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Xanthan Biopolymer in Pharmaceutical and Cosmeceutical Applications: Critical Review

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Polysaccharides, in the last decades, have received particular attention due to their potential for wide variety of applications in the pharmaceuticals and cosmeceuticals field. Xanthan is a natural polysaccharide, produced by the bacterium *Xanthomonas campestris*. This biopolymer displays several appealing characteristics for pharmaceutical applications, among which its high thickening capacity should be highlighted. In this review, we describe critical aspects of xanthan, contributing for its role in pharmaceutical and cosmeceutical applications. Physicochemical properties, biosynthesis, production process, as well as downstream process are described. The pharmaceutical and cosmeceutical applications are discussed in specific.

Keywords: xanthan, biosynthesis, pharmaceutical, cosmetics, applications

INTRODUCTION

In the recent years, microbial polysaccharides gained high interest based on their wide range of applications not only as filler but also as functional molecule with many pharmaceutical and therapeutic properties El Enshasy et al., 2010; Sarmidi and El Enshasy, 2012; Maftoun et al., 2013; Masri et al., 2017; Dailin et al., 2019. Of different biofactories applied, bacterial cells showed the capacity for the production of many important polysaccharides such kefiran, xanthan, and dextran Esawy et al., 2013; Dailin et al., 2015; Dailin et al., 2016; Elsayed et al., 2017; Abdul Hamid et al., 2018; Esawy et al., 2019).

Xanthan gum (CAS # 11138-66-2) with molecular formula $(C_{35}H_{49}O_{29})_n$ was discovered in the early 1960s by the Department of Agriculture under the trade name Kelzan and put into commercial production and was approved for food use in 1968 Mohan and Babitha, 2010. Xanthan gum is also known as corn sugar gum and gum xanthan with appearance of white or light yellow powder. The trade names are Ketrol, Satiaxane, NovaXan, Ziboxan and Ticaxan. Nowadays, in the United States, Canada, European countries, and many other nations, xanthan gum is approved as a safe food additive Presman et al. 2017. Xanthan gum is a polysaccharide formed by *Xanthomonas campestris* bacteria through the fermentation of glucose, sucrose, or lactose El Enshasy et al., 2011; Elsayed et al., 2016.

Upon drying, it is ground into a fine powder where gum or paste can be applied to the material. Xanthan gum can be used in everything from cleansers to masks, serums to peels. It is a popular ingredient in brands that produce organic skincare because of its natural origins. Xanthan gum is a heteropolysaccharide extracellular produced by many types of Xanthomonas spp bacteria such as *Xanthomonas campestris, Xanthomonas phaseoli and Xanthomonas malvacearum* (Leela and Sharma, 2000). *X. campestris* is the most commonly used xanthan manufacturer based on its high yield and high-quality product. The main structure of xanthan polymer consists of repeated units of pentasaccharide where every unit has two units of glucose, two units of mannose and one unit of gluconic acid (Sworn, 2009).

Among microbial polysaccharides, xanthan plays a dominant role due to its relative ease of processing and its exceptional properties. Because of its unique structure, xanthan exhibits different pseudoplastic properties, low viscosity, and solubility, increased stability over a wide range of pH values (Petri, 2015). High solubility, resilience and durability in acid or alkaline environments, stability of xanthan gum in the presence of salts and resistance to enzymes make xanthan gum one of the main polymers used in the food industry (such properties result in various applications of xanthan in different industries ranging from food industries to improved oil recovery in the oil fields. Xanthan contributes to the consumer's acceptance of food through specific sensory properties such as taste release, texture, and appearance (Wang and Wang, 2013; Katzbauer, 1998). Xanthan is also used in drug formulations such as herbicides and fertilizers, cosmetics and agricultural products. Xanthan is considered to be the most widely used biopolymer in the petroleum industry and is not only used as a mobility control agent for enhanced oil recovery, but also to control the rheological properties of the oil well drilling mud and to provide high viscosity to fracturing fluids at low concentrations (Bruna de Monaco Lopes et al. 2015). By 2026, the world market for xanthan-gum is expected to reach 523.7 million dollars, with a CAGR of 3.18% over the forecast period. The rising food and drink industry are encouraging the development of the demand for xanthan gum. For example, in 2017, the Food Industry represented 5 percent of the gross domestic product, 10% of the US total employment with revenues of US$ 1.4 trillion, according to the Committee on Economic Development.t. The key contributing factor to this growth is market expansion in Asia, Eastern Europe and the United States of America, especially China, which is growing at more than 10% per year, while Europe is growing at about 4.5% per year.

Xanthan gum physical characteristics

Xanthan gum can be soluble completely in hot or cold water, hydrated easily when distributed and helps to keep liquid highly viscous solutions at low concentrations and does not usually have a pH change. In most acids and bases applications, Xanthan gum can dissolve. Like all hydrocolloids, Xanthan gum binds water. Xanthan gum's viscosity remains stable for a long time at low pH and high temperatures and is not affected by high salt levels (Saha and Bhattacharya, 2010). Xanthan Gum solutions have strong freeze/thaw stability due to their air binding force. By itself, xanthan drastically increases the viscosity (thickness) of any liquid it is added to in very low concentrations. In high concentrations, it will form a mucus paste that looks like a gel but is not technically a gel.

Apparently, with the incorporation of thickening, suspension, emulsification, and stability, xanthan gum is the strongest biological gum in the world. At the end of the molecular side chain, the number of pyruvic acid groups can have a major effect on its properties. On the other side, Xanthan gum has the same general characteristics as long-chain polymers. On the other hand, it has more functional groups than the general polymers, so under some conditions, it shows some distinctive properties.

Molecular structure of xanthan gum

Xanthan gum is a very high molecular weight hetero-polysaccharide obtained from carbohydrate fermentation by the bacteria, namely *Xanthomonas Campestris*. The main chain consists of glucose units, the backbone is identical to cellulose and has trisaccharide (3 sugars in a chain) sidechains attached. The gum molecules have a helical structure in their stable state. The sides of the rectal chain are constructed from alpha-D-mannose, which contains a group of acetyls, beta-D-glucuronic acid and a terminal unit of beta-D-mannose connected to a group of pyruvates. The monosaccharide (beta-D-glucose, alpha-D-mannose, and alpha-D-glucuronic acid) present in xanthan gum can be found in 2:2:1. The beta-D-glucose (1->4) is bound to the cellulose-like backbone. A short 3 sugar branch composed of glucuronic acid sandwiched between two mannose units contains alternate glucose. Therefore, pentaaccharide is the ultimate repeating structure. A Pyruvate group can be attached to the terminal mannose and a C6 acetyl group can be attached to the mannose near the principal chain (Sworn, 2009; Casas et al. 2004; Lopes et al. 2015 Garcıa-Ochoa et al. 2000; Katzbauer, 1998).

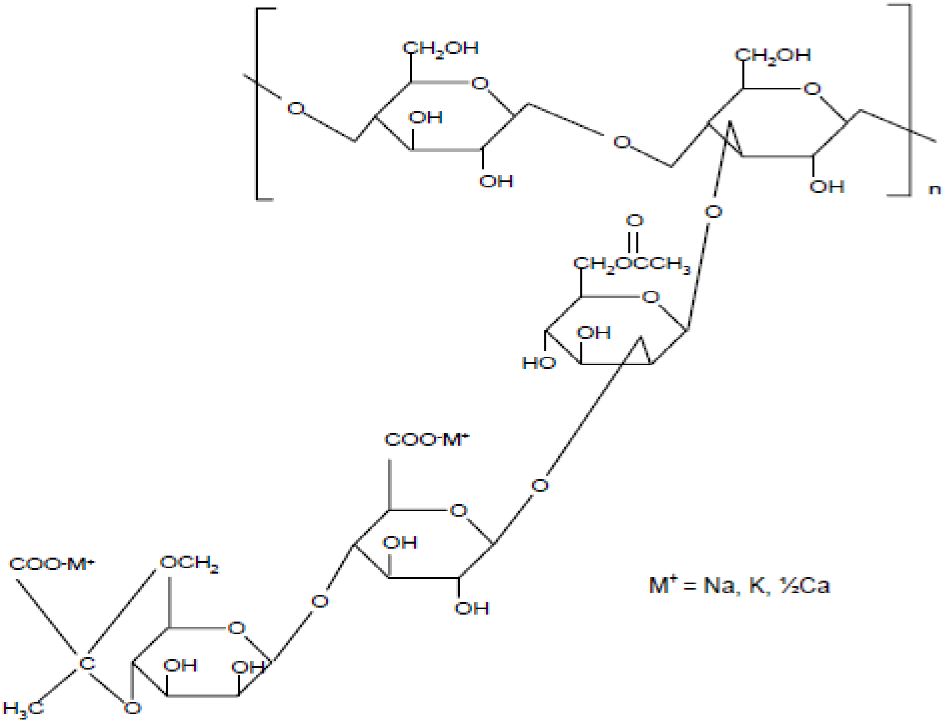

Figure 1: Structure of xanthan gum (Jansson et al., 1975)

Water-solubility superior

Xanthan gum can be dissolved easily in water and is therefore water-soluble preferably. Even in cold water, it is soluble, so it saves you from complex processes and makes easy use of it). Nonetheless, be sure to use it properly due to its high hydrophilicity. For example, if it is mixed directly with a small amount of water and not shaken evenly, the outer sphere can absorb water, expand into a micelle, stop water from reaching the inner sphere, and hamper its effects. Xanthan gum should be ready for use in the correct process in solutions. Dry powder should be mixed in dray dust, such as salt or sugar, and then add water gradually (García-Ochoa et al. 2000; Katzbauer, 1998; Sharma et al. 2006).

Thickening properties

The xanthan gum solution has low viscosity and is 100 times smaller than gelatin. The aqua solution has a high viscosity. It is a certain type of thickening agent. Xanthan gum thickener and stabilizer development and marketing have gradually increased at a rate of five to ten percent each year because of their better Physico-chemical quality de Mello Luvielmoa et al. 2016; Katzbauer, 1998; Sharma et al. 2006.

Pseudoplastic properties

Xanthan gum solution has a static or low shear rate of high viscosity. On the contrary, the viscosity of the molecular structure will drop dramatically at a very high shear rate. It will also quickly recover its original viscosity when the shearing action is stopped. The relationship between viscosity and shear action is plastic. The xanthan gum has an excellent pseudoplastic property and plays a significant role in stabilizing suspension Casas et al. 2000; García-Ochoa et al. 2000; Faria et al. 2011; de Mello Luvielmoa et al. 2016 Katzbauer, 1998; Sharma et al. 2006.

Stability of temperature

With the changes in temperature, the viscosity of xanthan gum is not affected. General polysaccharide tends to have a difference in viscosity due to heating, whilst there are hardly any improvements to the viscosity of the xanthan gum solution. Given a wide temperature range, the low concentration aqueous solution still has the stability of high viscosity (García-Ochoa et al. 2000; Faria et al. 2011; de Mello Luvielmoa et al. 2016; Sharma et al. 2006; Katzbauer, 1998)

The stability for acid-base

The solution of Xanthan gum for acid-basis is very stable. The viscosity in the pH zone of 5-10 is not affected, and its viscosity varies significantly when the pH is less than 4 or more than 11 Casas et al. 2000; García-Ochoa et al. 2000; Faria et al. 2011; de Mello Luvielmoa et al. 2016. The viscosity of xanthan solutions is almost constant from 1 and 13 pH. At pH 9 and higher, xanthan gum is slowly loosening diacetyl, but this has no effect on solution properties Sharma et al. 2006; Katzbauer, 1998.

The salt stability

The solution of xanthan gum can be mixed with many salt solutions, such as kali salt, sodium salt, calcium salt and magnesium salt that do not affect its viscosity. This maintains its solubility under hyper-salt concentration and is free from precipitation and flocculation in a concentrated solution of salt and has little to do with its viscosity (García-Ochoa et al. 2000; Faria et al. 2011; de Mello Luvielmoa et al. 2016; Sharma et al. 2006).

Enzyme hydrolysis stability

The xanthan gum can not degrade numerous enzymes like protease, amylase, cellulose, pectinase, and hemicellulose Sharma et al. 2006. Nevertheless, xanthan is largely biodegradable, and under certain environmental conditions it is subject to enzyme depolymerization by certain microorganisms. Xanthan is also degraded by heavy oxidizing agents such as peroxides and persulfates, in conjunction with other gums Sharma et al. 2006.

Xanthan biosynthesis

Xanthan gum is a complex exopolysaccharide produced by *Xanthomonas campestris* pv. campestris. which belongs to the plant-pathogenic microbiota. Xanthan is a pentasaccharide repeat units and formed with a cellulose backbone consisting tri-saccharide sidechains of [β-D-Manp-(1→4)-β-D-GlcpA-(1→2)-β-D-Manp-(1→)]. These sidechains are attached to alternate glucose residues in the backbone by α-1,3 linkages (Becker, 2015). Glucose is used as substrate for synthesis of UDP-glucose, UDP-glucuronate, and GDP-mannose which are the sugar nucleotide precursors. These molecules are the building blocks of the penta-saccharide repeating units of xanthan. The bacterial genome clustered with genes directing synthesis, polymerization and export of a specific polysaccharides Becker et al. 1998; Lopes et al. 2015. However, the genes involved in the synthesis of common nucleotide precursors are frequently uncoupled from the specific biosynthesis gene clusters. The genome of *X. campestris* consists of a 16 kb *Gum* gene cluster which encode glycosyltransferases, enzymes catalyzing the addition of non-sugar decorations, and proteins involved in the terminal steps of xanthan biosynthesis Katzen et al. 1996; Becker, 2015. There are twelve genes encoded by the genes gumB to gumM were clustered at a single location on the chromosome, all sharing an identical direction of transcription. The gum region is expressed as a single operon from a promoter located upstream of the first gene, gumB. A second promoter was identified upstream of gumK. The repeat units are built up at cytoplasmic membrane anchored un-decaprenylphosphate lipid carriers Schulte et al. 2019. A number of specific glycosyltransferases sequentially transfer the sugar moieties of the nucleotide sugar precursors onto the phosphorylated lipid carriers. This process is initiated by a glycosyltransferase encoded by gumD. GumD protein catalyses the addition of glucose-1-phosphate to polyisoprenol phosphate carrier, in a reversible reaction. This is the first step in the biosynthesis of lipid-linked intermediates in the xanthan biosynthetic pathway. Then, GumM catalyses addition of a β1,4-glucose, GumH add an internal α1,3-mannose, 2-glucuronic acid by GumK, and additional of a terminal b1,4-mannose by GumI. Protein GumL incorporates pyruvyl residues to the external β-mannose whereas GumF incorporates acetyl residues into an internal α-mannose and into the external β-mannose by GumG. Mature repeat units are polymerized and exported in a way resembling the Wzy-dependent polysaccharide synthesis mechanism of *Enterobacteriaceae* Becker et al. 1998; Becker, 2015; Lopes et al. 2015.

To date, none of specific controls of xanthan biosynthesis still have not been reported. In the natural process, synthesis of xanthan is regulated by plant pathogenicity activity by *Xanthomonas* spp Kang et al. 2019. Mutagenic studies involving *X. campestris* mutant has showed reduction in the pathogenicity also simultaneously decreased production of xanthan and some other extracellular enzymes. The synthesis of xanthan and other extracellular enzymes are activated by products from a five gene cluster of regulating pathogenicity factors, designated as *rpf*. Expression of these factors are balanced by unlinked genes that negatively regulates the synthesis of xanthan and other extracellular enzymes (becker et al. 1998). Xanthan gum is not necessary for plant virulence. Yet, the initial stages of xanthan biosynthesis are regulated as part of phytopathogenecity interaction between *Xanthomonas* spp. and plant Becker, 2015; Lopes et al. 2015.

Upstream process

Upstream process is one of the main stages in industrial fermentation. There are many factors contributing to the production of xanthan gum. These factors include the formulation of medium components; mainly carbon sources and nitrogen sources, processing parameters such as inoculum density, temperature, pH, agitation and aeration rate as well as other factors such as bioreactor type, impeller type and labour skills. Overall, the efficiency of xanthan production dependable with all of the factors stated above.

Medium production

Carbon source

Carbon source is believed to be the major source of macronutrients in xanthan production as they are needed mostly for energy and cell growth. Generally, there are two types of carbon source known as commercial and natural carbon source. Traditionally, commercial carbon source such as sucrose and glucose are the most carbon sources used for xanthan production at an industrial scale. Several previous studies reported that glucosePeters et al. 1989; Esgalhado et al. 1995; Leela and Sharma, 2000; Murad et al. 2019) and sucroseGarcía-Ochoa et al. 1992; Casas et al. 2000; Leela and Sharma, 2000; Chavan and Baig, 2016; Murad et al. 2019 have been used as substrates in the commercial production of xanthan gum. Other commercial substrates such as xylose, galactose and lactose are less frequently used because they result in decreasing the polymer productivities as bacteria unable to fully utilize them Singh et al. 2008; Zhang and Chen, 2010; Murad et al. 2019. Elsayed et al. 2016 reported that xanthan produced by *Xanthomonas campestris* DSMZ 19000 strain achieved 43.15 g/L when chemically defined medium supplemented with glucose was used in the fed-batch cultivation. Another study resulted a maximum xanthan gum production was obtained as 15.21 g/L proven that fermentation using *X. campestris* and sucrose as the carbon source was best combination for high xanthan yield (Chavan and Baig, 2016).

Table 1: Production of xanthan gum by *Xanthomonas campestris* by using different natural carbon sources.

Bacterial stain	Substrate	Xanthan production	Reference
X. campestris **NRRL B-1459**	Date palm juice	24.5 g/L	Salah et al. (2011)
X. campestris **MTCC 2286**	Acidified sugarcane molasses	10.3 g/L	Murugesan et al. (2012)
X. campestris **PTCC1473**	Date extract	11.2 g/L	Khosravi-Darani et al.(2013)
X. campestris **PTCC1473**	Date juice by-products	6.72 g/L	Moshaf et al. (2015)
X. campestris **PTCC1473 and** ***X. pelargonii*** **PTCC1474**	Cheese whey	16.77 g/L	Niknezhad et al. (2015)
X. campestris **LRELP-1**	Kitchen waste hydrolysate	11.73 g/L	Li et al. (2016)
X. campestris pv campestris **(b82)**	Grape juice concentrate	14.35 g/L	Ghashghaei et al. (2016)
X. campestris **NCIM 2961**	Jackfruit seed powder	51.62 g/L	Katherine et al. (2017)
X. campestris **(BeNa culture collection, China)**	Orange peels	30.19 g/L	Mohsin et al. (2018)

According to Murad et al. 2019, media containing lactose as a sole carbon source produced lower yield of xanthan because *X. campestris* has a low level of β-galactosidase enzyme which prevents the microorganism to ferment lactose efficiently as a carbon source. Nevertheless, recent studies reported that several natural carbon source which act as low-cost natural alternatives to serve as substrates were able to produce high xanthan production as shown in Table 1. The optimum carbon concentration in xanthan production was about 2-4% because lower or higher concentration of carbon source was not effective for maximum cell growth (Niknezhad et al. 2015).

Nitrogen source

Nitrogen source which can be classified into organic and inorganic nitrogen source also act as the essential macronutrients needed in a submerged fermentation of xanthan production. Basically, organic nitrogen sources such as peptone, yeast extract, corn steep liquor and soybean meal are much cheaper compared to inorganic nitrogen sources mainly originated from ammonium or nitrate salts. Previous findings showed that yeast extract and peptone were the most effective nitrogen source for xanthan production. Mohsin et al. 2018 found that the highest polymer production was produced with the presence of peptone compared to other nitrogen sources. Earlier, Selva and Babitha (2010) reported that maximum xanthan production was achieved as 0.615 mg/10 ml at 24 hours when using peptone as the nitrogen source. Another study conducted by Chavan and Baig (2016) showed that peptone contributed maximum biomass production of *X. campestris* as 23.91 g/L whereas the availability of yeast in the production media able to produce maximum yield of xanthan gum as 15.17 g/L. Bhatia et al. (2015) also reported that the usage of hydrolysed starch as substrate in the media was supported by yeast extract which contributed to the maximum xanthan production reached up to 10g/L. It was believed that by controlling the carbon:nitrogen (C:N) ratio in both cell growth phase and gum production phase of the fermentation, maximum xanthan gum production could be achieved. Several studies have reported that higher concentration of nitrogen source would lead to higher biomass concentration. However, too high nitrogen source concentration was unsuitable for xanthan production as it does not involve in the polysaccharide structure and mainly used for cell growth and enzyme production only Moshaf et al. 2015; Farhadi et al. 2012; Khosravi-Darani et al. 2013. Therefore, a low C:N ratio is recommended in the trophophase to obtain both high cell concentration and high specific growth rate which could eventually promotes to further xanthan production (Khosravi-Darani et al. 2013).

pH of cultivation

An optimum xanthan production significantly affected by the pH condition of cultivation media. This is because Xanthan gum is a charged polymer where changes in the pH leads to changes in the charge density of the xanthan gum. This causes the alteration in molecular associations between the xanthan gum molecules themselves which eventually affects their unique properties; mainly its viscosity (Rinaudo and Moroni, 2009; Murad et al. 2019). Most of the previous studies determined that the neutral pH is the optimum value for the growth of *X. campestris* range from (6 to 7.5) and the optimum pH for the xanthan production range from 7 to 8 Mohsin et al. 2018; Katherine et al. 2017; Gumus et al. 2010. According to Chavan and Baig (2016), xanthan production was at the highest yield of 15.22 g/L showed at the optimum pH 6 whereas the optimum pH for biomass production is 6.5 with the maximum production of 15.23 g/L. Several other studies also reported that during xanthan production, due to the presence of acid groups in xanthan, the pH decreases from neutral pH to values close to 5 which significantly supported that neutral pH is the optimum value for high xanthan production Bojana et al. 2017; Zorana et al. 2017; Borges et al. 2008.

Temperature

Temperature mainly during cultivation of *X. campestris* plays a crucial role in producing maximum functional xanthan gum. It was reported by many authors that the optimum temperature for maximal xanthan gum production was at the range of 28 °C-30 °C (Mohsin et al. 2018; Zakeri et al. 2017; Gumus et al. 2010). Another study concluded that the optimal temperature for *X. campestris* growth was 25–27°C and optimal temperature for xanthan gum production was 25–30°C Murad et al. 2019; Sherley and Priyadarshini, 2015. Most of the previous studies reported that cultivation temperature could affect the viscosity of xanthan due to the rise in temperature as it leads to molecular conformation changes from an ordered to a disordered state. They also found out that as temperature increased from 25°C to 35°C, the production of biomass and xanthan gum also increased but further increase in temperature lead to reduction in production of both biomass as well as xanthan gumMohsin et al. 2018; Chavan and Baig, 2016;

Sherley and Priyadarshini, 2015. However, as xanthan gum is unique in its rheological structures, it is able to retain its viscosity during temperature changes which makes xanthan differs from the other thickeners by considering the production media used (Sherley and Priyadarshini, 2015). As the conformational changes of xanthan gum are related to the amount of salts, it is suggested that any salts in the formulation are added to solution prior to the thermal treatment for maximization of stability and minimization of any effects of thermal treatment on xanthan rheology Sherley and Priyadarshini, 2015; Higiro et al. 2007.

Fermentation time

Xanthan production is significantly related to the fermentation time. It was reported by previous studies that maximum xanthan yield can be achieved at varies fermentation time probably depending on the cultivation conditions used for each experiment. Recent study showed that xanthan gum reached to the maximum level of production which was 30.19 g/L at 72 hours of cultivation time in 15-L bioreactor (Mohsin et al. 2018). In another study, different type of strains (*Xanthomonas campestris pv. campestris* 1866 and 1867) and different type of carbon source were used as alternative fermentable substrate (coconut shell and coconut husk). It reported that at 96 hours cultivation in shake-flask level, the results of xanthan gum production produced by strain 1866 varied between the coconut shell and coconut husk where 4.48 g/L and 3.89 g/L of xanthan yield respectively Silva et al. 2018. According to Katherine et al (2017), xanthan gum production using jackfruit seed powder was optimized and showed maximum xanthan gum yield of 51.62 g/L within 72 hours of cultivation. Therefore, in order to get high xanthan production, the fermentation time can be in the range of 72 to 96 hours depending muchly on the strains and cultivation conditions.

Downstream processing of xanthan

End of fermentation, xanthan is contained within a mixture of cells, medium and fermentation by-products. The harvesting process of xanthan requires series of purification steps to obtain pure xanthan. Downstream processing cost of xanthan can take up to 50% of total production cost (Palaniraj & Jayaraman, 2011). Therefore, selection of purification technique is important, and it differs to suit the end-application. Food and pharmaceutical grade are the highest purity of xanthan which associated with the highest purification cost. On the other hand, crude grade and industrial grade have lower purity with lower purification cost.

As shown in Figure 2, recovery of xanthan from fermentation broth generally involves cell removal, precipitation, drying, milling and packing (Garcıa-Ochoa, 2000). Generally, bacterial cells are removed from fermentation broth by using filtration or centrifugation. Precipitation of xanthan from media was performed by addition of water-miscible non-solvent followed by pH alteration and salt addition. The choice of solvent would depend on the application of the xanthan. Following precipitation, xanthan undergoes drying process, milling and finally packing.

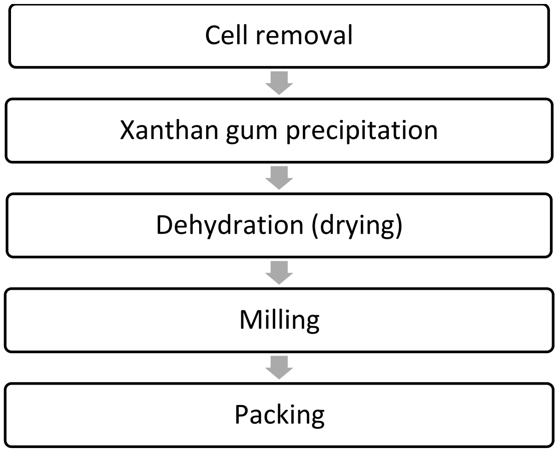

Figure 2: Downstream process of xanthan gum production

Fermentation conditions play an important role in changing the biological and rheological properties of microbial xanthan, hence determining the complexity of the downstream processes of this molecule. Xanthan can be separated from fermentation broth by phase separation technique using non-solvent for polysaccharide (Garcıa-Ochoa, 2000). Crude xanthan gum appears yellow in color due to the presence of residual xanthomonadins produced by *Xanthomonas* Dai et al. 2018. Phase separation and removal of this colored compound requires the addition of excess alcohol in the precipitation step. In addition, the fermentation broth is highly viscous, thus requires solvent more than three times of the fermentation broth volume to obtain white, purified xanthan, which increases the production cost.

Different alcohols of different volumes have been used in various study for xanthan precipitation. Xanthan from *Xanthomonas campestris* pv. mangiferaeindicae has been precipitated using ethanol with four times of fermentation broth volume Trindade et al. 2018. Ethanol with seven times volume of fermentation broth was used to purify xanthan gum from wild-type *Xanthomonas campestris* CGMCC15155 Dai et al. 2018. Isopropanol is prescribed by the FDA for xanthan gum that is to be used in food application. Acetone and methanol have also been used for phase separation of xanthan (Garcıa-Ochoa, 2000).

Salt can reduce xanthan solubility in water to enhance phase separation and helps to reduce the amount of solvent used (Morariu et al 2018). Cations of added salt can bind to the ionized groups of anions in polysaccharide, lead to its precipitation. Addition of non-solvent reagent in this stage decreases water activity, thus enhances cation binding and promotes precipitation. Higher valency of salt resulting in higher separation. This is proven when the highest precipitation yield of xanthan was obtained with $CaCl_2$ in isopropanol compared to that of KCl and NaCl with 25% and 6% higher recovery yield, respectivelyNiknezhad et al. 2015. Less volume of alcohol is demonstrated in the recovery of xanthan for pharmaceutical application, which was proceeded using only two volumes fermentation broth of isopropanol containing KCl Han etal., 2012. Addition of salt is also advantageous for xanthan used in food industry because it enhances pseudoplasticity of xanthan which improves its sensory quality. Addition of 5% Na^+ and 0.5% Ca^{2+} increased the viscosity of xanthan (Klaic et al. 2016). Therefore, addition of salt does not only improve the phase separation and reduces the non-solvent used, but also improves the viscoelastic properties of xanthan.

Dai et al. 2018 engineered a Δ*pigA*::*vgb* strain of *Xanthomonas campestris*, by deactivating pigA gene, which is required in xanthomonadin synthesis. Xanthomonadin, which is the yellow pigment produced along with xanthan during fermentation reduced significantly. As a result, a white xanthan gum was produced. When the same volume of ethanol used for xanthan purification, the whiteness of xanthan produced from engineered strain is 70.1% higher than that of the wild-type strain. While wild-type xanthan gum required seven times the fermentation volume of ethanol for purification, the engineered xanthan only required three times to produce the same whiteness. From this finding, using engineered bacteria could simplify the purification step and greatly reduce the cost for xanthan purification by reducing the amount of ethanol used.

Addition of sterilization step and protein deactivation is crucial for xanthan used in pharmaceutical application. This involves filtration and addition of protease to ensure no protein and endotoxin in the solution Han et al. 2012. Following precipitation, xanthan is collected by filtration or centrifugation and dried until it reaches a constant weight. Finally, the dried xanthan undergoes milling to desired particle size and is packed. Waterproof packing material is used because xanthan is hygroscopic substance and can undergo hydrolytic degradation.

Pharmaceutical application

Xanthan has been used commercially in a large number of pharmaceutical applications due to its unique rheological properties (Goswami and Naik, 2014) and biocompatible nature with similarities with biological system kumar et al. 2015. With the diverse ingredients used from one to other applications, their use in pharmaceutical is regulated by standards, such as United States Pharmacopoeia and the European Pharmacopoeia for quality management of such products. As compared with other polysaccharides from plant, xanthan from microbial origin is preferable as emulsifier, thickener, stabilizer, film form and gel nature in pharmaceutical ingredients Verma et al. 2017. Their use of market has been permitted by the US Food and Drug Administration since 1969 followed by the approval by the European Union under E-number 415 in 1980 Murad et al. 2019.

As a natural polysaccharide which are hydrophilic polymer with repeating monosaccharide units linked via glycosidic bonds, their characteristics differ based on the type of monosaccharide building unit, position of the glycosidic bond, chain substitution and the molecular weight Dadou et al. 2018. Compared to synthetic gums, xanthan gum that produced naturally from fermentation of *Xanthomonas campestris* was reported to be as excipients in many pharmaceutical formulations (Nur et al. 2015). Due to its viscous characteristics even at low concentration, xanthan has been employed in a broad scope of utility in conventional drug products (Dey, 2015).

Drug delivery system is an engineered technology that enables the introduction/or controlled release of therapeutic agents into a body and improves its efficacy and safety. Normally, natural gum is used in pharmaceutical as binders and disintegrates in solid drug products and as thickening, suspending and/or stabilizing agents in liquid oral and topical formulations Badwaik et al. 2013. Natural gum acts as a carrier that can rescue the drug to the site of pharmacological action without wasting the active ingredients (Benny and Ponnusamy, 2014). The interest to use natural gums, in the pharmaceutical industry are due to their biodegradability, non-toxic, low cost, easy availability and excreted directly by the kidney compared to the synthetic form.

In combination with other polymers, xanthan has been applied as excipient in tablets or as supporting hydrogels for drug release applications, particularly due to its acid resistance (Petri, 2014). Xanthan gum has been chemically modified using conventional chemical methods such as carboxymethylation Yahoum et al. 2016cross-linking with epichlorhydrine Zhang et al. 2017, glutaraldehyde (Manna et al. 2015) and also using a method of grafting such as free radical Kumar et al. 2017, microwave-assisted Anjum et al. 2015 chemoenzymatic (Kadokawa et al. 2019) and plasma assisted chemical to alter the physicochemical properties in biological applications. The physical method of polyelectrolytes complexation, ionotropic gelatin and freeze thaw technique (Patil et al. 2016) have also provided a highly acceptable controlled release delivery *system* to increase the effectiveness of drug therapy. Xanthan gum and xanthan gum derivatives currently the primary ingredients in hydrogel formulation to improve the rescue system and controlled release of drug and enzymes.

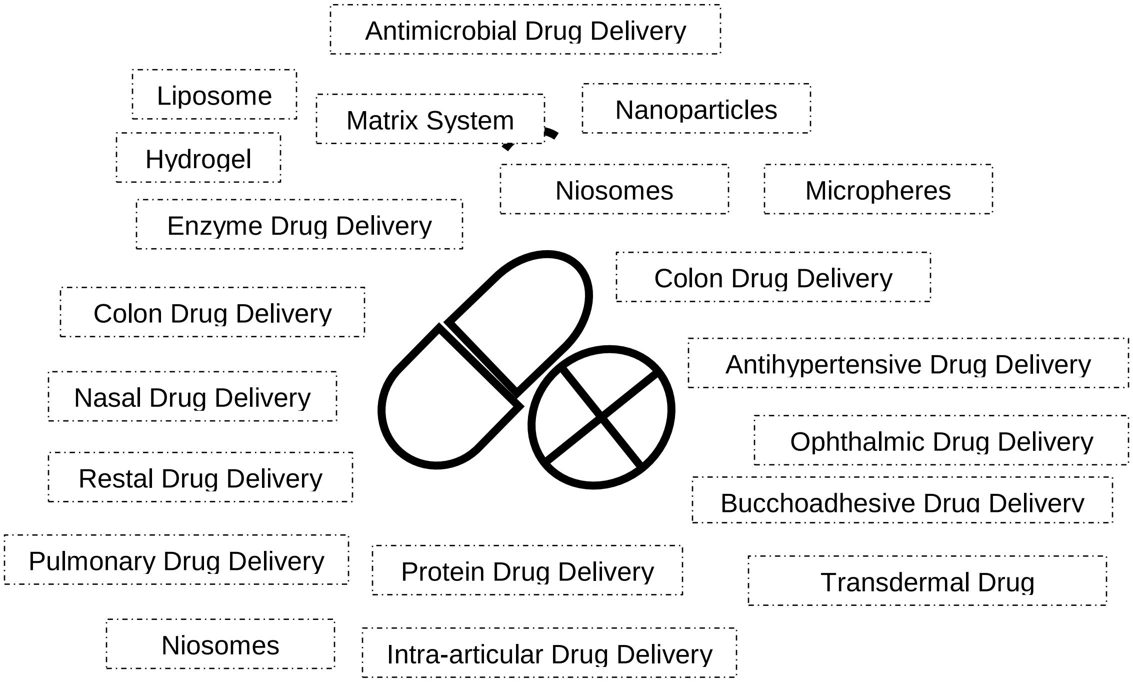

Figure 3: Xanthan applications for the delivery of drugs, proteins or biosolutes

Biocompatibility, abundance in nature and hydrogel's similarity with biological systems are the main criteria for the polysaccharides to be used effectively in biomedical applications Vinay et al. 2017.

Due to its ability to stabilize suspensions of a mixture of insoluble materials such as barium sulphate, xanthan is commonly employed in x-ray diagnoses Palaniraj et al. 2011. Figure 3 showed xanthan in the varied applications of drugs, protein and biosolutes.

Cosmeceutical Application

Cosmeceutical products are define as any substance that are intended to be directly in contact with various external part of the human body (Nagarnaik, 2015) through rubbing, pouring, sprinkling, or spraying Savary, Grisel et al. 2015. The parts of human body which is commonly applied for cosmeceutical products include the epidermis, hair, nails, lips, external genital organs as well as teeth and gums. These products are used for multiple purposes such as cleaning, perfuming, changing the appearance, correcting unwanted body odors as well as protecting and keeping the skin in optimal condition. The cosmeceutical products are used by consumers for a specific function and also mostly for the pleasure it promised to them. Among the various type of cosmeceutical ingredients, natural polymers and their derivatives are important classes of ingredients which has been widely used in delivery cosmetic products. It represent second largest class of ingredients in the cosmeceutical field (Savary, Grisel et al. 2015). Products resulted from fermentation or microorganism culture usually has a common name e.g. xanthan gum.

The application of xanthan in cosmeceutical industries has been receiving huge attention recently. Xanthan is one of the microbial polysaccharides besides pullulan, dextran, glucan and fructan that are largely used in cosmetics. Xanthan, which is an anionic biopolysaccharide was found suitable to be incorporated as one of the active ingredients for skin hydration purpose. It is also been applied in skin care, hair care and conditioners, toothpaste, aftershave, shower gel and shower cream, body lotion, shampoo, sunscreen, cleanser and many more Savary, Grisel et al. 2015. The main functions of xanthan in these cosmeceutical products are as thickener, water-soluble binder, emulsifier, stabilizer, film forming and gelling nature, suspending agent as well as release control agent in hydrophilic matrix formulations Alhalmi, Alzubaidi et al. 2018. Biodegradable polymer such as xanthan is highly compatible with human biological tissues and highly meets with consumers' demand for natural products (Kanlayavattanakul and Lourith 2015). Natural moisturizers are more preferable nowadays as it is considered safe compared to the traditional drugs being used by the dermatologists. This is due to some traditional drugs may cause inconvenient skin reactions from its topical preparation. Hence, natural moisturizers which are free from irritating substances will be the top choice for the consumers.

Xanthan has the value of giving health benefits in terms of suppressing skin dryness as well as acting as anti-aging ingredient for protecting and treating wrinkles on the skin surfaces. Xanthan has the ability to polymerize into viscous liquid with the existence of water which gives the ability to emulsify suspensions and this scenario is called as pseudoplastic fluid. This is due to the formation of helical coils characterized by a rigid backbone when xanthan is dissolved in solution Savary, Grisel et al. 2015. The pseudoplastic characteristic of xanthan improves sensory qualities of the final products, simplify the processing method together with ensuring good pourability (Alhalmi, Alzubaidi et al. 2018). The stability of xanthan emulsion greatly depends on xanthan concentration. A study by Krstonosic et al. (2015) reveals that when xanthan concentration ranges from 0.01 to 0.2 wt%, in continuous phase, droplet flocculation occurs and under 0.8 wt%, creaming is enhanced producing a phase separation in the emulsion. Meanwhile higher xanthan concentration (>0.8 wt%) shows a delayed time in creaming. It has also been reported that above a critical xanthan concentration, it triggers the establishment of a three-dimensional gel-like droplets network Aben, Holtze et al. 2012. Moreover, less flocculation will appear and the emulsions will mostly be stabilized by the continuous phase viscosity increase. The combination of pseudoplastic characteristic and shear-thinning property is normally applied in the preparation of cosmetic to enhance the stability against freeze-thaw processes. Xanthomonas campestris producing xanthan gum is the main and widely used source of bacterial exopolysaccharide. As xanthan concentration is the most important parameter, xanthan has been used for dermal skin care and also in baby products with different range of concentrations, respectively. Table 2 below shows the type of skin dryness characteristic and its adverse effects.

Table 2: Dryness characteristic of the skin and its adverse effects (Kanlayavattanakul and Lourith 2015).

No.	Characteristics	Adverse effects
1	**Sensory**	Dry texture, uncomfortable, itchy and painful, stings and tingles.
2	**Visible**	Redness, rough surfaces, dry white patches, flaky look, cracks and fissures.
3	**Tactile**	Rough and uneven surfaces.

Xanthan has been commercially used as one of the active ingredients in several cosmeceutical products. One of the famous products is the Active Powder® Volu Lips LS 9773, a product from Aquaxtrem^{TM}. The product is claimed to have three benefits which are as anti-aging agent, smoothing agent and moisturizing agent. Xanthan has also been used in colour cosmetics ingredients besides giving added values of collagen boosting and skin protection. The health benefits exerted by xanthan in suppressing skin dryness as well as protecting and treating wrinkles on the skin has made xanthan one of the trusted agents in cosmeceuticals ingredients.

Natural polymers are also known to be good in controlling formulations stability and texture. Basically, xanthan can efficiently stabilize complex mixtures as a consequence of its high molecular weight and thus large hydrodynamic volumes are induced for the chains when hydrated in an appropriate solvent. Furthermore, the ability of xanthan to efficiently act as a stabilizers is due to its ability inducing steric and electrostatic interactions, changing the interface viscosity and viscoelasticity, increasing the continuous phase viscosity which ultimately improving overall mixture's stability (Savary, Grisel et al. 2015). Additionally, thermal stability exhibited by xanthan has made xanthan superior than other water soluble polysaccharides Alhalmi, Alzubaidi et al. 2018.

Xanthan is in similar group as starch and hydroxyethylcellulose where it functions to enhance viscosity and/or weak gel establishment of cosmeceutical products by inducing weak interactions and/or chains overlap. In the contrary, gelatin, carrageenan and alginate function to obtain strong gels by intermolecular complex occurance. Nevertheless, the most commonly used natural polymer in the whole cosmetic market is xanthan as it able to provide high viscosity enhancement at rest with super low concentration and remarkable flow properties under shear. This characteristic is related to the xanthan well-known secondary, semi-rigid, and helix strand conformation. The presence of xanthan polymer results in increase in viscosity compared to the no added polymer in control emulsion. Additionally, emulsions containing xanthan gives higher viscosity at low shear. Following the stabilizing characteristic exhibit by xanthan due to its high suspending efficacy, xanthan is widely used in toothpaste which is one example of a concentrated dispersion. Xanthan is also used in hair shampoos as thickening agent. Savary, Grisel et al. 2015.

Another properties being taken into consideration for cosmeceutical products include sensory evaluation which is highly associated with the product's extensional properties. Due to the well-known elongation properties exhibited by the polymers, they play an important role for filament forming ability. The highest extensional properties was shown by xanthan-based emulsion followed by guar gum and cellulose emulsions. Various ingredients present in emulsions may interact synergistically to attenuate or strengthen the intrinsic extensional properties of polysaccharides and thus, aqueous solution containing xanthan showed lower maximum breaking length. Versatilities such as different shear thinning and weak gel properties of emulsions is a great interest for developing cosmeceutical products owning to their innovative texture. This can be achieved when xanthan polymer is used in the formulation of emulsions. Additionally, polymers such as xanthan and others is called as a real-multifunctional ingredients because it brings extra benefits in the performance of cosmetic formulations. The examples of these are in film former, skin hydration, conditioner and softener.

Natural polymers like xanthan are used in wide range of cosmeceutical products. However, these polymers exist among the minority ingredients which is commonly below 1 wt% and is indispensable to meet the requirements for cosmetic formulations in term of stability, rheological behaviours, and sensory as well as active properties. In general, a mixture of various polymers is required as one single polymer is not sufficient for satisfying the requirements. A study investigating the stability of xanthan polymer in aqueous solution containing salt or alcohols has been carried out by Morariu et al. (2018). This was an important study as most of the personal products formulations will include salt and/or alcohol as part of their ingredients. Besides, xanthan is also stable in mild acidic conditions and can be easily dissolves in many types of acidic solutions (Alhalmi, Alzubaidi et al. 2018).

However, despite the advantages of utilizing natural polymers for cosmeceutical ingredients, it has its own disadvantages. The inconsistence in terms of purity and their physical appearance imply variations in viscosity and microbial contamination and also relatively higher in price compared to the synthetically produced polymers (Savary, Grisel et al. 2015). This is also added by the difficulties to obtain stable supplies. Overall, cosmeceutical products consist of many ingredients in a complex mixture involving many interactions. The ability of natural products including xanthan to act as stabilizing agents may be reduced or enhanced depending on the presence of other ingredients.

CONCLUSION

Xanthan gums are a promising biodegradable polymeric material, provides versatile industrial uses across food technology, personal care, paints, ceramic glazes, inks and water-based drilling fluid formulation. In the biomedical or biotechnological field novel applications of xanthan appear continuously. Xanthan is advantageous over the synthetic gums in the drug carrier system by improving the efficacy towards degradation and toxic effects due to rapid release occurred during transportation to the target sites, thus maintaining the therapeutic benefits. Thus, in the years to come, there will be continued interest in natural gums and their modifications aimed at the development of better materials for drug delivery.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

NZN, ARR, RAM, NIWA, NHAM and SS wrote the manuscript. DJD designed, wrote and reviewed the manuscript. DNAZ, RAAA, DS and HEE reviewed the manuscript. All authors read and approved the final version.

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