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Original article

The pharmaceutical applications of a biopolymer isolated from *Trigonella foenum-graecum* seeds: Focus on the freeze-dried matrix forming capacity

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A B S T R A C T

The aim of the present study was to evaluate the funtion of fenugreek seed mucilage (FSM) as potential matrix forming agent for orodispersible pharmaceutical lyophilisates. The FSM was isolated and characterized. FSM colloidal dispersions were prepared and the rheological evaluation was performed. Oral lyophilisates (OLs) with different FSM concentrations, containing meloxicam as model drug were prepared by freeze drying method. The OLs were characterized and compared to gelatin containing tablets, prepared under the same conditions.

The FSM dispersions revealed shear thinning flow type. Based on colloidal dispersions' rheological properties, five FSM concentrations were taken forward to the lyophilization step. Completely dry and elegant tablets were obtained. Texture analysis indicated highly porous structures, confirmed by SEM analysis, which explain the fast disintegration properties. All the prepared tablets disintegrated in less than 47 s. The disintegration process was prolonged by the increase in FSM content, due to the high viscosity the polymer creates in aqueous media. FSM tablets presented longer disintegration times, as compared to gelatin tablets, but also higher crushing strength. Considering the fast disintegration and the high crushing strength, FSM is a good candidate as matrix forming agent for fast disintegrating dosage forms or other freeze-dried preparations.

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1. Introduction

Orally dispersible tablets are solid dosage forms that quickly disintegrate in the oral cavity, without the need of water for swallowing. Several techniques were used to obtain ODTs, having as common objective the production of porous or low strength matrices, which would easily disintegrate in aqueous media. Among these, lyophilization delivers high porosity matrices, called oral lyophilisates (OL), which disintegrate in the mouth in a few seconds (AlHusban et al., 2011, Lai et al. 2011, 2014). In recent years, many of the freeze-drying studies have focused on finding and testing excipients that could provide convenient mechanical strength, fast drying rates, long stability in time and fast dissolution of the active principle (Kasper et al., 2013). Actually, the greatest challenge concerning oral lyophilisates formulation involves finding proper types and ratios of excipients that could achieve simultaneous fast disintegration and high mechanical strength. The matrix forming agents are excipients that determine both the disintegration capacity and the mechanical strength. Several polysaccharides like xanthan gum, dextran and alginic acid salts

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and protein derivatives like gelatin were studied for this purpose (Prajapati et al., 2013).

On the other hand, lately, many novel natural polymers had drawn the attention of the scientific community for the diverse panel of pharmaceutical applications such as binders, disintegrants, thickeners, gelling agents, being used for the development of sustained release dosage forms, mucoadhesive dosage forms, suspensions, emulsions and gels (Prajapati et al., 2013). The fenugreek (*Trigonella foenum graecum*) seed mucilages and gums consist of polysaccharides - galactomannans, namely linear chains of ($1 \rightarrow 4$) linked β-D-mannose, with single units of α-D ($1 \rightarrow 6$) D-galactose attached as side chains (Chang et al., 2011, Mishra et al., 2006, Youssef et al., 2009). The galactomannans differ by the mannose:galactose (M/G) ratio, from 1.54 for guar gum, to 3.75 for locust bean gum. Apparently, the one extracted from fenugreek presents the highest percentage of galactose, with a M/G ratio close to 1, which determines its high water solubility (Doyle et al., 2009, Kamble et al., 2013). The polysaccharides isolated from fenugreek seeds have been studied for their disintegrant properties in ODTs (Kumar et al., 2009), mucoadhesive properties (Datta and Bandyopadhyay, 2005, Nayak et al., 2013, Nayak and Pal, 2014) and suspending capacity (Nayak et al., 2012). They have also been mentioned in several studies for their hypoglycemic effect (Kamble et al., 2009, Kumar et al., 2005) as well as for antioxidant and anti-inflammatory actions (Sindhu et al., 2012).

Up to date, there has been no report in the literature on the development of a freeze dried dosage form, using the fenugreek seed mucilage (FSM) as matrix former agent. Therefore, the present study aimed to prove the utility of FSM as matrix forming agent at the manufacture of OLs, having meloxicam as model drug and mannitol as cryoprotectant.

Meloxicam is an oxicam derivative, part of the non-steroidal anti-inflammatory drug (NSAID) group, used for the treatment of rheumatoid arthritis, osteoarthritis and postoperative pain. Considering the conditions for which is prescribed, the fast onset of effect could be helpful. In addition to that, the target population is often consisting of elderly, who may also suffer of disphagia; both hypothesis justify the formulation of OLs containing meloxicam, which could provide fast disintegration and increase patient compliance (Loza, 2008, Ochi et al., 2014).

The first stage of the study concerned the isolation and characterization of the mucilage obtained from indigenous cultures of fenugreek. Secondly, colloidal dispersions with various concentration of FSM were prepared and their rheological behavior was tested. Considering the results, the experiment went further to the optimization of the freeze drying process and then to the preparation of tablets. The variable factor in the tablet formulation was the FSM concentration. In order to be able to state objectively the FSM's properties as matrix forming agent, the tablets containing FSM were compared to tablets containing gelatin – the standard polymer used as matrix forming agent in OLs - prepared under the same conditions.

2. Material and methods

2.1. Materials

Meloxicam (Uquifa SA, Barcelona, Spain) and mannitol (Pearlitol 200M, Merck, Germany) were used. Fenugreek seed mucilage was isolated from fenugreek seeds that were purchased from a local plant material producer. All other chemical reagents used were analytical grade. Xylose, Arabinose, Fructose, Glucose, D-Galactose (Gal) and D-Mannose (Man) were purchased from Fluka and trifluoroacetic acid from Merck, Germany.

2.2. Isolation and characterization of FSM

2.2.1. Isolation of FSM

FSM was isolated according to a literature reported method (Nayak et al., 2013). Briefly, 100 g of fenugreek seeds were soaked in distilled water (0.75 l) for 12 h at room temperature and then boiled until the formation of slurry. The slurry was kept in the refrigerator for another 12 h, the upper clear solution was decanted and concentrated on water bath to 1/3 of its original volume. The solution was cooled at room temperature and then it was poured into acetone, under continuous stirring. The precipitate was washed several times with acetone, then dried at room temperature and kept over sillica gel, in desiccators until further use.

2.2.2. HPLC analysis of monosaccharides

1.0348 g of FSM was hydrolyzed with 20 ml trifluoroacetic acid (TFA) 6M, for 6 h in a sealed glass tube. After evaporation for complete removement of TFA, the hydrolysate was dissolved in distilled water then assessed for monosaccharide composition using a Shimadzu Prominence system (Kyoto, Japan) equipped with a refractive index detector (model RID 10A). Monosaccharides were separated isocratically at 80 °C, using a Shodex SP-0810 column (80×300 mm) and water (Millipore, Bedford, MA, USA) as eluent. The injection volume was 20 μl. A monosaccharide standard mixture consisting of xylose, arabinose, mannose, fructose, glucose and galactose was used at a concentration between 2 and 10 mg/mL in order to get the equation of calibration curve. Monosaccharides were quantified from peak area measurements using response factors obtained with standard monosaccharides.

2.2.3. Preparation of colloidal dispersions

Colloidal dispersions, with concentrations of 0.01%, 0.02%, 0.05%, 0.1%, 0.2%, 0.25%, 0.5%, 0.75%, 1%, 1.25%, 1.5% and 2% (w/w) were prepared. FSM was hydrated with distilled water for 30 min, at room temperature, maintained in water bath at 50 °C, for 2 h and kept under stirring at 1000 rpm, for 30 min, until complete homogenization.

2.2.3.1. Determination of the polymer size, Zeta potential and conductivity of the FSM colloidal dispersions. The average size measurement of polymers in dilute FSM dispersions was performed by dinamic light scattering, at a backscattering angle of 90°, using a Malvern Zetasizer Nano ZS. The size measurements were performed on dilute FSM dispersions, with concentrations ranging from 0.01% to 0.2% (w/v). At least 3 measurements, at 25 °C, were done for each dispersion and the average size was calculated.

2.2.3.2. Determination of the rheological behavior of FSM colloidal dispersions. The rheological behavior was evaluated using the Brookfield DV III Ultra viscosimeter on the concentrated dispersions, with FSM content starting from 0.25% to 2% (w/w). The viscosity was measured at increasing rotation speeds, from 0.3 rpm to 100 rpm, then decreasing to 0.3 rpm again. All measurements were done in triplicate, at room temperature and the plots for dynamic viscosity vs. shear stress were recorded. For a better characterization of the rheological behavior, Power-law model was used, according to Eq. (1):

$$\tau = \mathbf{K}\gamma^{\mathbf{n}} \tag{1}$$

where τ is the shear stress (mPa), γ is the shear rate (s^{-1}), K is the consistency index (mPasn) and n is the flow behavior index (dimensionless). In order to calculate K and n values, log τ vs. log γ were plotted and K was determined as the resulting straight line's intercept, while n was the slope of the resulting line.

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