioactive that is absorbed due to certain interactions with the biopolymer in the gel network, and when the bond is interrupted the bioactive will be released. For example, an electrically charged bioactive is present in a hydrogel particle due to electrostatic appeal with a biopolymer molecule. However, if the pH or ionic strength is changed, the electrostatic attraction weakens, then the bioactive will be released. Some of the molecular interactions used are van der Waals forces, hydrogen bonding, hydrophobic interactions, and covalent bonds (Berger *et al*., 2004; Tamai *et al*., 1994).

Release Mechanism

In general, the bioactive release profile of hydrogel particles is determined by two main factors: (i) the physicochemical properties of hydrogel tissue; (ii) bioactive locations and interactions with hydrogel networks (Lin cc, 2006). The incorporation of bioactivity may be carried out before, during, or after the formation of hydrogel particles. Many of the physicochemical characteristics of hydrogel particles are involved in determining the overall release profile, including dimensions, morphology, pore size, cross-link type and numbering, as well as specific interactions. However, the overall release mechanism can easily be categorized into three main groups: controlled release-release; controlled swelling; and, controlled degradation (Zhang *et al*., 2015).

Guar Gum for Controlled Release Targeted Systems Drug Delivery Targeted-to the Colon

Currently, the delivery of specific drugs to the large intestine has attracted attention and is still under development. Much research has been done in particular to develop a specific excipient in the delivery of drugs capable of releasing drugs especially in the colon. The reasons that trigger it are the number of diseases associated with the colon, reducing the side effects of the drug and maintaining the stability of the drug to arrive at the target of therapy especially for drugs that cannot stand in the acidic atmosphere. Guar gum is potentially used as a biodegradable material for the preparation of specific delivery systems to the gut by compressing guar gum into tablets as a matrix or chemical modification (Prabaharan, 2011).

It has been studied previously in several active substances, one of them is dexamethasone and giving the result of a tablet matrix with guar gum base with dexamethasone active substance has shown good results. The same result for other anti-inflammatory agents. Studies show drug release in simulated fluid of the stomach and low intestine whereas in colonic fluid simulations there is a significant increase. This study showed that galactomannanase (~ 0.1%) accelerated the dissolution of dexamethasone and budesonide from the matrix of guar gum tablets in the guar gum environment. The extent of drug dissolution depends on the concentration of galactomannanase. Delivery of dexamethasone to the colon (guinea) using guar gum is tested on healthy volunteers (Prabaharan, 2011). One formulation is designed for rapid discharge while the other three are designed for delayed release. Serum concentration and scintigraphs profiles show that tablet immediate release is destroyed in the digestive tract. One form of sustained relese preparation begins to disintegrate in the small intestine (intestinal). While the other two tablets, each showing a disintegration of 5.8 ± 2.3 and 3.6 ± 1.6 h, the three formulations were completely destroyed in the intestine, releasing 72-82% of the drug, thus indicating a suitability to deliver medicine to the colon.

Rama Prasad *et al*. were studying about indomethacin tablet matrix with guar gum. This tablet was found to maintain its integrity in 0.1 M HCl for 2 h and in Sorensen phosphate buffer (pH 7.4) for 3 h, and total active ingredient released only about 21% of the drug during 5 hours in the gastrointestinal tract.

The application of this matrix to controlled drug release has been investigated by United State Pharmacopeia (USP) by drug dissolution methods, under different pH environments. It has been found that with a higher percentage of grafting the drug release rate is lower. There was further observed the rate of drug release by using guaranumed guar gum matrix and found in the low acid release enzyme environment and higher in neutral and alkaline environments, thereby further optimizing the grafting of the guar gum matrix as potential material for gastrointestinal targeted release.Pharmacokinetic evaluation of mebendazole with guar gum matrix tablet formulation against drug release was performed on human volunteers (Krisnajah *et al*, 2003). Six healthy volunteers participate in crossover studies and designs. Mebendazole is administered at a dose of 50mg in both the immediate release tablet and the tablet targeted to the colon. The results showed that guar gum-based tablets for colon-targets did not release medications in the stomach and small intestine, but drug release occurred in the large intestine resulting in slower drug absorption and making drugs available to locally in the colon (Prabaharan, 2011).
Guar gum matrix can also be used directly as a carrier in the form of a hydrogel. As research conducted by (Seeli & Prabaharan, 2017). The research was conducted by designing guar gum hydrogel which was synthesized with oleic acid and grafting using cross-link method with PMAC (poly-methacrylic acid) (GGO-g-PMAc) using EGDMA (ethylene glycol dimethacrylate) as cross-link agent. This design is made for controlled release purposes specified to the intestine with pH-dependent properties in which the drug is expected to not release on the stomach and small intestine but on the colon.

The active ingredient used in this study was ibuprofen, the GGO-g-PMAc hydrogel structure characterized by the analysis of -IR, 1H NMR and X-ray diffraction (XRD) (Seeli & Prabaharan, 2017). The rate of swelling hydrogel GGO-g-PMAc pH 7.4 was higher than pH 1.2. A drug release study conducted on a buffer solution of pH 7.4 and 1.2 at 37 ° C indicates that the level and amount of drug released from GGO-g-PMAc hydrogel at pH 7.4 is higher than pH 1.2 . The MTT test showed that there was no cytotoxicity caused by GGO-g-PMAc hydrogel in the 0-100 g/ml concentration range against mouse mesenchymal line cell (C3H10T1/2). The results show that GGO-g-PMAc hydrogel can be a prospective pH-sensitive carrier for drug delivery targeted to the colon (Seeli & Prabaharan, 2017).

CONCLUSION

Guar gum and its derivatives are stable, safe and easy to unravel. With these favorable properties, it is widely considered potential as a carrier for controlled delivery systems especially for delivery of specific targeted drugs. Based on several studies guar gum (GG) proved able to be a carrier for specific delivery of large intestine (colon), but also as a drug carrier in the form of matrix and coating tablets. In order to obtain a guar gum hydrogel with a good controlled release, a modified synthesis should be performed such as grafting and cross-linking the hydrogel polymer. The guar gum cross-linked modification is useful for controlled release systems especially on some drugs. To achieve the pH and the responsive temperature of the guar gum hydrogel is grafted (graft) with a pH-responsive polymer such as poly (acrylamide) and poly (acrylic acid) and the temperature-responsive polymer, poly (N-isopropylacrylamide).

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