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Review

Gums' based delivery systems: Review on cashew gum and its derivatives

António J. Ribeiro[d,e,*], Flávia R. Lucena de Souza[a], Janira M.N.A. Bezerra[a], Claudia Oliveira[d,e], Daniela Nadvorny[a], Monica F. de La Roca Soares[a], Lívio C.C. Nunes[b], Edson C. Silva-Filho[b], Francisco Veiga[c,d], José L. Soares Sobrinho[a]

[a] Núcleo de Controle de Qualidade de Medicamentos e Correlatos—NCQMC, Departamento de Ciências Farmacêuticas, Universidade Federal de Pernambuco—UFPE, Brazil
[b] Laboratório Interdisciplinar de Materiais Avançados—LIMAV, Centro de Ciências da Natureza—CCN, Universidade Federal do Piauí—UFPI, Brazil
[c] CNC.IBILI, Universidade de Coimbra, 3000-548 Coimbra, Portugal
[d] Faculdade de Farmácia, Universidade de Coimbra, 3000-548 Coimbra, Portugal
[e] I3S, Instituto de Investigação e Inovação em Saúde, IBMC—Instituto de Biologia Molecular e Celular, Genetics of Cognitive Dysfunction, Rua do Campo Alegre 823, 4150-180 Porto, Portugal

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The development of delivery systems using natural polymers such as gums offers distinct advantages, such as, biocompatibility, biodegradability, and cost effectiveness. Cashew gum (CG) has rheological and mucoadhesive properties that can find many applications, among which the design of delivery systems for drugs and other actives such as larvicide compounds. In this review CG is characterized from its source through to the process of purification and chemical modification highlighting its physicochemical properties and discussing its potential either for micro and nanoparticulate delivery systems. Chemical modifications of CG increase its reactivity towards the design of delivery systems, which provide a sustained release effect for larvicide compounds. The purification and, the consequent characterization of CG either original or modified are of utmost importance and is still a continuing challenge when selecting the suitable CG derivative for the delivery of larvicide compounds.

Contents

Abbreviations: Dox, doxorubicin; CG, cashew gum; AO, *Anacardium occidentale*; CMCG, carboxymethylated cashew gum; Con, concanavalin; ALG, alginate; CHI, chitosan; LsEO, *Lippia sidoids* essential oil; DDVP, dichlorvos [2,2-dichlorovinyldimethyl phosphate]; MOS, *Moringa oleifera* seeds.

* Corresponding author at: Faculdade de Farmácia, Universidade de Coimbra, 3000-548 Coimbra, Portugal.
E-mail address: aribeiro@ff.uc.pt (A.J. Ribeiro).

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1. Introduction

The pharmaceutical and food industries are constantly trying to develop delivery systems and to discover new agents that could be used in a selective form for specific applications, thus, obtaining the desired effect. Polymeric systems obtained by mixing and/or in combination with different polymers in the form of gels, particles, and networks have received attention from researchers in recent years, mainly, due to their extensive use in the pharmaceutical, medical, technological and agricultural fields (Paula, de Oliveira, Abreu, & de Paula, 2012; Yang, Han, Zheng, Dong, & Liu, 2015).

Among natural polymers, carbohydrate polymers or polysaccharides have been proposed as delivery systems for compounds with activity against pathologies such as high blood pressure, cancer and diabetes. For instance, polysaccharide-doxorubicin nanoparticles prepared *via* conjugation of doxorubicin (Dox) to galactoxyloglucan (Joseph et al., 2014) and chitosan (Su et al., 2015) revealed superior therapeutic efficiency as compared to free Dox. Besides, they allow for postsynthetic modifications with the aim of tailoring their physicochemical properties towards an improvement of the active compound to achieve the desired action locally without suffering degradation (Liu, Jiao, Wang, Zhou & Zhang, 2008).

Gums, like cellulose and alginate are polysaccharides. They differ from them in structure, more precisely in the chemical configuration and in the way the monomeric units are joined. Those monomeric units, monosaccharides or its derivatives are linked in a bewildering variety. The term gum refers to polysaccharide hydrocolloids, which do not form a part of the cell wall, but are exudates or slims (Prajapati, Jani, Moradiya & Randeria, 2013). They have a large variety of compositions and rheological properties that cannot be easily mimicked by synthetic polymers. These properties can be an advantage for several applications, for instance the preparation of solutions with a high content in solids and low viscosity, as well as its low cost, low risk of side effects, biocompatibility, environmentally friendly processing and local availability.

Cashew gum (GG) is a polysaccharide extracted from *Anacardium occidentale,* and Brazil's average production of CG/tree/year is 700 g, with a potential annual CG production around 50,000 tons (Cunha, Paula & Feitosa, 2009). This versatile, naturally occurring biopolymer has been used recently in the pharmaceutical (Hani, Krishna & Shivakumar, 2015; Pitombeira et al., 2015) and food industry (Porto & Cristianini, 2014).

CG is a hydrophilic, branched polysaccharide with a high molecular mass whose properties have been investigated (Lima, Lima, de Salis & Moreira, 2002; Ofori-Kwakye, Asantewaa & Kipo, 2010; Owusu, Oldham, Oduro, Ellis & Barimah, 2005; Paula, Heatley & Budd, 1998), however, there is a lack of understanding of its physicochemical properties thus limiting its utilization in food and pharmaceutics. Chemical structure, solubility and molecular weight of CG closely affect its solution properties as well as its interactions with other polysaccharides. The modification of CG can improve its technological and functional properties (Porto, Augusto, Terekhov, Hamaker & Cristianini, 2015). The long-term strategy for promoting the use of CG in the industry is therefore to understand and exploit the physicochemical properties of the gum, in its original state or chemically modified, either isolated or blended with other polymers.

In this review, production, focused on purification procedures, and physicochemical properties of CG and its derivatives are described. Its current and potential applications, mainly focused on the development of submicron delivery systems such as micro- and nanoparticles, are described and the reported applications are explored and discussed.

2. Cashew gum

2.1. Source and production

Cashew gum is an exudate extracted from *A. occidentale*, a popular tree known as cashew. Cashew is a rustic tree that can grow up to 12 feet tall and can be easily found in tropical countries like Brazil, mostly in the northern and northeastern regions such as Piauí, Ceará, and Rio Grande do Norte.

The exudate is produced naturally by the bark's epithelial cells in response to mechanical stimuli or attacks by pathogens. Its production can occur in all parts of the tree and its qualitative and quantitative composition depends on tree maturity and environmental conditions (Kumar, Moin, Shruthi, Ahmed & Shivakumar, 2012).

The extraction is performed physically by making incisions into the bark (similar to the extraction of latex in the manufacturing of rubber) or chemically by introducing substances such as ethylene oxide, benzoic acid derivatives and 2-chloroethylphosphonic acid into the bark (Araujo, 1991). The collected brown resinous mass (Fig. 1A) is refined through solubilization, centrifugation, filtration, and precipitation in ethanol. Then it undergoes a drying step resulting in a polysaccharide rich yellow powder as we can see in Fig. 1B (Rodrigues, de Paula & Costa, 1993).

2.2. Purification

Natural polysaccharides, such as gums, are often contaminated with inorganic salts, proteins, lignins, and nucleic acids that need to be separated. That is why purification must be performed, including chromatographic separation, complexation of metallic ions or quaternary ammonium salts, precipitation with ethanol or acetone, and drying (Rodrigues et al., 1993).

Purification of CG has been performed over several decades accompanied by the improvement of techniques enhanced to obtain increasingly purer CG in less time. Like all biopolymers, purification is an essential step in ensuring a credible alternative to the use of synthetic polymers, however many of the disclosed processes are not described well enough in order to be understood and reproduced. CG was separated from most of its impurities and their acid constituents neutralized (Costa, Rodrigues & de Paula, 1996) as it can be seen in the flowchart of Fig. 2. The first purification aimed to replace the cations present in the gum by sodium, through the addition of excess of NaCl, and remove the remaining impurities. Upon the addition of sodium chloride the system was submitted to filtration and precipitation of the gum. The precipitated CG was washed with ethanol and acetone, and the excess sodium chloride was eliminated in the second purification step. To accomplish this second purification, CG was dissolved again in water and submitted to the same steps discriminated for the first purification. To guarantee that all the gum was in the form of a sodium salt, an ionic exchange column with NaCl at 1 M was used, followed by freeze-