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Research paper

# Konjac glucomannan/xanthan gum enzyme sensitive binary mixtures for colonic drug delivery

Felipe Alvarez-Manceñido, Mariana Landin *, Ramón Martínez-Pacheco

*Departamento de Farmacia y Tecnología Farmacéutica, Universidad de Santiago de Compostela, Santiago de Compostela, Spain*

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**Abstract**

The polysaccharide konjac glucomannan (KGM) is degraded in the colon but not the small intestine, which makes it potentially useful as an excipient for colonic drug delivery. With xanthan gum (XG) KGM forms thermoreversible gels with hitherto unexplored biodegradation properties. In this work, rheological measurements of KGM and KGM/XG systems incubated with and without *Aspergillus niger* β-mannanase (used to mimic colonic enzymes) showed that KGM was degraded by the enzyme even when interacting with XG. Tablets with KGM/XG/sucrose matrices that varied in accordance with a simplex design and bore diltiazem as a typical highly soluble drug load were prepared by wet granulation, and in most cases were found to possess satisfactory mechanical strength and exhibit slow, nearly zero-order drug release. Drug release from these tablets remained zero-order, but was accelerated (presumably due to degradation of KGM), in the presence of *A. niger* β-mannanase at concentrations equivalent to human colonic conditions. However, marked differences between Japanese and American varieties of KGM as regards degree of acetylation and particle size led to significant differences in swelling rate and drug release between formulations prepared with one and the other KGM: whereas a formulation with Japanese KGM released its entire drug load within 24 h in the presence of β-mannanase, only 60% release was achieved under the same conditions by the corresponding formulation with American KGM, suggesting that with this KGM it will be necessary to optimize technological variables such as compression pressure in order to achieve suitable porosity, swelling rate, and drug release. To sum up, the results of this study suggest that sustained release of water-soluble drugs in the colon from orally administered tablets may be achieved using simple, inexpensive formulations based on combinations of KGM and XG that take the variability of KGM characteristics into account.


*Keywords:* Konjac glucomannan; Xanthan gum; Synergistic interaction; Colonic drug delivery; Enzymatic degradation

## 1. Introduction

In recent years, drug delivery systems based on polysaccharides have been receiving considerable attention, especially as regards their potential for controlled release [1] and the targeting of specific *in vivo* delivery sites [2]. Colon targeting would not only allow local treatment of colonic diseases, but would also constitute a potential alternative route for systemic absorption of drugs, peptides and proteins [3–6].

Xanthan gum (XG) is a negatively charged microbial exopolysaccharide consisting of a cellulose backbone and trisaccharide side-chains composed of a glucuronic acid residue between two mannose units. XG solutions have high intrinsic viscosity and exhibit weak gel-like properties at low shear rates, but XG does not form true gels at any concentration or temperature [7]. XG is nevertheless an effective excipient for sustained release formulations, achieving near zero-order drug release kinetics [8]. Drug release from XG matrices is a Fickian diffusion process during the first half of the dissolution period, but during the second is mainly due to the erosion or dissolution of

* Corresponding author. Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain. Tel.: +34 981 563 100; fax: +34 981 547 148.
*E-mail address:* mlandin@usc.es (M. Landin).

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the highly hydrophilic XG [8,9]; it is strongly dependent on the ionic strength of the dissolution medium. The possibility of enhancing the release-control capacity of xanthan gum matrices by strengthening them through interaction with galactomannans, hydroxypropylmethyl cellulose or chitosan has been studied [8,10–12].

Konjac glucomannan (KGM) is a water-soluble polysaccharide used in Asian cuisine. It consists of 1,4-linked β-D-mannose and glucose units in a mole ratio of 1.6:1. It is a slightly branched polymer with acetyl groups on between one-ninth and one-nineteenth of its backbone units [13–15]. These acetyl groups contribute to its solubility and swelling properties and help in making it the soluble fibre with the highest viscosity and water-holding capacity in nature [16–18]. Although unmodified KGM by itself only forms gels that are at best very weak, when modified, or in combination with other polymers, it is of proven efficacy as an excipient for controlled release of hormones [19] and macromolecules such as dextrans, insulin and bovine serum albumin [5,20,21]. In particular, good drug release behaviour may be expected from the thermoreversible gels it forms with polysaccharides such as κ-carrageenan [22], acetan [23] and XG [24–30]. KGM varieties from the three main producing areas for excipient harmonization exhibit significant differences in rheology and capacity to interact with another polysaccharide, apparently because of differences in their degree of acetylation [21,29]. In particular, previous studies of the Japanese and American varieties used in the present work found the Japanese variety, which is the more acetylated, to afford more viscous KGM/XG mixtures than the other [29].

KGM is degraded by the action of β-mannanases produced by colonic flora [31], but is not degraded in the small intestine. This suggests the possibility of its use for colonic drug delivery: a sufficiently strong gel formed by a mixture of KGM and another polysaccharide might retain its integrity and its drug load while passing through the UGIT, but gradually release its load when attacked by colonic flora. In the study described in the remainder of this paper we characterized a range of KGM/XG-based diltiazem formulations [30] only studied tablets with a 1:1 KGM:XG ratio, and we investigated the probable behaviour of such formulations in the colon. Specifically, the goals of this study were (*a*) to check that KGM and KGM/XG gels are susceptible to degradation by *Aspergillus niger* β-mannanase, an enzyme employed in previous studies to mimic the colonic biodegradation of mannose-based polysaccharides [32]; (*b*) to determine the mechanical properties and drug release profiles of a range of KGM/XG-based matrices containing diltiazem as a model of a highly soluble drug; (*c*) to determine, for selected matrix formulations, drug release profiles in simulated colonic medium containing β-mannanase; and (*d*) to evaluate the extent to which the above properties are affected by the above-noted differences among KGM brands. Since the 2005 study [30] found that release from 1:1 KGM/XG-based tablets was faster at pH 1.2 than 7.5 (which suggests that a gastroresistant coating may be necessary to prevent pre-colonic release). In the present study, we only worked at pH 7.5 assuming that the formulations have successfully reached the colon. The addition of enzymes simulates colonic conditions. The effect of pH or ionic medium strength variations on the formulations behaviour is not evaluated in this paper and should be an interesting field for future works.

## 2. Materials and methods

### 2.1. Raw materials

Two KGMs with different suppliers and geographical origins were used: a US brand from Triple Crown America Inc. (Lot 3500 C), and the Japanese brand Propol A® (Lot AKG07). These KGMs were characterized in our laboratory as having mean particle sizes of 0.055 mm [standard deviation (SD) 0.049 mm] and 0.176 mm (SD 0.054 mm), respectively, and acetylations of 0.6% and 1.9%, respectively; they were used as received, as was XG, which was supplied by Guinama, Spain (Lot 016). Diltiazem hydrochloride Eur. Ph. was supplied by Roig-Farma, Spain (Lot 0307362), sucrose and magnesium stearate NF by C. Barcia (Spain), and *A. niger* β-mannanase (specific activity 45 U/mL at 40 °C and pH 4.0; Lot 00801) by Megazyme (Ireland). All other reagents were of analytical grade.

### 2.2. Rheological characterization of the enzymatic degradation of KGM solutions and KGM/XG gels

The degradation of KGM solutions and KGM/XG gels by *A. niger* β-mannanase was evaluated by rheological measurements (when this was possible; see Section 3), the rheological properties of polysaccharides being significantly affected by enzymatic degradation [33,34]. Solutions or gels of KGM and 1:1 KGM/XG mixtures in simulated intestinal fluid (pH 7.5) were prepared at a total polysaccharide concentration of 0.5% (w/v) by mechanical stirring in a hermetic container for 1 h at 85 °C and 400 rpm. For viscosimetry, samples were left to cool and equilibrate overnight, 0, $5.53 \times 10^{-4}$, $5.53 \times 10^{-3}$ or 0.270 U/mL of β-mannanase was added, and viscosity at 37 °C was determined from steady shear measurements carried out over 210 min at a shear rate of $10\ s^{-1}$ in an AR1000-N cone-and-plate rheometer from TA Instruments, Newcastle, UK (cone angle 2°, diameter 60 mm, gap 59 μm). For measurement of complex shear moduli, solutions or gels were prepared by stirring for 1 h at 85 °C as described above, the required amount of enzyme was added at 70 °C, the mixture was left at 37 °C for 210 min, and dynamic oscillatory measurements were performed over a frequency range of 0.05–50 rad $s^{-1}$ at a controlled strain within the linear viscoelastic range. Rheological characterization was performed at physiological temperature (37 °C).