Application of Xanthan Gum and its Derivatives in Drug Delivery: A Review

Sandhyarani Panda1*, Mrutyunjaya Satpathy2, and Anubhuti Koshle1

1. Faculty of Biological and Chemical sciences, Mats University, City campus, Raipur, Pandri, C.G.
2. Department of Pharmacy, Govt Womens Polytechnic, Byron Bazar, Raipur, C.G.

ABSTRACT

Xanthan gum is a well known polysaccharide having immense applications in diverse fields due to its unique rheological properties. They are used in pharmaceutical industries, agricultural industries, textile industries, etc. This particular polysaccharide is produced by Xanthomonas campestris bacteria utilising glucose as the major carbon source. Xanthan gum is used in pharmaceutical formulations as a gelling agent, binder and disintegrant. In this review article, application of xanthan gum in various drug delivery systems has been discussed.

1. Introduction

Xanthan gum is a natural high molecular weight polysaccharide produced by a fermentation process. Xanthan gum swells in the intestine, which stimulates the digestive tract to push stool through. It also might slow the absorption of sugar from the digestive tract and work like saliva to lubricate and wet the mouth in people who don’t produce enough saliva. Xanthan gum is an extracellular bacterial exopolysaccharide synthesized by Xanthomonas campestris.

The unique properties of xanthan gum make it versatile to be used in different applications. They are highly soluble in water, stable over a wide range of temperature, acidic and alkaline conditions.

It is resistant to enzymatic degradation and also exhibits synergistic interactions with other hydrocolloids. Xanthan gum is produced by natural microbial fermentation process which converts glucose to produce this product of economic importance. Xanthan gum is an acidic polymer with repeating pentasaccharide units having two glucose units, two mannose units and one gluconic acid unit in the ratio of 2.8:2.0:2.0. Xanthan Gum was “discovered” by a team of USDA researchers in the 1960’s. In 1968 it was approved for use as a food additive in the US and Europe. The research laboratories of the US Department of Agriculture discovered that the bacterium Xanthomonas campestris found in on cabbage plants produces an extracellular polysaccharide with exceptional rheological properties. Since then a number of improvements in polysaccharide manufacture have been taken place. Today, xanthan gum is the most important microbial polysaccharide available commercially. Xanthan gum has been widely used in many important preparations, such as cosmetic and pharmaceutical products as suspending agent, emulsifying agent.
2. Properties

This gum is soluble in cold and hot water. At high temperature and in low ionic strength, xanthan gum exists in solution as a disordered coil, but on cooling and/or addition of salt it undergoes a co-operative conformational transition. Xanthan gum solutions are non-Newtonian, highly pseudo plastic. The marked shear-thinning behavior of xanthan gum solutions may be explained by the conformational status of the polymer molecules. On shearing the extent of aggregation is reduced resulting to a lower solution viscosity. This pseudo plasticity enhances sensory qualities in food products and guarantees a high degree of miscibility, pumpability and pourability. The three-dimensional network formed by the associated chains makes xanthan gum an efficient stabilizer for suspensions and emulsions. Xanthan gum is widely used as suspending and thickening agent and a potent ligand for TLR4 and exerted antitumor activities in vivo. In order to adjust the desired flow behavior xanthan gum is often used in combination with other hydrocolloids. As xanthan gum is a naturally occurring polymer it is fully biodegradable (completely within 2days, DIN 38412-L25). Xanthan gum is, like many other gums (except starch products), non-digestible in humans and serves to lower the calorific content of foods and improve their passage through the gastrointestinal tract. The calorific value of xanthan gum is about 0.6 kcal/g.

3. Chemical modifications of xanthan gum

Chemical modification of xanthan gums not only minimizes these drawbacks but also enables them for use in specific drug delivery systems. The grafting of vinyl monomers such as vinyl pyridine, methacrylic acid, 2-hydroxyl ethyl methyl acrylate, ethyl acrylate, acrylamide, 2-acrylamido-2-methyl propane, and 2-acrylamido glycolic acid onto xanthan gum has gained considerable attention in preparing new polymeric materials with special characteristics with enlarged range of its utilization. The properties of grafted polymers depend upon characteristics of monomer, its concentration along with grafting conditions. Grafting of xanthan gum with 2-acrylamido-2-methyl-propane sulfonic acid enhances swelling and metal sorption capacity; while 2-acrylamidoglycolic acid improves flocculation, solubility, thermal stability, binding strength, water retention and resistance to biodegradation properties of xanthan gum.

4. Drug Delivery

The versatility of xanthan gum and its derivatives in drug delivery can be judged from investigations summarized below.

4.1 Colon drug delivery

Colon targeting drug delivery has gained attention for a variety of colonic disorders such as inflammatory bowel diseases (IBD), infectious diseases and colon cancer. For systemic absorption of peptide and protein drugs, colon is also found to be a promising site because of its less hostile environment compared with stomach and small intestine. The various approaches for colon targeting of orally administered drugs include coating with pH-dependent polymers, design of timed-release dosage forms and the use of the carriers that are degraded exclusively by colonic bacteria.

Investigation suggests that sustained release of watersoluble drugs in the colon from orally administered tablets may be achieved using simple, inexpensive formulations based on combinations of KGM and XG. The mixtures of konjac glucomannan and xanthan gum for sustained release drug delivery systems is recommended. A synergistic interaction between konjac glucomannan and xanthan gum in the gel phase, influencing the rate of drug diffusion, can effectively retard the drug release from the matrix tablets. Further investigations on the mixed polysaccharides have indicated a strong synergistic interaction between KGM and XG in solution as well as in the gel phase. A binary mixtures of Gleditsiasinensis galam and xanthan can be used as novel sustained release materials for controlled drug delivery. For controlled delivery of theophylline, in different ratios and evaluated their release-controlling performances. The synergistic interactions between galactomannan and xanthan effectively delayed the drug diffusion. A controlled release tablet formulation of diclofenac sodium in xanthan gum matrix was evaluated in vitro and was found to release the drug at a uniform rate. Gastro retentive floating microspheres of ranitidine hydrochloride with HPMC, xanthan gum & eudragitin various ratios were prepared. Interpenetrating network (IPN) beads of sodium carboxymethyl xanthan (SCMX) and sodium alginate (SAL) were prepared by ionotropic gelation buffer solution depending upon the need. The results showed that the IPN beads of SCMX and SAL could be a suitable dosage form to retard the drug release in acidic solution and to control the release of drug in intestinal tract.

4.2 Anti-hypertensive drug delivery

For the treatment of several diseases of the cardiovascular system, especially angina and hypertension, floating tablets of diltiazem HCl using xanthan gum as carrier was prepared. The drug release from prepared tablets was found to be related to the concentration of the polymer, xanthan gum. The study was concluded with a possibility of developing floating drug delivery system by use of xanthan gum as a carrier. The feasibility of xanthan-grafted copolymer of acrylamide (AAM) as a controlled release (CR) matrix for antihypertensive drugs such as atenolol (ATL) and carvedilol (CDL) is explored. Matrix tablets containing various graft copolymers of xanthan gum were prepared and evaluated for in vitro drug release studies. From PAAM-g-XG matrix tablets containing ATL, the release continued up to 24 h and 85% of the drug was
released in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) media. However, in case of plain XG matrix, the release increased to 99% in 12 h. In case pAAm-g-XG, the release time increased with increasing the grafting ratio of the grafted copolymer. On the other hand, there was no significant difference in the release rate with plain XG tablet formulations and with graft copolymer (pAAm-g-XG) tablet formulation of CDL 32.

The multiunit sustained release dosage form of diltiazem using a natural polymer from a completely aqueous environment is reported by Ray et al. Diltiazem was complexed with resin and the resinate loaded carboxymethyl xanthan (RCMX) beads were prepared by interacting sodium carboxymethyl xanthan (SCMX), a derivatized xanthan gum, with Al\(^{3+}\) ions. The beads maintained their initial integrity throughout the dissolution process in both SGF and SIF media. Based on scanning electron microscopic studies, higher swelling of the beads in simulated gastric fluid than in simulated intestinal fluid has been considered as the reason for faster release in SGF 30. A multiunit sustained release dosage form of diltiazem hydrochloride using a natural polymer, sodium carboxymethyl xanthan gum and polyethyleneimine (PEI) from a completely aqueous environment was prepared 31. In vivo pharmacokinetic studies in rabbits showed slow and prolonged drug release when compared with diltiazem solution. The prepared beads were suitable for prolonged release of a water soluble drug under a complete aqueous environment using xanthan gum.

4.3 Ophthalmic drug delivery

A patented ophthalmic preparation containing xanthan gum has been reported by Fukiko et al. 32. The formulation contained echothioiopate iodide and xanthan gum. Xanthan gum has been claimed responsible for improvement of the treatment effect of echothioiopate iodide. In addition, an ophthalmic containing xanthan gum and a carbonic anhydrase inhibitor has been disclosed, where xanthan gum is claimed to improve ophthalmic bioavailability of the carbonic anhydrase inhibitor. For the purpose of improving ophthalmic bioavailability of a drug, xanthan gum is used, and an ophthalmic composition containing a carbonic anhydrase inhibitor, a prostaglandin derivative and xanthan gum has been disclosed. An ophthalmic composition containing quaternary nitrogen containing ethoxylated glycoside and xanthan gum has been disclosed for the treatment of dry eye. Similarly, an ophthalmic preparation containing xanthan gum, which is gelated upon contact with the eye, has been disclosed.

Ophthalmic formulation with xanthan gum and glucose was used for the treatment of corneal epithelial disorder. Invention concluded ophthalmic composition containing xanthan gum and glucose had superior usability since it contains xanthan gum showing pseudo plasticity 33.

4.4 Transdermal drug delivery

A transdermal drug delivery device may be of an active or a passive design, enable to provide an alternative route for administering medicament. These devices allow for pharmaceuticals to be delivered across the skin barrier. Transdermal films were prepared using xanthan gum (XG) and sodium alginate (SA) by varying the composition of the blends. The study concludes that, the prepared transdermal films can be used to achieve controlled release of domperidone with improved bioavailability. Kulkarni et al. synthesized electrically sensitive poly (acrlalamide-g-xanthan gum) (PAAm-g-XG) hydrogel for transdermal delivery of ketoprofen. Drug loaded PAAm-g-XG hydrogel were cross linked with polyvinyl alcohol for formation of rate controlling membrane films. The skin histopathology study demonstrated that PAAm-g-XG hydrogel could be useful as transdermal drug delivery of ketoprofen 34.

4.5 Intra-articular drug delivery

An intra-articular (IA) injection of Xanthan gum showed protective effect on articular cartilage in the papain-induced osteoarthritis (OA) model. Results showed that XG injection was of high transparency, low protein content and was free from endotoxin. IA injection of XG could protect the joint cartilage and this was shown a probable effective therapeutic method of osteoarthritis 35.

4.6 Protein drug delivery

The most challenging task in the development of protein pharmaceuticals is to deal with physical and chemical instabilities of proteins. Instability of proteins is one of the major reasons for which protein pharmaceuticals have been administered traditionally through injection rather than oral, like most small chemical drugs. Peptide and protein drugs are readily degraded by the low pH of the gastric medium in the stomach. In order to achieve success in oral delivery of protein drugs, they need to be protected from the harsh environment in the stomach. The natural pH environment of GI tract varies from acidic (pH~1.2) in the stomach to slightly alkaline in the intestine (pH~7.4) 36. While designing oral delivery of peptide or protein drugs, pH sensitive hydrogels have attracted increasing attention. Swelling of such hydrogels in the stomach is less, and thus the drug release is also less. As the hydrogels pass down the intestinal tract the extent of swelling increases due to increase in pH. A variety of synthetic or natural polymers with acidic or basic pendant groups have been employed to fabricate pH sensitive hydrogels for getting the desired controlled release of protein drugs. Xanthan gum (XG) was derivatized to sodium carboxymethyl xanthan gum (SCMXG) and then cross-linked with aluminum ions (Al\(^{3+}\)) to prepare bovine serum albumin loaded micro particles (MPs) from a completely aqueous environment. The protein release in acidic dissolution medium was faster than that in alkaline medium and was considered for the higher swelling ratio of the MPs in acidic environment.
Moreover, the pH of the gum solution used to prepare the MPs also influenced the swelling and consequently protein release considerably.

### 4.7 Enzyme delivery

Utilization of the excellent performance of bioactive substances, such as enzymes that catalyze complex and specific chemical reactions by converting them into easily releasable forms, is a considerable challenge for material scientists and engineers. However, to maintain its performance in an industrial chemical process, immobilization techniques have particular importance for sustaining enzyme stability, exhibiting large catalytic surface, allowing re-use of expensive enzyme, etc.  

Encapsulation is a critical technique for stabilizing active biomaterials in cases where the stabilized substances must be loaded into a pre-determined space (such as a specific part within the human intestinal tract) and at expected time. Freeze-dried hydrogels were prepared from a colloidal suspension of chitosan and xanthan gum blend, and were used for encapsulating a model enzyme, firefly luciferase. Prepared samples were found to be sensitive to the pH of external solution and the release rate of the enzyme was higher at pH 6.0 than at pH 8.0. The extent of encapsulation and release rate of enzyme, firefly luciferases were confirmed, suggesting that the chitosan and xanthan gum hydrogel formulation were useful for encapsulating bioactive substances such as enzymes.

### 4.8 Pulmonary drug delivery

Pulmonary route presents several advantages in the treatment of respiratory diseases. Inhalation of drug enables a rapid and predictable onset of action and induces fewer side effects than administration by other routes. A new micro particle for drug delivery to lungs was developed by coating liposomes with chitosan (CH–xanthan gum (XG) polyelectrolyte complexes. Two groups of liposomes were prepared using a mixture of soy phosphatidylcholine and hydrogenated soy phosphatidylcholine in two different concentrations to evaluate their capability to entrap required amounts of the model drug rifampicin (chitosomes). Studies indicated that nebulization and rheological properties of chitosomes were affected by the CH–XG weight ratio. In particular, CH–XG 1:0.5 (w/w) coating was able to greatly improve the total mass output and deposition of drug in the lower stages of the impinge.

### 4.9 Antimicrobial peptide delivery

The field of antimicrobial peptide is growing rapidly in response to the demand for novel antimicrobial agents for resistant microbes. Antimicrobial peptide are polypeptides of fewer than 100 amino acids that are found in host defense settings, and that have antimicrobial activity at physiological concentrations under conditions prevailing in the tissues of origin. Generally, these peptides have a net positive charge at neutral pH, which favours interaction with negatively charged membrane of target cells.

It has been concluded that xanthan is an appropriate vehicle for antimicrobial peptide in retention increasing formulation. The presence of xanthan resulted in an increase of LC<sub>50</sub> value of synthetic cationic peptide from 2.6 to 5.8. It has been concluded that xanthan is an appropriate vehicle for antimicrobial peptide in retention increasing formulation. The presence of xanthan resulted in an increase of LC<sub>50</sub> value of synthetic cationic peptide from 2.6 to 5.8.

### 4.10 Rectal drug delivery:

Xanthan gum and loust bean gum based rectal gel were prepared for rectal administration of buprenorphine hydrochloride (BN) in rabbits. A simple applicator is required for rectal administration of soft devices such as hydrogel. The tube used for rectal gels is suitable and it may allow good patient-controlled intake because of convenient self medication.

### 5. Conclusion

Xanthan gum is an extracellular bacterial exopolysaccharide synthesized by Xanthomonas campestris. The unique properties of xanthan gum make it versatile to be used in different applications. They are highly soluble in water, stable over a wide range of temperature, acidic and alkaline conditions. It is resistant to enzymatic degradation and also exhibits synergistic interactions with other hydrocolloids. Xanthan gum can be modified by conventional chemical methods like carboxymethylation and by reaction with formaldehyde to improve its dissolution rate. Such modified xanthan gum reduces intermolecular interactions, so that gelatinous layer cannot form, or even if it forms, the molecules present on to the surface of particle leave rapidly facilitating the dissolution as compared with unmodified gum. For sustained release and colon targeting drug delivery, carboxy methylated xanthan gum moieties are cross-linked with the oppositely charged anions to make it resistant to dissociation in acidic pH but can be slowly degradable in the intestine. This article screens the current applications of xanthan gums and its derivatives in the field of colon targeted, anti-hypertensive, transdermal, ophthalmic, rectal, Intra-articular drug delivery, pulmonary, proteins, enzyme, antimicrobial peptide delivery. This article could become a valuable reference for the researchers intend to work in the area of xanthan gum modification and applications.

### References:

3. Talukdar MM, Kinget R. Swelling and drug release behaviour of xanthan gum matrix


27. Ray S, Banerjee S, Matti S, Laha B, Barik S, Sa B, Bhattacharya UK. Novel interpenetrating network microspheres of...


